

**THE USE OF EARLY ECONOMIC EVALUATION TO INFORM  
MEDICAL DEVICE DEVELOPMENT DECISIONS:  
AN EVALUATION OF THE HEADROOM METHOD**

by

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## **ABSTRACT**

The headroom method proposes to offer medical device developers a simple way to integrate health economics into the decision of whether or not to develop a device, so that only commercially viable innovations are pursued. The aim of this PhD research is to evaluate the headroom method on this basis. A mixed-methods approach is used to assess both its prognostic ability and its usability by developers.

Two prospective case studies demonstrate the method's early application, whilst efficacy is assessed by twenty further case studies where the headroom method is applied retrospectively. The headroom method predicted NHS uptake with a sensitivity of 92% and a negative predictive value of 67%; however, results reflect the close-to-market context of the study sample. When numerical headroom assessments were considered alongside qualitative factors identified (relating to the clinical and market context), the method generally offered a good indication of future market potential. Interviews with twelve potential users of the method identified practical issues around time, expertise and objectivity, which varied according to the participant's involvement in the innovation process. The headroom method is demonstrated to be a flexible approach, which could ground development choices in the value that a device might offer the health service.

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## LIST OF ABBREVIATIONS

<b>AHP</b>	Analytical hierarchy process	<b>NHS</b>	National Health Service
<b>CBA</b>	Cost-benefit analysis	<b>NHSC</b>	National Horizon Scanning Centre
<b>CEA</b>	Cost-effectiveness analysis	<b>NICE</b>	The National Institute for Health and Clinical Excellence
<b>COPD</b>	Chronic obstructive pulmonary disease	<b>NIHR</b>	National Institute for Health Research
<b>CTS</b>	Clinical trial simulation	<b>NHS</b>	National Health Service
<b>CUA</b>	Cost-utility analysis	<b>NPV</b>	Net present value
<b>DAP</b>	Diagnostics Assessment Programme	<b>NSR</b>	Next Stage Review
<b>FC</b>	Fixed cost	<b>P</b>	Price
<b>FEV<sub>1</sub></b>	Forced expiratory volume in one second	<b>PFO</b>	Patent foramen ovale
<b>GDP</b>	Gross domestic product	<b>QALY</b>	Quality-adjusted life year
<b>GOLD</b>	Global Initiative for Chronic Obstructive Lung Disease	<b>QoL</b>	Quality of life
<b>HITF</b>	Health Industries Task Force	<b>R&amp;D</b>	Research and development
<b>HRQoL</b>	Health-related quality of life	<b>RCT</b>	Randomised controlled trial
<b>HTA</b>	Health technology assessment	<b>SC</b>	Service costs
<b>ICER</b>	Incremental cost-effectiveness ratio	<b>SIG</b>	Strategic Implementation Group
<b>IPG</b>	(NICE) Interventional procedure guidance	<b>SLF</b>	Spiral laminar flow
<b>LOS</b>	Length of stay	<b>SME</b>	Small and medium enterprises
<b>MATCH</b>	Multidisciplinary Assessment of Technology Centre for Healthcare	<b>TA</b>	(NICE) Technology appraisal
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency	<b>TC</b>	Total cost
<b>MMTSG</b>	Ministerial Medical Technologies Strategy Group	<b>TTO</b>	Time trade-off
<b>MNC</b>	Multi-national corporation	<b>TTT</b>	Transpupillary thermotherapy
<b>MRP</b>	Maximum reimbursable price	<b>TVT</b>	Tension free vaginal tape
<b>MTAC</b>	Medical Technologies Advisory Committee	<b>VBP</b>	Value based pricing
<b>MTEP</b>	Medical Technologies Evaluation Programme	<b>VC</b>	Variable cost
		<b>VOI</b>	Value of information
		<b>WTP</b>	Willingness-to-pay



# CHAPTER 1 INTRODUCTION

Over the past decade, the UK's growing healthcare budget has supported the development of many innovative technologies from the medical device industry. In light of the (ongoing 2007- 2012) economic downturn and the tightened public spending that has followed, the National Health Service (NHS) is now expected to make huge spending cuts, placing unprecedented strain on healthcare resources and activity. Rather than this connoting ruin for the medical device industry, device developers have an important part to play in ensuring that these savings are made through the increased efficiency of spending, and not at the expense of the quality of care received by patients; the market is therefore ripe for innovation. In acknowledging that cost-effectiveness is an important criterion for purchasing decisions, now more than ever, the **headroom method** proposes to integrate consideration of health service value into early device development decisions. Thus, the aim is to better inform the go / no-go decision to develop a device, which is critical to get right. This thesis evaluates the headroom method in relation to this goal.

## 1.1 Introduction of concepts

### 1.1.1 Economic evaluation in healthcare

In the context of healthcare, an economic evaluation is simply the comparison of two clinical interventions (generally current practice versus its proposed replacement) in terms of their costs and consequences (Drummond, O'Brien, Stoddart, & Torrance 1997). The way in which consequences are measured determine whether an economic evaluation is a cost-effectiveness analysis (CEA: outcome generally measured in natural units such as number of

hospital days avoided or life years gained), a cost-utility analysis (CUA: outcome measured in terms of [health-related] utility), or a cost-benefit analysis (CBA: outcome measured in monetary terms). Despite these commonly accepted definitions, the often interchangeable use of these terms in the literature can be confusing; the reasons for this will be described in chapter 4.

The economic evaluation of a medical product or healthcare intervention is included as part of the health technology assessment (HTA)<sup>1</sup>—or ‘technology appraisal’—process of The National Institute for Health and Clinical Excellence (NICE). In the UK, NICE develop evidence-based guidelines on the effectiveness of medical interventions, and consider whether they are likely to represent a cost-effective use of NHS resources. A cost-utility approach is employed (though it is often labelled a CEA), where benefit is measured in quality adjusted life years (QALYs): a measure which accounts for both the duration of health outcome as well as the health-related utility experienced. Thus, a life year is adjusted for health-related quality of life (HRQoL), a quality weighting on a scale of 0 to 1: one QALY is equivalent to one year in full health.

By considering the trade-off between the cost and QALY implications of two different interventions, NICE consider the new intervention’s incremental cost-effectiveness ratio (ICER) (cost per QALY), which helps determine whether any increase in cost can be justified by the health benefit. In order to make this judgement NICE apply a threshold ICER, the derivation of which will be explained in chapter 4, which is based on the opportunity cost of health service spending in terms of the health gain that could be generated elsewhere in the

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<sup>1</sup> HTA and economic evaluation are sometimes used synonymously in the literature, with the former often being used to describe the CEA of a new technology. In reality, whilst determining cost-effectiveness is an important feature of an HTA, an HTA will consider other aspects of the innovation or its impact which are not captured (or not fully captured) by its cost-effectiveness, but which are nevertheless important to the decision-maker.

system. The ICER threshold range applied by NICE is £20,000 - £30,000 per QALY, implying that an intervention where each extra QALY costs less than £20,000 is considered to be cost-effective. If this health benefit is generated at a cost to the health service of over £30,000, however, the intervention is perceived to be too expensive; the same investment could buy more health elsewhere. This is represented in the cost-effectiveness plane in Figure 1.1, where delta ( $\Delta$ ) denotes incremental costs or benefits (as compared with current practice which represents the baseline). The incremental cost represents the net cost implication for the health service of the intervention, and the incremental QALY effect is equal to the total health utility impact. The ICER threshold, also referred to as the 'willingness to pay' (WTP), is represented by a single threshold value for simplicity. The implied coverage decision is either to reject the proposed technology (shaded area) or to accept it.

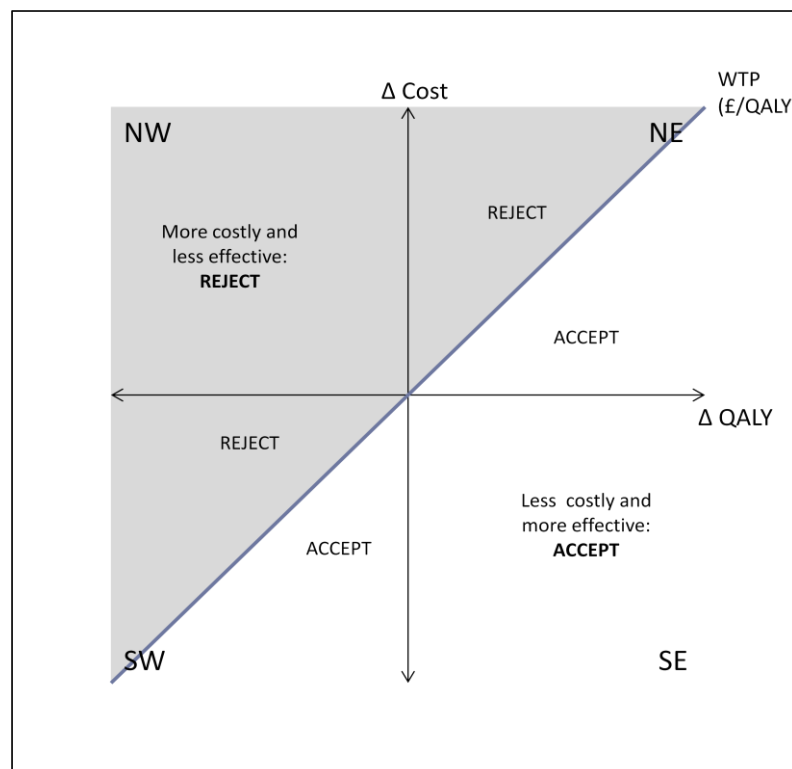


Figure 1.1 The cost-effectiveness plane

The north-west and south-east quadrants of the cost-effectiveness plane produce intuitive coverage decisions: if the intervention is more costly and less effective (is dominated by current practice) it will be rejected, and if it is more effective and less costly (dominates current practice) it will be accepted. The south-west and north-east quadrants require a more discerning judgement to be made on value for money. Whilst a new product located in the south-west quadrant would technically provide a cost-effective use of resources if it were located to the right of the ICER line, it may be ethically or politically unpopular to introduce such an intervention. For a new product or intervention to be situated in the north-east quadrant is a common proposition for new medical interventions, and the WTP threshold provides the means to judge whether the increased cost can be justified by its health benefit to patients.

### 1.1.2 Medical devices

The term ‘medical device’ covers a huge range of healthcare products and equipment, from tongue depressors to body imaging scanners to prosthetic heart valves; they play a vital role in preventing, diagnosing, monitoring and treating ailments and diseases (European Commission 2012).<sup>2</sup> The main differentiating factor between medical devices (often used synonymously with the term ‘medical technologies’ in the literature and in this thesis) and other healthcare products is their mechanism of action, which is physical rather than biochemical. As apparent

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<sup>2</sup> According to the European Commission’s medical device directive 93/42/EEC: *‘Medical Device’ means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:*

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

*and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.*

(The council of the European Communities 2007, pp. 5-6)

from the European Commission's definition, products with a diagnostic function are a sub-category of medical device, and in this thesis are considered as such (though will be discussed specifically where relevant).

### 1.1.3 The headroom method

The headroom method of early economic evaluation, which will be described in detail in chapter 4, allows device developers to incorporate consideration of the demand-side reimbursement process (decision to buy) into supply-side investment decisions (decision to develop). By grounding the development decision in the potential future value of a device to the purchaser, it is thought that development decisions can be better informed. The method is intended to be applied as early as possible, ideally at 'concept stage'. It optimally provides an estimation of the maximum reimbursable price (MRP): the greatest price at which the healthcare provider might fund the device, which represents the total value of the product to the health service based on early expectations of health and cost impact (Girling, Chapman, Lilford, & Young 2012). The method is simple and intuitive, which may be particularly important for small businesses who dominate the industry and who are likely to lack the resources and health-economic expertise of larger companies (a discussion of the industry landscape is presented in chapter 3).

Whilst the headroom method could be applied within the context of any healthcare provider, the context chosen for this thesis is that of the UK, in order to maintain consistency with the value perspective described in section 1.1.1.

## **1.2 Motivation for the study**

Whilst economic evaluation is well developed in the context of late-stage HTA and coverage decisions by providers, its use to inform the early stages of development for industry is less well developed, and applied mainly to pharmaceuticals in the literature. The scene-setting chapters 2 and 3 will highlight the gap for the headroom method, both in the literature as well as in relation to the device industry's composition and structure.

Whereas in the past, evaluation activity in the health sector was based almost entirely on concerns of quality, safety and efficacy—known as the three ‘hurdles’ to market (Cookson & Hutton 2003)—demonstrating a product's cost-effectiveness is now increasingly emphasised, such that it has become known as the fourth hurdle to market (Taylor, Drummond, Salkeld, & Sullivan 2004). This project explores the potential for cost-effectiveness considerations to be incorporated into routine decision-making by industry using the headroom method, thus converting this so-called fourth hurdle to market into the first. The potential benefit of this is twofold: reduced spending by developers on ultimately unsuccessful products, and the speedier development and uptake of those innovations that could benefit patients and the healthcare system.

The motivation for this particular study—an evaluation of the headroom method—derives from the absence of a critical appraisal of this or any other method of early economic evaluation in the literature. By evaluating the method in terms of its ability to usefully inform early investment decisions made by device developers, the study provides guidance around how useful the method might be and in what ways. The research questions upon which the evaluation is based are described in the next subsection.

### **1.3 Research questions**

The current literature base for the headroom method, outlined in the forthcoming literature review chapter, mainly describes the method and applies it to a small number of case studies (Cosh et al. 2007;McAteer et al. 2007;McAteer 2011). By purporting its value to the device industry, the implicit hypothesis made by these publications is that the headroom method will improve decision-making. The evaluation presented in this thesis makes this hypothesis explicit and, in doing so, matches the study's design with the research questions necessary to understand the whether this hypothesis is correct:

Research question 1: *Does the headroom method 'work'?*

Research question 2: *Is the headroom method 'usable' by device developers?*

The first of these questions relates to whether or not the headroom method can usefully predict future uptake (the method's efficacy), whilst the second relates to whether it could feasibly be incorporated into the decision-making practices of device developers (its usability). The efficacy and usability of the headroom method therefore form the key evaluation criteria for this study, the definition of which are described in greater detail in the methodology chapter 5.

### **1.4 Methodological approach**

A mixed-methods approach is employed to consider the headroom method's potential value to device developers. By adopting this pluralist stance, method choice and design is guided by the research questions, which underpin the whole study. Case study analysis and interviews are undertaken, which address not only the predictive capacity of the method and its

compatibility with the intended users, but also what pertinent factors are left out and in what additional ways it could be useful to device developers.

## **1.5 Structure**

A review of the literature is presented in chapter 2, which sets both the headroom method and this evaluation within of the wider research landscape. Further background and rationale for the research is presented in chapter 3 in relation to the UK's medical device market. The chapter explores the distinguishing features of medical devices and how they mould the landscape for innovation as well as its late-stage economic evaluation, which underwent reorganisation in the UK in 2009/10 to better reflect these device-specific considerations.

The theoretical underpinning of economic evaluation in healthcare is provided in chapter 4, which describes how these health economic principles can be embedded into early commercial decisions using the headroom method. A detailed exposition of the headroom method and the way it is applied within this thesis is then presented, which also describes how its application has been advanced by the present study. The methodological approach to the project is then presented in chapter 5, which describes the research questions in detail and how these will be addressed by the mixed-methods evaluation design.

The first of two prospective case studies—the near-patient monitor for chronic obstructive pulmonary disease (COPD)—is presented in chapter 6, and provides a headroom analysis of a device in the very early stages of development. The retrospective case study investigation is then presented in chapter 7, in which 20 devices (identified from the national horizon scanning centre (NHSC)'s 2000-2009 database) are retrospectively evaluated using the headroom method, with information searches date restricted to mimic the concept stage of the developer. The method is applied systematically using a pre-specified approach and time



limit (under the principle of ‘headroom in a day’). These are then followed-up to the present day to observe actual market uptake, from which the predictive value of the method is considered. This is followed by the final prospective case study presented in chapter 8, which considers the headroom for a protective stocking for leg ulcers, and is conducted using the same systematic approach as that developed for the retrospective studies.

Chapter 9 presents the thematic analysis of interviews with 12 stakeholders, representing a range of the method’s potential users spanning from small and large businesses, to those involved in innovation within the NHS, to consultants and individual innovators. These provide a deeper insight into the method’s value and explore its potential role in device development. In chapter 10, the thesis discussion, results across the whole evaluation are synthesised and the convergence of findings is explored. A critique of this study is presented, and implications of the research discussed. The chapter finishes with a conclusion of the headroom method’s potential use in informing medical device development decisions.

## **1.6 Summary**

This thesis, for the first time, assesses the possible implications of basing device development decisions on early expectations of reimbursement value. It investigates whether using the headroom method to explore commercial viability is feasible or even desirable for device developers, and in what ways this may differ according to the type of device or the type of developer. By grounding the research in its real-life context and its real-life implications, the study assesses the potential impact of the headroom method, and in what form it should be carried forward.

## **CHAPTER 2 LITERATURE REVIEW**

### **2.1 Introduction**

The health economics literature is continually growing, and at an ever-increasing rate. Cost-effectiveness analysis within HTA has long been recognised as a compelling way to ascertain value for buyers. The remit of this project is to explore the use of health economics at the beginning rather than the end of the development process: to embed its principles into the innovator's decision to develop. This overview of the literature provides a summary of the wider on-going dialogue in the subject area, noting some of the key influences and setting out the gaps that this project intends to address.

After describing the origins and impact of health economic evaluation, the current state of play in the early economic evaluation literature will be explored. This is followed by an overview of the studies relating specifically to the headroom method. Consideration of this literature base reiterates and substantiates the goals presented in the introduction, by describing the current knowledge base and, more importantly, outlining its omissions.

### **2. 2 Health economic evaluation**

In the leading article of the research journal *Pharmacoeconomics*' first issue, Wells (1992) describes the UK healthcare landscape of the late 1980s, where 80% of medicines expenditure was in primary care. In an effort to contain expenditure, the UK Department of Health responded by issuing personalised spending targets to GPs (Wells 1992). This inclination toward cost containment has always been a priority for commissioners, and if anything will only be prioritised further in the future (the recent plans to make GPs responsible for their

own budgets could be seen as a further step in this direction). However, it is only when outcomes are considered in conjunction with costs that true efficiency can be considered; this is the basis of health economics. This section briefly presents its application over recent decades.

It is generally accepted that the free market would lead to a suboptimal allocation of healthcare resources due to reasons of equity, uncertainty surrounding future need, externalities, uninformed customers and potential for collusion between providers (Sloman 2003). Moreover, health is regarded as a merit good whose provision should be on the basis of need rather than willingness or ability to pay; that is, we should be regarded as citizens, rather than consumers of healthcare (Williams 1997). In the UK these considerations have inspired healthcare services to be organised centrally by the set-up of the publicly funded NHS in 1948.

Health economics deals with the relationship between input and output, input being healthcare spending and output being improved outcomes for patients. In 1971 Archie Cochrane described this relationship as unsatisfactory, declaring that large increases in NHS spending were not being accompanied by markedly improved outcomes (Cochrane 1971). Based on the proviso of a limited budget, health economic evaluation offers decision-makers the tools to maximise output relative to a fixed budget input.

Economic evaluation within healthcare has developed rapidly over the past 50 years. Drummond and colleagues (1997) provide a much cited overview of the topic in their book 'Methods for the economic evaluation of health care programmes'. Economic evaluations (in the form of CEA/CUA/CBA) have applications in many subject areas; one fundamental requirement for their use to assess healthcare interventions is clinical outcome data on which

to base comparisons. Although the principles of randomised controlled trials (RCTs) were set out as early as the 1930s, they were not carried out widely until many years later. The use of CEAs within healthcare developed momentum in the mid-sixties with the availability of such RCT data, and the term health technology assessment (HTA) was first coined in 1967 (Banta 2003). Previous to this, the use of economic evaluation within the sector was not well established, and used crude measures of outcome such as labour productivity (Blumenschein & Johannesson 1996). HTA activity has continued to grow, in response to ever increasing healthcare costs and rapid technological developments.

The speed of development in HTA activity has been especially pronounced in countries with publicly funded health services such as Canada, Australia, the UK and Sweden (Banta 2003;Hutton et al. 2006). Established in 1999, NICE was the first example within Europe of an explicit HTA decision-making body, and is regarded internationally to be the most organised and generously funded HTA body in the world (Banta 2003;Hutton et al. 2006). Substantial progress has been made toward ensuring that decision-making is as systematic and transparent as possible, which has been facilitated by the continual discussion and debate around the appropriate stance, methods, and analytical framework of HTA and economic evaluation within it (Hutton 2012).

Although in the UK a specific threshold range for WTP for health benefit in HTA decisions has been stated (see chapter 4), this is not the case for all countries. Whilst those countries with a similar approach tend to have a comparable threshold to that employed by NICE, others do not explicitly set such a threshold (Vernon, Goldberg, & Golec 2009). In Germany, for example, economic evaluations undertaken by the Institute for Quality and Efficiency in Health Care (IQWiG) do not consider an explicit trade-off between costs and QALYs; indeed, no specific instrument to measure health benefit is recommended over any

other. The MRP (used to make coverage decisions rather than set prices) is determined by information on existing alternatives within specific therapeutic areas (generating ‘efficiency frontiers’), and not within the context of healthcare spending in general (Caro et al. 2010;IQWiG 2009). Efficiency is therefore judged on the ability to provide equivalent or increased benefits at equal or lower costs (much like the new medical technology committee within NICE, which is discussed further in the next chapter).

Although economic evaluation is applied in various forms across different healthcare systems, there is no doubt that consideration of value for money is increasingly prioritised by today’s healthcare purchasers. As described, demonstrating evidence of cost-effectiveness is now commonly labelled the ‘fourth hurdle’ to market approval (Hutton et al. 2006;Taylor, Drummond, Salkeld, & Sullivan 2004). This assumes, however, that purchasers routinely perform economic evaluations in all coverage decisions, which is not the case in practice: NICE evaluate a very small proportion of NHS activity. Hoffman and colleagues (2002) investigate the use of economic evaluation by decision-makers within two UK health authorities, and identify three main barriers: inflexibility of budgets, poor understanding of health-economic outcomes, and the preference that appraisals should be performed and disseminated by a trusted source. Whilst the expansion of NICE’s appraisal activity over the past decade go some way to addressing the last concern, a more recent assessment finds that, at a local level, cost-effectiveness still plays a minor role in decision-making (Williams, McIver, Moore, & Bryan 2008). Whilst this is of huge practical importance, these issues are for now left to one side and decision-makers are presumed to be rational. Reconsideration of these issues will appear later in the thesis when headroom results are compared with actual uptake of new medical devices.

Economic evaluation has been presented here in its capacity to inform demand. These evaluations are often organised by industry, to demonstrate the value of their products. Pharmaceutical companies pump many more resources into conducting late-stage economic evaluations than do medical device companies (Cookson & Hutton 2003). This tendency exists for many reasons, reflecting the commercial makeup of the industry and the nature of the products themselves: their lifespan, cost impact, relationship with current practice, and compatibility with the clinical trial and economic evaluation process. The factors that set devices apart are well documented in the literature (Siebert et al. 2002;WHO 2010b). A detailed discussion of these issues and how they interrelate is reserved for the next chapter.

In 1991 Drummond investigated the use of economic evaluation by the pharmaceutical industry, finding the activity to be more akin to marketing than scientific investigation due to the lack of rigorous standards and bias being common as a result (Drummond 1991). There has been much development in health economic methods since then, and the critical lens through which economic evaluations are appraised is increasingly well defined. The use of economic evaluation by industry at the *early* stages of development is what interests me, and is explored from section 2.3 onwards.

## **2.3 Early health economic evaluation**

*'Economics is the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses.'*

(Robbins 1945, p. 16)

We have seen that economic evaluation can help buyers determine value for money, based on the premise of maximising health subject to a budget constraint. The use of economics to maximise the output of scarce resources must also have a role in the allocation of research and

development (R&D) resources by companies. This section describes the literature relating to economic methods applied in the early stages of development. Competing methods of early economic evaluation are presented in section 2.3.1, which is followed by a summary of the literature that explores their application in practice (section 2.3.2). The literature on early economic evaluation for medical devices specifically is then summarised in section 2.3.3.

### 2.3.1 Methods of early economic evaluation

The supply-side of the health economy is a long way from optimising the use of pharmacoeconomics<sup>3</sup> in the early stages of development (Miller 2005). However, the increased use of economic evaluation to inform demand has given rise to the development of sophisticated early economic modelling techniques. In the literature, these methods have been discussed mainly in relation to pharmaceuticals, partly reflecting their substantial commercial value, but also due to the vested interest of the NHS and national agencies in big-impact new drugs. The incorporation of economic evaluation into the early stages of development can be considered under many relevant headings. The term ‘early economic evaluation’ renders limited results in a literature search. However, incorporating search terms such as investment appraisal, net present value, decision-support, and R&D brings to light a wealth of significant intellectual input.

In a study of (general) new product development, Cooper and Kleinschmidt (1986) conclude that more emphasis should be placed on the initial screening of ideas (the go/no-go decision to allocate funds to a proposed project), finding this activity to be both poorly executed and highly related to the overall success of a project. Whereas the headroom method (as applied in this thesis) considers product value at the preliminary go/no-go decision

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<sup>3</sup> Traditionally referring to the health economic evaluation and technology assessment of pharmaceuticals, the term pharmacoeconomics is now often used to refer to health economic activity in general, for any type of healthcare product or intervention.

stage, the methods presented in the literature relating to the ‘early’ use of economic evaluation refer to its employment anywhere along the development process.

Sculpher and colleagues (1997) present a framework of iterative economic evaluation, applied initially in the early stages of development (once the basic science has been investigated), and with estimates being firmed up progressively as more information is gathered (though this is explored within the context of publicly funded HTA rather than specifically by industry). These authors were not the first to promote this iterative approach. Banta and Thacker (1990) likewise noted the importance of continual reassessment. Grabowski (1997) and Fenwick et al. (2000) also emphasise that early health economic analyses should be refined iteratively, and that new data should be incorporated as it becomes available using Bayesian methods. Rather than representing a method in itself, a Bayesian approach involves estimating prior distributions (e.g. around cost-effectiveness) based on current information from available statistical data or from experts and their personal beliefs, which can be later updated and transformed into a posterior distribution when more information becomes available (Briggs 1999).

The net present value (NPV) of a project, assessed by valuing the future flow of costs and benefits in today’s terms, is a widely employed framework to assess project viability. The NPV exercise has been advocated for investment decision-making within the healthcare industry for many years (Long 1979). Consideration of a product’s potential value within the healthcare market is unique, as it is not the consumer who determines value but a third-party payer. Backhouse (1998) outlines how drug companies can use NPV and profit considerations to optimally design clinical trials. To this end, the author presents a demand and revenue function which, given its date of publication, does not employ a collective WTP threshold which is now implicit (even explicit) in many countries. Indeed, Vernon and



colleagues (2009) describe the use of NPV to determine maximum WTP using payer reimbursement signals (such as cost-effectiveness thresholds). This approach is closely related to the proposed framework provided by the headroom method, and will be elaborated in section 2.4.

Uncertainty inevitably surrounds any product development decision, so the objective of some economic models is to incorporate this parameter into decision-making. Palmer and Smith (2000) describe the use of ‘option value’ (also ‘real options’) for HTA decisions, to extend allowance for uncertainty from simple bounds (within which actual cost-effectiveness is expected to lie) to incorporate the possibility of decision deferral. Miller (2005) describes this framework in relation to NPV calculations for drug development decisions, and goes on to set out four more pharmacoeconomic approaches for use in the early phases of drug development: clinical trial simulation (CTS), investment appraisal, threshold analysis and value of information (VOI). Whilst CTS and ‘investment appraisal’ require a synthesis of available knowledge (usually from phase I/II clinical trials) and manipulation of these using Monte Carlo simulation, Miller’s description of ‘threshold analysis’ seems more intuitive but still requires partial information about the drug’s performance. VOI is described by Miller and others as identifying the returns of future research, i.e. evaluating the cost of current uncertainty by estimating the expected value of perfect information (Dong, Coyle, & Buxton 2007). VOI has traditionally been used to improve the cost-effectiveness of research spending, from a societal perspective (Fenwick, Claxton, Sculpher, & Briggs 2000), but has been suggested for adaptation to commercial decisions by comparing the cost of making the wrong decision to the cost of collecting further information to reduce uncertainty (Vallejo-Torres et al. 2008).

Bartelmes and colleagues (2009) provide perhaps the most comprehensive account of assessment methods for innovative healthcare products in the early stages. The authors present the results of a systematic literature search as well as an extensive manual search, the executive summary of which is available in English. The 379 references demonstrate that research around development-accompanying assessments is extensive. Specific methods identified include the innovation assessment algorithm for drug innovation, expert systems, fuzzy-logic, and the analytical hierarchy process (AHP) (Bartelmes et al. 2009). Most are discussed in relation to drugs, and are not intended for pre-development decisions. However, those that are commonly discussed in the literature, along with their potential limitations, are summarised in Table 2.1 (discussion of which is largely informed by a MATCH research paper by Johal and Williams (2005)).

**Table 2.1 Summary of development-accompanying methods of economic evaluation**

<b>Method</b>	<b>Description</b>	<b>Limitations</b>
NPV	Making decisions based on the net present value of a project is a generic approach to project assessment (and is what the headroom method proposes to facilitate). By estimating the (monetary) value of future benefits and costs, identifying when these are likely to be realised / incurred, and applying a relevant discount rate based on the time-value of money, the net present value of the project may be assessed. If this is positive, this would indicate a favourable development decision.	This technique does not account for possibility of decision deferral, and does not explicitly incorporate any uncertainty valuation. Additionally, the appropriate discount rate will vary between users and may be difficult to estimate.
Real Options	The real options approach derives from the financial market, where the holder of an option has the right (but not the obligation) to hold on to it in the future. In a similar respect, product development can be seen as a series of investments, where the decision to abandon (or adjust) a project may be made in the future (Johal, Oliver, & Williams 2008). By allowing for this decision deferral option, the present value of an investment opportunity is increased.	The approach is complicated and difficulties are likely to arise in applying it to the product development setting. The requirement of a volatility value (a measure of economic uncertainty), for example, may be unrealistic in practice.
AHP	The analytical hierarchy process is one form of multicriteria decision analysis, where both quantitative and qualitative factors may be combined. A hierarchy of relevant decision inputs can be created, which are weighted by making pair-wise comparisons and using mathematical techniques (which can be consolidated into computer programmes) to create weightings (Hummel, Van Rossum, Verkerke, & Rakhorst 2000).	As well as potential inconsistencies in the numerical scales utilised, no theoretical foundation for their imposed link with the verbal descriptions exists (Johal & Williams 2005). Additionally, the approach makes choices between alternatives, rather than determining whether either are acceptable.

Fuzzy logic	Fuzzy logic allows decision-making to incorporate current knowledge, past experience, and subjective judgements. It does this by transforming descriptive linguistic values or qualitative statements into fuzzy numbers (called 'fuzzification'). These are then assigned weights and aggregated to assess value.	The concept and application of fuzzy logic is quite abstract, and requires expert input.
Expert systems	An expert system is an artificial intelligence technique, which uses an imputed knowledge base and inference engine to solve a problem. It has been applied in the pharmaceutical sector to assess the chances of success of a novel pharmaceutical product (Akoka & Leune 1994).	The knowledge base required by the system is time consuming, and it may be difficult for experts to express and input their knowledge in terms of specific rules and confidence factors (Johal & Williams 2005).

Information adapted from a MATCH research paper (Johal & Williams 2005)

### 2.3.2 The use of early economic evaluation in practice

Many question the applicability to industry of the methods described due to their conceptually challenging nature and reliance on a strong set of assumptions. Mayhew (2009), for example, finds only limited use of the options approach in practice, whilst Bartelmes et al. (2009) note that despite the wide methodological literature, methods are generally described vaguely and seldom proceed beyond pilot implementation. The limitations described in Table 2.1 suggest practical usability issues for industry. Annemans and colleagues (2000) outline methods of early modelling for drug therapies, and describe their capacity to inform go/no-go and priority setting decisions. Whilst presenting some of the difficulties associated with early modelling, the authors offer no guiding framework, but stress that early models must be designed to meet the requirements of 'full-blown' (late stage) models (Annemans, Genesté, & Jolain 2000). The stance taken in this thesis is that this is not practical or even desirable for very early decisions; I aim to investigate whether so called 'quick and dirty' models can offer a useful insight into potential value.

The contribution of early economic evaluation to decision-making within industry has been reviewed by Hartz and John (2008), who searched for both methodological contributions and empirical studies using early data. The review reflects the main body of research in the

area, where ‘early’ refers to any stage pre-market. Even those methods described to accompany ‘go/no-go’ decisions incorporate data from early clinical trials. The headroom method fits most appropriately into the short section relating to the business opportunity within pre-clinical market assessment. Others refer to this as the ‘early value proposition’ (Davey et al. 2011). Hartz and John (2008) emphasise the importance of identifying unsuccessful products as early and accurately as possible, and find that the value of early modelling for this purpose is not fully exploited.

The industry’s use of early economic evaluation is, perhaps unsurprisingly, not well documented (Annemans, Genesté, & Jolain 2000;Hartz & John 2008). Nevertheless, the benefit of terminating the development of unsuccessful products early is clear. DiMassi (2002) finds that if one quarter of all decisions to abandon drug development were shifted from phase II to phase I, cost savings of around 8% per approved new drug could be realised. The consequences may be even greater for medical devices, whose industry is dominated by small companies which rely on a very small number of products.

### 2.3.3 Early economic evaluation of medical devices

As with the findings from the wider literature for early economic evaluation, where the timescale of intended application ranges from early clinical trials (Álvarez 2001) to its later role in informing pricing (Dranitsaris & Leung 2004), the methodological literature relating to devices specifically is wide in scope. The use of iterative health economic modelling for medical devices specifically has been advocated by Vallejo-Torres and colleagues (2008;2011), who explain how Bayesian methods can be used to incorporate all available information at the various stages of development. However, the increased complexity of this approach as the stages of development progress may pose difficulties to its use in practice by device companies (Vallejo-Torres et al. 2008).

Dong and Buxton (2006) describe an early assessment of cost-effectiveness for computer-assisted knee replacement in the absence of formal evidence from clinical trials, based on early cost and outcome data which are manipulated using transition probabilities in a Markov model. A year later they supplement this with a VOI analysis to assess the returns of further research, though this is addressed from a societal rather than commercial perspective (Dong, Coyle, & Buxton 2007). Research into the use of early HTA has also been provided by Craven and colleagues (2009), who describe a straightforward decision-tree spreadsheet tool, which was used with the intention of establishing a common understanding of value between device developers and the NHS National Innovation Centre. Whilst many highlight that the integration of health economics into early decisions is particularly absent from the device industry (Craven, Morgan, Crowe, & Lu 2009), even in large pharmaceutical companies pharmacoeconomics is employed to a much greater extent for marketing and reimbursement than for R&D, despite economic factors being the second leading cause for research termination (DiMasi, Caglarcan, & Wood-Armany 2001; Grabowski 1997).

Pietzsch & Paté-Cornell (2008) provide a model of early technology assessment for new medical devices. The model considers risk attitude and current information on relevant technologies, and builds these into a quantitative model to explore potential effectiveness, safety and superiority over existing treatments. Although presenting a sophisticated approach to engineering risk analysis, the model only explores investment 'value' in terms of physical device performance, despite listing cost-effectiveness in the critical components of an early HTA. Ijzerman & Steuten (2011) provide a recent overview of the potential for HTA to inform decisions made by medical technology developers. The authors suggest a framework of development stages, within which the headroom method would fit into 'very early HTA'; indeed, the authors incorporate a brief reference to the early work presented on the headroom

method by Cosh et al. (2007). The authors go on to indicate that the method requires the existence of a prototype for the product, and that it should be adapted so as to incorporate a ‘clinical case analysis’ (Ijzerman & Steuten 2011). The headroom method’s application, as explained and implemented in this thesis, will demonstrate that early views on clinical potential are an integral part of the method, and that it is suggested for the most preliminary of feasibility decisions (pre-prototype).

I have identified limited research into the use of early economic evaluation methods by the medical device industry. Since the inception of MATCH<sup>4</sup>, two studies have been undertaken to investigate the decision-making practices of MATCH’s industry partner base. The first, reported in 2005, provides the findings of a postal questionnaire sent to six companies: five ‘large’ (turnover greater than £200 million) and one ‘small’ (fewer than 15 people) (Johal & Williams 2005). The authors found five to incorporate formal economic evaluation in product development, but only three at the concept stage. Four companies used an NPV approach (though no details around the derivation of value are provided). One company incorporated a real options approach, and four used internally-developed scoring checklists (Johal & Williams 2005). More recently Craven and colleagues (2009), through a series of interviews with MATCH’s industry partners (12 in total), note that few used health economics in early development decisions and none amongst the start-ups or small and medium enterprises (SMEs) (no description of the sample is provided). Though not strictly comparable, the divergent findings may reflect the changing industry partner base of the organisation, which in the earlier days of MATCH seemed to be much larger companies with

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<sup>4</sup> MATCH (the Multidisciplinary Assessment of Technology Centre for Healthcare) is the research collaboration within which this PhD has been undertaken. The research collaboration is between four UK universities (Birmingham, Brunel, Nottingham and Ulster) as well as a cohort of industrial partners.

more developed processes (reflected in the job roles of the questionnaire respondents, which included an R&D director, technology valuation manager and health economics manager).

As illustrated, early health economic methods have generated substantial research, though investigations into their use at the concept stage are largely absent, and their relevance to developers remains unaddressed. The next section describes the literature relating to the headroom method specifically.

## **2.4 The Headroom Method**

The literature reviewed thus far relates to decisions made throughout the development process, relies on fairly complex models, and has been mainly explored in relation to pharmaceuticals. The headroom method, which will be explained in detail in chapter 4, aims to quantify the reimbursement prospects of a device idea, to allow the developer to compare this with projected costs of production and development. The feasibility of profit may thereby be considered before any substantial investment is made. The basis of this approach is by no means novel, but its perspective is distinct. It represents the application of health economics where effect is supposed rather than known. The outcome, rather than a cost-effectiveness ratio, is the identification of the maximum cost to the health service at which the device would be cost-effective. In this context, the term ‘headroom’ was coined in Cosh et al. (2007) and appears in several publications that have emerged from the MATCH collaboration (Davey et al. 2011;Girling, Young, Brown, & Lilford 2010;McAteer et al. 2007).

The theoretical underpinning of the headroom method is most frequently described in relation to Sculpher et al.’s description of the ‘effectiveness gap’ (Sculpher, Drummond, & Buxton 1997), which describes the extent to which current practice could be improved (which

is what the headroom method seeks to quantify). However, the current headroom literature largely fails to identify some important parallels with other relevant research, due probably to differences in terminology used by this other research and its focus on pharmaceuticals.

One paper discusses the potential implication of cost-effectiveness thresholds on the commercial viability of new drugs, and conceptualises this in a very similar way to headroom (Vernon, Goldberg, & Golec 2009). By describing the cost of a new therapy as the sum of its price and associated costs, the authors set out the ICER inequality, and disaggregate the maximum price at which the therapy would be cost-effective: *'...by decomposing a new drug's price from the total costs of the intervention, firms may "solve" for product price levels that satisfy a given threshold...'* (Vernon, Goldberg, & Golec 2009, p. 800). They go on to describe societal efficiency in R&D investment being achieved where products attract investment based on their NPV to the company. Jena and Philipson (2008) also consider the implications of CEA on innovation incentives, whilst Danzon and Towse (2002) identify a similar ' $P^{\max}$ ' (maximum price) as that illustrated by Vernon and colleagues. In the latter, which considers the novel use of gene therapy, the authors also outline a useful transformation of the maximum price equation into the producer's break-even profit constraint (Danzon & Towse 2002). Similar outlooks can be found in both older research (e.g. Grabowski's 'simulation model' (Grabowski 1997)) and new (such as a recent presentation at the European Conference on Health Economics titled 'Early health economic evaluation and value based pricing in the development phase of medical products' (Koerber 2012)).

The derivation of an MRP using the headroom method is conceptually akin to a term that is now rife in the literature: value based pricing (VBP). VBP was recommended by the Office of Fair Trading in 2007 for the pricing of pharmaceuticals to the NHS, and is to be rolled out by 2014 (Department of Health 2010b;Office of Fair Trading 2007). This has inspired much



debate in the literature, reflecting widely varying shades of opinion. Under VBP, the whole ‘value’ of an innovation would be reflected by its price, meaning that all surplus would accrue to the producer until patent expiration. As a concept, VBP has been addressed by others under different names, for example the use of cost-effectiveness as a ‘price control’ (Jena & Philipson 2007). Although not being suggested in this thesis as a pricing tool for medical devices, the headroom method is based on the same principle, assuming that the health service should be willing to pay *up to* the maximum ‘value’ of a device—its MRP.

In introducing the headroom method, McAteer et al. (2007, p. 344) pose the question: ‘*would it be cost-effective if it works as well as we hope?*’. Whilst acknowledging that sufficient headroom does not guarantee commercial success, for example where a product turns out to be less effective than expected, the authors propose that its utilisation as a rule-out tool (for those technologies which will never be cost-effective to buyers) will reduce the risk of pursuing failures. To inform the headroom analysis of tissue engineered products, the authors supplement a literature search with ‘technical updates’ from companies and the input of expert urologists. Two potential tissue engineering applications are identified: a bowel substitute in cystoplasty for bladder carcinoma, and for urethroplasty in place of buccal mucosa (lining of the cheek). They find headroom to be large for the first indication, but possibly too small for the second. Utilities are elicited using the time trade-off method from four clinicians in the first case, and from members of the public in the second. This time-intensive means of HRQoL elicitation, which is at odds with the remit of the headroom method (to provide a quick and simple overview of market potential), is addressed by McAteer in her thesis (McAteer 2011), in which she applies the headroom method to four areas of regenerative medicine (two of which are outlined above). In recognition of the utility elicitation problem, she provides an alternative approach: the ‘utility ladder’. This will be

discussed further in chapter 4, where I present an alternative method of intuitive HRQoL estimation.

Cosh and colleagues (2007) present the same two case studies, and place the headroom method within a wider ‘decision framework’, beginning with considerations of strategic fit. As in the paper by McAteer et al. (2007), the QALY benefit for the tissue engineered bladder is not discounted despite its ten year duration. The headroom method has also been applied to two health service interventions, the first of which considers the cost-effectiveness of a ‘deep cleaning’ initiative in UK hospitals (Brown & Lilford 2009), and the second of which estimates the value to the health service of improved patient handover of care between hospital and the community (Yao et al. 2012). Application of the headroom method outside of the MATCH program of research is presented in a discussion paper by Latimer and colleagues (Latimer et al. 2011), who assess the cost-effectiveness of a new neck collar for patients with motor neurone disease. Girling and colleagues (2010) extend the concept of headroom to incorporate developmental uncertainty, finding that, when combined with the flexibility offered by later decision gates, uncertainty enhances early stage valuations. The authors also relate the theory clearly to some of the relevant terms that have been overlooked by others (such as the NPV and VBP). A pricing model is proposed by the same authors (Girling, Lilford, & Young 2011). Although interesting mathematically, the incorporation of uncertainty considerations into the headroom method’s application within this thesis is limited to the exploratory testing of alternative assumptions or scenarios. This is so the method is kept straightforward, and as intuitive and accessible as possible to device developers.

Vallejo-Torres and colleagues (2011) present an important study which builds on the literature advocating the incorporation of Bayesian methods into iterative HTA. The authors undertake a retrospective analysis of absorbable pins for treating hallux valgus (bunions),

calculating its perceived cost-effectiveness at the early, mid and late stages. The authors restrict literature searches to information that would have been available at the various stages of development, an approach also taken in the retrospective case studies presented here (chapter 7). Early headroom/‘effectiveness gap’ analysis is used to place an upper bound on the MRP, which can be compared to expected costs. The authors assumed that the need for surgical removal of metallic pins would be eliminated and half of all stress fractures and infections would be avoided, leading to a cost saving of £465. A QALY impact of 0.05 was elicited from five experts and assumed to last for the patient’s remaining lifetime, leading to overall headroom of £21,306, deemed to be sufficient to warrant development. Probabilistic sensitivity and VOI analysis is incorporated into the mid-stage evaluation, and more detailed data from clinical trials into the late stage, all of which provided a positive case for the innovation (though early expectation of outcome was too optimistic); the device has achieved commercial success. A similar approach (though not retrospective) is presented by van de Wetering and colleagues (2012), who employ a step-wise approach to the early HTA of a point-of-care diagnostic test for heart failure patients, beginning with a headroom assessment and, given favourable results, following this with progressively more sophisticated models.

Some important contributions have been made in the literature surrounding early economic evaluation. The next section outlines the ways in which this project contributes to the current knowledge base.

## **2.5 How this project fits into the literature**

The motivation for this project was described in the introduction. An outline of the relevant literature demonstrates the gaps in the current research base that this thesis intends to address.

This concluding section of the literature review offers a recap of (a) how the headroom method complements or differs from other methods of early economic evaluation, and (b) how this project contributes to this field of research.

The main divergence of the headroom method from other methods of early economic evaluation in the literature is in the definition of ‘early’, which in much of the literature refers to any stage pre mass-market. In the context of this research, the focus is on the concept-stage of development. The various methods presented above aim to increase the efficiency of R&D spending by the ‘*faster termination of uneconomic projects*’ (Miller 2005, p. 11). In this thesis I consider a framework whereby the projects that could never be cost-effective are never embarked upon. Of course, very early estimates of value will inevitably be speculative, and may be seen as lacking the sophistication of other more rigorous approaches that can be used in the later stages of development. However, this thesis aims to evaluate the headroom method according to its ability to provide a useful and pragmatic approach to investment decisions by device developers.

The current headroom publications, outlined above, offer only a small handful of examples of the method’s application, therefore providing limited insight into the methodological issues and considerations which may vary according to device type, relationship with current practice (which is not always a direct replacement), clinical area, etc. By drawing upon a relatively large number of case studies—two prospective and twenty retrospective—these methodological issues can be explored further, in order to identify any barriers or qualifications for the successful application of the method. By following up the retrospective case studies, an initial validation of the method is presented, something that Bartelmes and colleagues (2009) describe as largely absent from the literature. Additionally, there is a strong call for an investigation into the value and usability of early decision-making

tools for stakeholders (Ijzerman & Steuten 2011;Vallejo-Torres et al. 2008). As well evaluating the method according to considerations of validity, the project also considers whether the headroom method might feasibly be integrated into real decision-making by developers—surely an important qualification of a decision-making tool.

# CHAPTER 3 THE UK'S MEDICAL DEVICE MARKET—THE LANDSCAPE FOR INNOVATION AND ITS EVALUATION

## 3.1 Introduction

As this project focuses on medical devices, it is appropriate to describe what sets devices apart from other healthcare products. In doing so, this chapter outlines the wider medical device landscape and thereby describes the context within which the headroom method is proposed to be applied. The background of and progress towards recent changes in the evaluation of medical devices in the UK is also explored, and will be shown to be sensitive to the particular characteristics of the device industry.

The importance of the life sciences sector—covering pharmaceuticals, medical technology and biotechnology—cannot be overstated, given its contribution to both the UK economy and the health of the population. The ever-increasing demand for health and healthcare products in the UK is demonstrated in Figure 3.1 by the upward trend in healthcare spending since the 1960s. Total healthcare expenditure in 2010/11 was £151.3 billion, equivalent to 10.3% of gross domestic product (GDP) (Hawe, Yuen, & Baillie 2011).

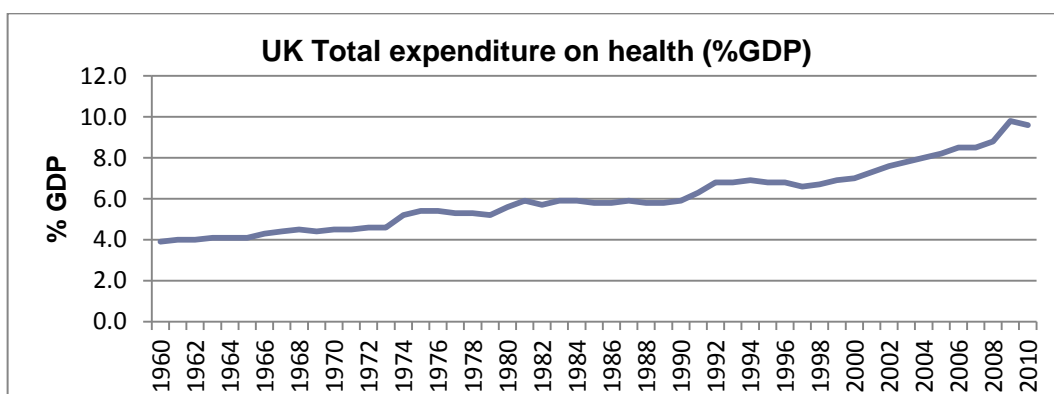


Figure 3.1 Health expenditure in the UK as percentage of GDP

Data retrieved from OECD health data (OECD 2012)

The ageing of the population and ever higher standard of living expectations means that this upward growth in demand is likely to continue, despite constraints to public expenditure. The wider fiscal situation suggests that the large yearly increases in inflation-adjusted NHS spending which have set the precedent over the past six decades will not continue in the immediate future. However, this does not imply a reduced demand for the output of the life sciences industry. The NHS is in fact reliant on the sector's innovative output to make current spending go further, and to achieve the 'efficiency savings' that are required of it—£20 billion by 2014 (Department of Health 2010b). This dependence is reciprocated; according to OECD health data, 83% of total health expenditure in the UK in 2010 was publicly funded (OECD 2012), implying that the NHS is a very important customer for the healthcare industry. This interdependency means it is essential that both industry and those making NHS procurement decisions are mindful of each other's norms, processes and concerns.

The headroom method offers a mechanism by which industry, at a very early stage, can consider the future NHS demand for their products. As a means of providing some context to the topic, this chapter considers the two ends of a spectrum for medical devices in order to then observe how they interact: the industry and decision-makers—supply and demand. By considering the market environment for medical devices, and then the process by which devices are evaluated, we will see how this second system is adapting to suit the first. This complements the basic premise of this thesis which is essentially to do the opposite: to align industry behaviour with the adoption process.

The chapter is divided into four parts. Firstly, the distinguishing characteristics of devices are presented in section 3.2 by comparing them to pharmaceuticals in terms of their process of innovation, with section 3.3 considering the impact of these differences on industry structure. Section 3.4 explores the ensuing difficulties in evaluating and regulating medical devices, and

includes a review of national appraisal activity over the past ten years. In section 3.5 the response to these difficulties as reflected by changes in the UK's appraisal system is investigated, and an initial critique of the new evaluation pathway for devices is presented.

## **3.2 What makes devices different?**

Devices and pharmaceuticals have the same primary objective: to improve patient health. They differ in their mechanism of action; whereas pharmaceuticals generate biochemical reactions, a device relies on its physicality to treat patients (Campbell 2008). For this reason, drugs interact directly with patients whilst devices do so through a third party—the operator (which could be a clinician or even the patient themselves) (Taylor & Iglesias 2009). This dissimilar mechanism of action is the fundamental distinction between drugs and devices, and holds important implications for all of the issues explored in this section and indeed the rest of the chapter.

### **3.2.1 Process of Innovation**

Whereas advances in pharmaceuticals derive from a discovery of new chemical entities or combinations, new devices are invented (Campbell 2008). The innovative proposition of new medical devices is therefore wide in scope, ranging from an incremental development of an existing technology, to a completely new treatment modality which solves a problem that is not managed by existing treatment options. Of course there are many types of device innovation in between, which will be demonstrated by the wide variety of ways in which the 20 case studies presented in chapter 7 propose to change or supplement current practice.

Although the scope for pharmaceutical innovation is also wide, the inherent difficulty in identifying new chemical entities and developing them for commercial use means that there



are relatively few novel pharmaceutical products; there are 218 drug targets<sup>5</sup> (Imming, Sinning, & Meyer 2006). This contrasts with the medical device sector which is in a state of constant development, and is currently made up of around 500,000 products (Campbell 2008;Eucomed 2011). Being user-driven, a single medical device may be subject to continuous iterative improvements or modifications, and often stem from individual clinicians, researchers, or engineers. This is in contrast to drugs, where innovation is generally a result of laboratory work by large teams of scientists and the discovery of new compounds with limited scope for alteration. Once approved, a drug may remain on the market for many years with no fundamental changes (World Health Organisation 2010b).

Whilst there are of course examples of medical devices that become and remain the ‘gold standard’ of treatment for a long time, the trend within the sector of continual redesign and replacement means that the typical lifecycle of a device has been estimated to be around 18 months (Eucomed 2011). Minor modifications allow others to produce products outside the original patent terms, as designs are visible and thus easy to replicate. By contrast, the patent protection of a chemical entity allows companies to maximise the lifetime of their products: the EU has the highest level of market protection for pharmaceuticals in the world, with patent regimes stretching to 25 years (Lowe 2004). An investigation into the historical lifetimes of 455 drugs in England identified a mean lifetime of 57 years (Hoyle 2010).

Spending on R&D in the UK device industry is relatively high: £300 million in 2007/8, accounting for 5.5% of sales (BIS 2009a). For the same year, however, the pharmaceutical and biotechnology sector spent 15.3% of sales on R&D, contributing over a quarter of all industrial R&D in the UK (ABPI 2011b;BIS 2009b). This disparity reflects industry

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<sup>5</sup> A drug target is the native protein or cell structure in the body which can be targeted and modified by a drug, to produce a therapeutic effect.

structure. As the lifecycle of a product is also its investment recovery period, pharmaceuticals have far greater scope for recouping the vast resources they direct towards R&D, although there is a significant lag period—on average 10 to 12 years (ABPI 2011b)—before returns can be realised. This is one reason why the pharmaceutical industry is better suited to large scale firms that can afford to invest large amounts into this R&D process, and indeed the sector is dominated by large multi-national corporations (MNCs). This differs to the situation for devices whose investment recovery period tends to be much shorter and more immediate. Section 3.3 demonstrates that although the device industry has some big players, there is a high proportion of SMEs in this sector.

### **3.3 UK Market Composition**

The outputs of both the pharmaceutical and medical devices industries are increasingly important for society's wellbeing. Their contribution to the health of the population is obvious, but they also provide a valuable contribution to the British economy, not least by fostering a more healthy and productive workforce. A brief consideration of the nature / application of devices and drugs, and what constitutes 'innovation' in the two industries, has indicated why their set up should be so different. This section demonstrates the translation of these differences into market composition, which is explored quantitatively. It is split into four parts: demand in the UK, how the national industries fit into the global marketplace, their size and structure, and their contribution to the UK economy.

#### **3.3.1 Demand for devices and pharmaceuticals in the UK**

Aneurin Bevan, the Minister for Health in post-war Britain, is acknowledged to have orchestrated the creation of the NHS, which was established in 1948 with the belief that

health should be a fundamental right for all citizens. Bevan believed that, within a few years of running, a healthier population would lead to diminished healthcare needs and reduced expenditure requirements (George & Julious 2006). As outlined above, spending on healthcare has actually risen consistently over the past 60 years, and now stands at around £151 billion in the UK, 83% of which is from public expenditure (Hawe, Yuen, & Baillie 2011;OECD 2012). The NHS is now the world's largest publicly funded healthcare supplier (NHS Choices 2011), and thus a major buyer of healthcare products in the UK. However, (perhaps as a result) the UK is considered to be remarkably slow in the uptake of new healthcare technology, especially for new medicines (ABPI 2011a).

As well as the growing life expectancy and raised expectations in standard of living, technological advances in the life sciences sector are also considered to place upward pressure on healthcare expenditure. However, the direction of this relationship is contested by many, as the net outcome of technological progress is based on a complex interplay of effects, which can be both cost-reducing as well as cost-increasing (Pammolli et al. 2005). Spending on devices and drugs represents a significant portion of spending, though not equally so. Of total healthcare expenditure in the UK, around 12% is spent on pharmaceuticals, which is nearly three times as large as device spending at just over 4% (OECD 2012;Wilkinson 2011). This demonstrates the large economic impact of both sectors but particularly the pharmaceutical industry, which is corroborated by further statistics presented below.

### 3.3.2 'Global players'

The pharmaceutical and medical device sectors are huge global industries. Based on global sales, the pharmaceutical industry is nearly four times as large as the medical device industry whose global market is estimated to be worth between £150 and £170 billion (BIS UKTI DH 2011;IMS 2011). Both industries are expected to grow, but the predicted magnitude of this

growth is larger for medical devices than pharmaceuticals—10% versus 3-6% over the next five years (BIS UKTI DH 2011;IMS 2011). In fact, the global pharmaceutical market has exhibited a steady decline in sales growth, which was 11.8% in 2001, and which has decreased year on year, standing at 4.1% in 2010 (IMS 2011).

The UK representation within both industries is similar, making up around 4% of global sales and 13-14% of European sales (Office for Life Sciences 2010;Wilkinson 2011), implying a UK market size of around £6 billion for devices and £23 billion for drugs.<sup>6</sup> Annual turnover (income from sales) in 2011 was £15 billion for medical devices and £31.8 billion for pharmaceuticals (BIS UKTI DH 2011). These figures, however, do not tell the full story. For example, the UK's sales share of the world's top 100 prescription medicines is 16% (higher than any other country after the USA), and 20% of them were discovered and developed in Britain (ABPI 2011b). Both sectors have two UK representatives in the top 10 global firms according to sales: GE Healthcare and Covidien for devices and GlaxoSmithKilne and Astrazeneca for pharmaceuticals (IMS 2010;Quotec Ltd. 2009). The UK is thus a large stakeholder in both of these healthcare sectors.

### 3.3.3 Contribution to the UK economy

Table 3.1, adapted from a document produced by the Pharmaceutical Industries Task Force (PICTF 2001) outlines some of the ways in which national and foreign owned health technology companies, both home and abroad, contribute to the UK's economic welfare.

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<sup>6</sup> This is based on the global market value estimates presented above. The difference between sales value and turnover is not clear in the sources indicated, or indeed in the wider literature; it can be seen from the figures reported that estimated turnover appears to be significantly larger than sales value (or 'market size'). It is presumed, therefore, that turnover is equal to the total income from sales, whereas sales value refers to the net revenue from those sales.

**Table 3.1 National economic contribution of device and drug companies**

		OWNERSHIP	
		UK	Overseas
LOCATION	UK	Benefits to patients Gross profits Employment income Better terms of trade R&D spill overs in UK	Benefits to patients Tax revenues in UK Employment income Better terms of trade R&D spill overs in UK
	Overseas	Net profits Employment income of UK nationals	

Source: Pharmaceutical Industry Task Force (PICTF 2001)

Both sectors contribute positively to the UK’s balance of payments. In 2008 the medical device sector ran a trade surplus of £300 million and that of pharmaceuticals was £6 billion (BIS 2009a;PICTF 2010). However, other sources suggest that the UK is a net importer of medical devices (BIS UKTI DH 2011;Wilkinson 2011).

A key metric of productivity is value added per employee, which measures the average contribution to the economy by each employee in a particular sector. The Department for Business Innovation and Skills (BIS 2010) report that the gross value added per employee for the medical technology sector was £49,000 in 2007 (similar to that of ‘All Manufacturing’), compared to pharmaceutical’s £121,000.

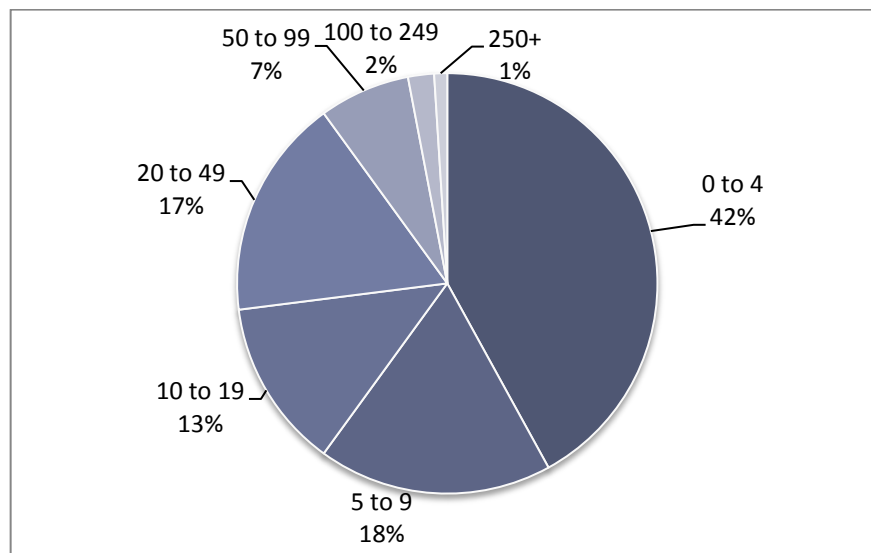
### 3.3.4 Size and structure

The differing size and composition of the device and pharmaceutical industries are largely due to the differences in innovation described above, and the resulting scale and duration of market capture. The regulatory frameworks of the two industries are undoubtedly another key influence, which is discussed further in section 3.4.1. Along with the lower regulatory hurdles for devices which lead to lower R&D spend, the fast-paced and competitive nature of the device industry and the user-led provenance of many innovations (which often incrementally develop previous models), mean that there is an important role for small

businesses in the sector. In contrast, the investment required to bring a new pharmaceutical product to market (about £1 billion (ABPI 2011b)) means that drugs are more feasibly developed and marketed by larger companies. This is reflected by the data presented below.

Within the UK there are 3,113 device companies, which employ 64,000 people in total (BIS UKTI DH 2011). An estimated 99% of these (3,082) are SMEs (companies that employ less than 250 people), with 42% (1,307) employing four people or less (BIS UKTI DH 2011).

Figure 3.2 illustrates this dominance of small businesses.



**Figure 3.2 The UK's distribution of medical device companies (total:3,113) by number of employees**  
Data from Government report 'Strength and Opportunity' of the Life Sciences industry (BIS UKTI DH 2011)

This offers a contrast to the UK's pharmaceutical sector which consists of around 365 companies and nearly 78,000 employees (BIS UKTI DH 2011). Whilst 81% of pharmaceutical companies are SMEs, the remaining 19% employ 89% of the UK pharmaceutical sector workforce (BIS UKTI DH 2011). The pharmaceutical sector has become increasingly concentrated over the years, with the top ten global companies sharing 62% of total UK turnover in the sector (BIS UKTI DH 2011). Pharmaceutical companies also tend to be more mature than medical technology companies, with 67% being over 10 years old versus devices' 52% (BIS UKTI DH 2011).

The Government's report on the life sciences sector also offers a breakdown of the medical technology industry by sector (BIS UKTI DH 2011). The largest sector in relation to turnover is single use technology, followed by wound care and orthopaedic devices. Professional services (consultancy) is the biggest sector in terms of employment and number of companies, which is followed by in vitro diagnostics and single use technology in terms of employment, and by assistive technology and single use technology for number of companies.

Table 3.2 provides a summary of the main comparisons drawn through section 3.3.

**Table 3.2 Headline comparative statistics for the UK's Device and Pharmaceutical Sectors**

	<b>Medical Devices</b>	<b>Pharmaceuticals</b>
<b>Products (estimated number available globally)</b>	500,000, belonging to 10,000 generic groups (Eucomed 2011)	218 'Drug targets' (Imming, Sinning, & Meyer 2006)
<b>Lifecycle of product</b>	Around 18 months (Eucomed 2011)	Mean lifetime: 57 years (Hoyle 2010)
<b>R&amp;D spend as % of sales, 2007/8</b>	5.5% (BIS 2009a)	15.3% (BIS 2009b)
<b>Spending as % of UK's total expenditure on health, 2006</b>	4.5% (Eucomed 2007)	12.3% (OECD 2010)
<b>Turnover, 2011</b>	£15 billion (BIS UKTI DH 2011)	£31.8 billion (BIS UKTI DH 2011)
<b>Value (sales) of global market, 2010; Forecasted growth per annum over next 5 years</b>	£150-170 billion; 10% (BIS UKTI DH 2010)	£589 billion; 3-6% (IMS 2011) <sup>1</sup>
<b>UK presence on the world market, 2009</b>	4% of global sales; 13% of European sales (Wilkinson 2011)	4% of global sales; 14% of European sales (Office for Life Sciences 2010) <sup>2</sup>
<b>Trade surplus, 2008</b>	£300 million (BIS UKTI DH 2009)	£6 billion (PICTF 2010)
<b>Value added per employee, 2007</b>	£49,000 (BIS 2010)	£121,000 (BIS 2010)
<b>Number of companies, 2011</b>	3,113 (BIS UKTI DH 2011)	365 (BIS UKTI DH 2011)
<b>Employment, 2011</b>	64,000 (BIS UKTI DH 2011)	77,795 (BIS UKTI DH 2011)
<b>Size distribution, 2010</b>	99% SMEs (BIS UKTI DH 2010)	81% SMEs (BIS UKTI DH 2011)

Figures refer to UK statistics unless otherwise stated

<sup>1</sup>Converted from U.S. dollars to pounds using the exchange rate: £0.673 to the \$, the average exchange rate of 2010

<sup>2</sup>This is noted to exclude over-the-counter drugs

The British medical devices industry is, in general, on a smaller scale to that of the pharmaceutical industry. Nevertheless, the sector is important for the economy and provides a large number of jobs, not to mention the crucial contribution it makes to patient care. The pharmaceutical sector is dominated by larger companies, the advantages of which include economies of scale, more established marketing distribution channels, steady funding, and a greater collection of expertise and experience (Scully, Van der Walde, & Choi 2002). Smaller companies can face some unique challenges, especially with regards to providing evidence for HTA. However, device companies face more than financial barriers in demonstrating clinical / cost-effectiveness. These barriers are outlined in the next section and, like the industry structure described in this section, are intrinsically linked to the nature and application of devices.

### **3.4 Evaluation Issues**

The way healthcare products are brought to market is undoubtedly affected by the system of regulation and adoption. In this section devices are again compared with pharmaceuticals: after describing regulation in the UK, the prevalence of device appraisal by NICE is outlined, followed by a consideration of why devices do not lend themselves easily to providing evidence for evaluation. This then sets the scene for section 3.5 which describes the response to these issues by the formation of a new evaluation pathway specific to devices.

#### **3.4.1 Regulation**

Regulation should ensure that products are safe and that they function for their intended use, which is of particular importance in the healthcare market where the consequence of a fault or drop in standards could be fatal. However, it has long been recognised that the models of



regulation for drugs and devices cannot and should not be interchangeable. Historically, a significant development in medical device legislation in the U.S. arose from a report submitted by the Cooper Committee in 1970. The committee recommended that a regulatory approach specific to devices be created, which would be sympathetic to their differences to pharmaceuticals (Link 1972;Pilot & Waldmann 1998). The EU regulatory system for medical devices was established 25 years after that of the U.S., and was some 25 years behind the European regulation of pharmaceuticals (Altenstetter 2003).

Until the early 1990s each EU member state ran its own system of device regulation. This was seen to be an unnecessary barrier to trade, and so in 1993 regulation across Europe was harmonized by the implementation of the European Medical Device Directive (McAllister & Jeswiet 2003). This is now supplemented by two related directives: Active Implantable Medical Devices Directive and the In Vitro Diagnostic Device Directive. In the EU medical devices are categorised into four classes according to risk: class I, class IIa, class IIb and class III (see (European Commission 2010) for full classification rules). The directives are implemented by private sector ‘notified bodies’, which issue a mark of Conformité Européenne (CE) to devices that are approved. This is in contrast to pharmaceuticals which in the UK are approved directly by the Medicines and Healthcare products Regulatory Agency (MHRA), an executive agency of the Department of Health (MHRA 2011). Once on the market, the system of market vigilance for devices and drugs in the UK is similar, both being overseen by the MHRA. The scale and profitability of the industries, as described in the previous section, is reflected in the way the MHRA’s regulation activity is funded: principally by public monies for device regulation and by fees from the pharmaceutical industry for the regulation of medicines.

Whilst the regulation policies for devices and pharmaceuticals both aim to ensure that only safe and effective products are approved, the level of clinical evidence required is much more rigorous for pharmaceuticals (World Health Organisation 2010a). The licensing of pharmaceuticals generally requires clinical trial evidence, whereas the EU regulation of devices is founded upon quality management. This includes a specification of the design process, a risk assessment, and a clinical evaluation which need not necessarily be a clinical trial, depending on device type and risk classification (this could for example be lab test data, data for similar preceding devices, etc.) (Carlisle 2011). The differential evidence requirement reflects a device's (generally) more predictable outcome, though the topic is controversial. Particular sources of contention include the manufacturer being allowed to choose the notified body, as well as the private nature of the CE mark decision which is not made publicly available (Cohen & Billingsley 2011).

Many new products generated by the devices sector represent minor developments of previous models; to demand a randomised controlled trial (RCT) for each would be unfeasible and would discourage companies from making these improvements.<sup>7</sup> Obtaining approval for devices that are 'substantially equivalent' is therefore purposefully straightforward (Avorn 2010). However, many incremental changes may together lead to new functions or risks, which if untested may compromise effectiveness or safety (Garber 2010). The balance between fostering innovation and ensuring safety is therefore delicate, and different interested parties have competing perspectives. Predictably, device companies believe that UK regulation is cumbersome and restrictive, whilst doctors and patients often consider the rules to be too lax (Watts 2012). This trade-off is given the spotlight when faulty devices cause

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<sup>7</sup> Reed, Shea and Schulman, for example, demonstrate how altering the regulatory environment of devices to be in line with pharmaceutical regulation would significantly decrease the value derived by a company for developing a device, as a result of higher evidence standards and the costs required to meet them (Reed, Shea, & Schulman 2008).

adverse events, as exemplified by metal-on-metal hip replacements which have been found to have high failure rates (Smith et al. 2012), or the defective silicone breast implants which have inspired news articles to liken the regulation of an implantable medical device to the regulation of a yo-yo (Boseley 2012). This places under real scrutiny the differential evidence requirement for devices, especially those that are implanted into the body. Indeed, whereas drugs may simply be discontinued if harmful side-effects are identified, the irreversibility of some implantable devices can be problematic.

Conditions for innovation are considered more favourable in the EU than in the U.S., whose regulatory system is often accused of being too risk-averse, leading to unnecessarily slow adoption and thus impeding technological progress (Cohen & Billingsley 2011; Kramer, Xu, & Kesselheim 2012). The safeguarding of patients is certainly an issue of high interest and debate; difficulties are inevitable, especially in a sector whose regulation system is relatively young. As medical technology gets increasingly more sophisticated, the risks posed by certain products are higher than ever. Altenstetter and Permanad (2007) suggest that the differences between the device and pharmaceutical sectors in this respect are starting to blur, implying that the regulation systems may eventually adapt to reflect this.

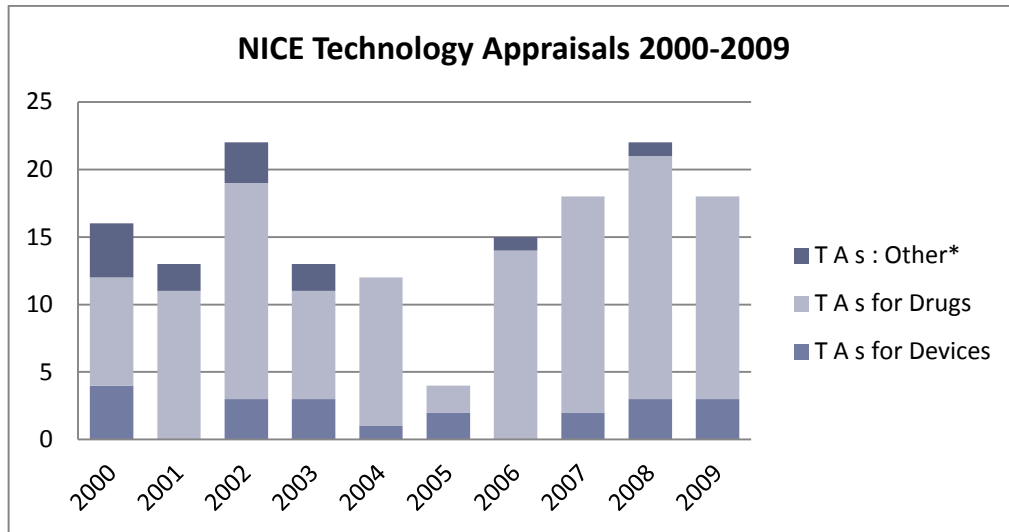
Before a medical device can be sold in the UK it must work and be safe. The system which aims to ensure this in the UK has been described. However, regulation considers the *risk-benefit* relationship in order to justify whether a device can be sold, not whether it should be bought (not least with public money). In the UK the NHS charge NICE with the task of considering the *cost-benefit* relationship, in order to determine value for money. The next sub-section explores the prevalence of device evaluation by NICE, and is followed by a presentation of some of the pertinent challenges that devices pose to the evaluation process.

### 3.4.2 NICE technology appraisals

The formal incorporation of economic analysis into healthcare decision-making is a relatively recent phenomenon. Having first been incorporated into Australian drug evaluation in 1993, economic analysis is now a part of decision-making across New Zealand, Canada and half of Europe (Drummond 2012). Across Europe and Canada, Hutton (2012) finds that the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) and NICE are the only national-level assessment systems to appraise devices and procedures, with all other systems focusing solely on funding decisions for innovative drugs.

NICE *'provides independent, authoritative and evidence-based guidance on the most effective ways to prevent, diagnose and treat disease and ill health, reducing inequalities and variation'* (NICE 2012a). NICE guidance falls into three main areas: Public Health, Clinical Practice, and Health Technologies, the last of which includes Technology Appraisals (TA), Interventional Procedures Guidance (IPG), and additionally Medical Technologies Guidance and Diagnostics Guidance which were introduced in 2010. In order to appreciate the evaluation scene from which the new medical technologies pathway has arisen, all TAs conducted by NICE since the first in 2000 until the close of 2009 (from which point the new evaluation pathway considers medical devices specifically) have been reviewed and classified (data collected from NICE published TAs (NICE 2012e)).

Over the ten years considered, NICE produced 178 TAs, 153 of which were new appraisals (the 25 remaining were reviews of previous TA decisions). Of the new appraisals, 21 (14%) were for medical devices. The total number of (new) TAs by year is shown in Figure 3.3, which also exhibits the breakdown of technology type appraised. The appraisal of medicines is dominant—78% of new TAs over the ten years.



**Figure 3.3 NICE Technology Appraisals by technology type**

\* Surgical procedures, Imaging/screening, Behavioural therapies, Training/education programmes & Process.

The decision outcomes of technology appraisals were largely favourable; 88% of non-devices were approved (either for routine or restricted use), compared with a 95% approval rate for devices. Of those devices approved, 40% (eight) were approved for routine use and 60% (twelve) for restricted use. For all other TAs, 34% of those approved were for routine use. The decision to reject the one medical device that was not approved was on grounds of clinical ineffectiveness. Overall, cost-effectiveness played a role in 61% of all rejection decisions. NICE now publishes a summary of all TAs and decision outcomes on their website, though these are not categorised by technology type (NICE 2011c).

Others have also considered the preponderance of pharmaceuticals in NICE appraisals. Linden and colleagues (2007) find a similar overall proportion of drug and device TAs for the years 2000 to 2006 (75% and 14% respectively). These authors also describe the tendency for NICE appraisals to address new rather than existing technologies, highlighting concerns that neglecting to appraise existing ineffective / inefficient technologies means forgoing significant NHS savings, and placing an upward pressure on spending (Linden, Vondeling, Packer, & Cook 2007).

The tendency for NICE to appraise drugs over other health technologies is clear, but is this irrational? It can be partly explained by the market factors already described. Drugs expenditure is nearly three times that of devices, implying that new and more efficient drugs could have a big impact on overall spending, making them particularly relevant for national evaluation. Additionally, the costs and benefits arising from an approved drug are generally immediate; some devices may have a more delayed or less direct impact on budgets, sometimes requiring training or service reorganization (Drummond, Griffin, & Tarricone 2009). Another factor is the continual redesign and replacement of devices, making their lifetime short and thus making the time and resource intensive appraisal process less relevant and less valuable (Linden, Vondeling, Packer, & Cook 2007). Furthermore, the lower evidence requirement for regulatory approval means that the data required to conduct a device appraisal may not be available. The characteristics of the industries further explain the better provision of evidence for pharmaceutical appraisals, but for medical devices, evidence generation is further complicated by specific issues beyond the financial constraints of the companies that produce them. These are described in the next subsection.

### 3.4.3 Hurdles to providing evidence for HTA

HTA activity has increased substantially over recent years, but particularly so for pharmaceuticals. It could be that pharmaceutical companies, keen to make claims of cost-effectiveness, have driven this trend. However, this is further compounded by their ability to produce trial data. The difficulties that arise in the generation of evidence for medical devices relate to their nature and application (described in section 3.2) and are outlined below.

The HTA of a product is an essential component of an informed reimbursement decision. By comparing the new technology to current practice, its impact on overall costs and health outcomes can be observed. Two essential criteria for this are (a) to identify the ‘gold

standard' in current clinical practice, and (b) to generate evidence upon which a comparison can be based. These both present difficulties for device manufacturers.

Standard clinical practice for pharmaceuticals tends to be better established than for many devices. Devices (like other manufactured goods) are often tailored to user preference, with many co-existing devices designed for the same purpose. Clinical practice can therefore vary from place to place—even doctor to doctor—making the question of a 'gold standard' comparator difficult. Moreover, individual device manufacturers may stand less to gain from the HTA process, as even a positive decision is unlikely to lead to full market capture.

Clinical trials play a fundamental role in the generation of evidence. According to the 'Clinical Trial Magnifier' there were 1,107 industry-sponsored medical device trials globally between October 2005 and June 2009, equivalent to only 7% of trials for drugs and biologics (Karlberg 2009). This can be partly explained by the lower evidence requirement (in the main) for devices compared to drugs, but also reflects the set-up of the industry described in section 3.3. European pharmaceutical manufacturers spend vast amounts on evaluating new products, more in fact than total European spending on evaluating all other health technologies, procedures and policies (Cookson & Hutton 2003).

Aside from the financial context and structural set-up of the industries, the very nature of devices makes performing an RCT—thought to be the most rigorous way to provide evidence of the cause-effect relationship between treatment and outcome—difficult, biased or even unfeasible. Three specific issues are especially problematic: confounding factors, recruitment / drop out, and blinding.

That devices are administered by a third party (generally the clinician or patient) can act as a confounding factor, being itself responsible for some variation in clinical outcome.

Effectiveness thus depends not on the device alone but also on the skills and experience of the user, or the context of its use (Cookson & Hutton 2003). For example, a clinician's skill is paramount in the outcome of a surgical intervention, compared with the formulaic and replicable process of prescribing medicines (Lilford, Braunholtz, Harris, & Gill 2004). This provokes a second, related issue: the skill of a clinician using a new technology is likely to improve over time. This 'learning curve' phenomenon may result in an unfair comparison between a new technology and a ready established technique (Drummond, Griffin, & Tarricone 2009; Taylor & Iglesias 2009).

One fundamental mechanism by which RCTs minimise bias is the random allocation of treatment. This randomisation should lead to equivalent treatment groups, maximising the chance that observed differences in outcome are the result of treatment effect rather than differing baseline characteristics of the groups. Any CE marked device (which must be obtained before a trial) is in the public domain, making preconceptions a real threat (Medilink UK Review 2009). Where these preconceptions exist for patients, there may be difficulty in recruiting the required sample size, or drop-out may be high. If clinicians act on their own pre-conceptions, then allocation bias may occur (Wittes 2001). A quotation from Cochrane (1971, p.68) draws an eloquent picture of the difficulty in this randomisation aspect of an RCT: *'On one occasion I was trying to persuade a senior consultant to participate in an RCT. He told me that the protocol was morally and ethically unacceptable as he knew what the result would be. On another occasion I was trying to persuade a headmaster to randomise caning and detention for boys who were caught smoking. He answered by claiming that the trial was unnecessary as he always knew which boy should be caned and which should not. I checked as far as I could later and it looked as though his method was quite simple. He caned them all.'* (Cochrane 1971).



Lack of blinding (or ‘masking’) is another important source of bias for RCTs, which involves the patient / clinician / third party observer being aware of treatment allocation, and adjusting behaviour (either consciously or subconsciously) as a result. Whereas the masking of drugs is usually easy, devices can look very different and involve dissimilar procedures. This has been noted to be especially problematic in surgical trials (Ergina et al. 2009;Lilford, Braunholtz, Harris, & Gill 2004). For example, while placebo-controlled drug trials are straightforward, sham surgery is ethically undesirable (Becker & Whyte 2006;Lilford, Braunholtz, Harris, & Gill 2004).

HTA for medical devices can also be problematic outside the issue of evidence generation specifically. The perspective of the decision-maker must in some cases be broad, where new devices pose wide health or economic implications or require local service reorganisation (Drummond, Griffin, & Tarricone 2009); the COPD case study to be presented in chapter 6 provides an example of this. Whilst in an economic evaluation it is possible to account for cost impact seen in other parts of the health service, NHS budgets are in reality not so transferable, thus making the outcome of an HTA theoretically sound but less directly applicable (Buxton 2006). A long time perspective is often required, particularly for pieces of equipment which may require large upfront costs (Ferrusi, Ames, Lim, & Goeree 2009). Additionally, some device benefits are not fully captured by the standard HTA framework, such as the utility associated with the process of healthcare—‘process utilities’ (Donaldson & Shackley 1997). For example, a non-invasive treatment option which yields the same health outcome as an invasive alternative will produce a similar QALY gain. The multiple potential applications of some devices further complicates the valuation of new technologies for HTA (Drummond, Griffin, & Tarricone 2009). Many of these issues are illustrated through the course of this thesis.

The output of a NICE appraisal is an ICER ( $\Delta \text{ Cost} \div \Delta \text{ QALY}$ ), which establishes the cost-effectiveness of a new technology over current practice. However, for medical devices the real ICER is rarely static due to the variability of both numerator (costs) and denominator (QALYs), making the timing of an HTA worryingly important. The operator's influence and learning curve phenomenon demonstrate the potential inconsistency of outcome, which may imply that an HTA conducted early in a product's lifecycle may underestimate its QALY impact and therefore cost-effectiveness (Holmes, Jr. et al. 2008). As regards the numerator, unlike drugs whose price remains reasonably constant until the patent expires, the price of a new device tends to fall quickly given its short lifetime. However, the price of the technology that it replaces is likely to fall even faster (Drummond, Griffin, & Tarricone 2009; Holmes, Jr. et al. 2008). This affects perceived cost-effectiveness and may even imply that a decision to fund a new device based on its cost-effectiveness should be reversed soon after it is made.

*'Adopting a pharmaceutical paradigm, based on expectation of multiple RCTs being available at the time of launch, may lead to restrictions on access to many new medical technologies. A device specific paradigm must be recognised.'* (Eucomed 2008, p. 2). This quotation reiterates the need for drugs and devices to be regarded separately. In section 3.4 I have addressed why UK national appraisal activity has focused on pharmaceuticals, and why the TA system can be problematic, unnecessary or unfeasible for device manufacturers. The topic has been explored from its very roots: the characteristics inherent to a medical device; its mechanism of action; the resulting industry size, structure, and operations; and subsequent difficulties in providing evidence for HTA. The new system of evaluation that intends to address these issues is described in the next section, which focuses exclusively on devices and describes the progress towards this change, and what it might mean for industry.

### **3.5 Response: How the evaluation landscape has adapted**

Innovation is imperative for the continual development and improvement of a healthcare system. New cost-effective medical technologies have a substantial impact on patient quality of life, the health budget, and the wider economy; slow uptake means these important benefits are delayed. Whilst having a globally recognised industry scene, as illustrated in section 3.3, the delayed adoption of new medical technology within the NHS was highlighted in the Wanless Report in 2002 (Wanless 2002). The underuse of new devices was also stressed by the House of Commons Health Committee (2005), who blamed the fragmented nature of the NHS and its preference for short-term savings over long-term gains. Together with the difficulties for industry described above, this slow and often misdirected procurement landscape was the backdrop for the work which began in 2003 to review the medical technology scene in the UK, and identify ways to maximise its potential.

#### **3.5.1 The development of strategic dialogue**

With so many interested parties in the devices sector, any progress needed to be collaborative. An attempt at such a collaborative venture was first made possible by the Health Industries Task Force (HITF) in October 2003, a year-long initiative and the first Government / healthcare industry collaboration of its kind in this sector. It aimed to facilitate the common understanding of problematic issues, to suggest ways to address them, and to encourage wider adoption of new technologies (HITF Market Access- Working Group 1 2003). This strategic dialogue is what, six years later, would ultimately pave the way for a new system of evaluation for devices. Figure 3.4 sketches the development of implementation groups and action points following the HITF report.

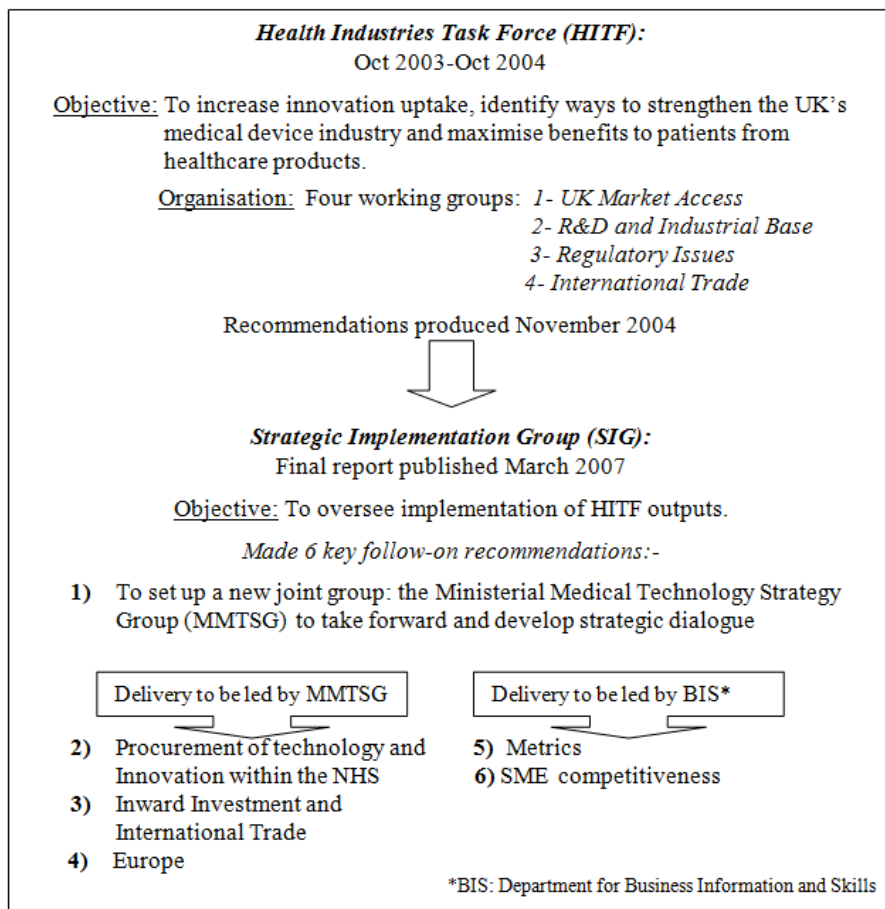


Figure 3.4 The development of strategic dialogue between government and industry

The organisation of the HITF into four working groups demonstrates the array of issues important to the health technology industry and government, for which it was believed progress needed to be made. During the first meeting of UK Market Access working group in December 2003, some of the pertinent points raised (as detailed in the meeting minutes) were: timeliness of procurement, the understanding of ‘value’, the increasing demand for evidence (and the troubles this posed for SMEs), and the need to streamline and speed-up the process of adoption (HITF Market Access- Working Group 1 2003). These concerns all reflect the matters highlighted in this chapter, and clearly demonstrate the developing need for a new system of evaluation.

### 3.5.2 Early HITF output and the Next Stage Review

The initial impact of the HITF report included a shift in emphasis to adoption (the Device Evaluation Service turned into the Centre for Evidence-Based Purchasing), and changes in procurement approaches, e.g. Payment by Results (Wilkinson 2005). The National Innovation Centre was created to stimulate demand for technology and to support industry (especially SMEs), R&D capacity was built up in the NHS, and funding was provided to train professionals in using new products (Secretary of State for Health 2005). To advance the progress made by the HITF, the Strategic Implementation Group (SIG) made a series of recommendations relating to increased uptake of innovation, support for SMEs, consistent decision-making, and continued collaborative engagement (SIG 2007).

Significant changes were made in response to Lord Darzi's report, *High Quality Care for All: NHS Next Stage Review* (NSR) (Department of Health 2008a), in which he reiterated the slow-uptake of technology. Darzi advocated the creation of a new, single evaluation pathway for medical technologies which would "...simplify the pathway by which they pass from development into wider use" (Department of Health 2008a, p. 13). The Ministerial Medical Technology Strategy Group (MMTSG), successor of the HITF and SIG, identified four work streams to deliver on NSR output: the new evaluation pathway, 'intelligent demand' from the NHS, more receptive procurement, and metrics to measure uptake (MMTSG 2009). There is a clear connection between the industry's concerns relating to those problems outlined in sections 3.3 and 3.4 of this chapter, and these recent efforts to modernise the system.

### 3.5.3 Single Evaluation Pathway for Devices and Diagnostics

NICE was asked to lead the evaluation pathway programme for medical technologies in winter 2008/9, which was later rebranded as the Medical Technologies Evaluation

Programme (MTEP). Subsequent development has been fairly rapid; recruitment for the Medical Technologies Advisory Committee (MTAC) took place over summer 2009, the programme was officially announced late autumn, MTAC's inaugural meeting took place in November, the Methods and Process guides were issued for consultation in June 2010, and the first Medical Technology Guidance was published for consultation in July 2010.

The principal aims of MTEP are to (a) simplify access to evaluation and subsequent adoption, (b) to speed up this process, and (c) to increase capacity. It provides a single entry point for manufacturers to submit products for evaluation, which are then routed (if eligible) to the appropriate evaluation programme within NICE: TA, clinical guidelines, interventional procedures, diagnostic assessment programme (DAP, also a new programme), or, if fulfilling certain criteria, to MTAC's own evaluation and subsequent 'medical technologies guidance'. The suggested timeframe is around 10 weeks from notification to routing, and a further 38 weeks for in-house evaluation by MTAC for those selected (NICE 2011b). Building on its founding principles, the new pathway is seen to be an opportunity for collaboration and increased understanding between industry and the NHS (NICE 2009d). The committee comprises academics, practitioners, industry, regulatory experts, NHS trust members and lay members (NICE 2009d), who have a particular focus on fostering future research for new medical technologies where this is required (Campbell 2011).

To be eligible for MTEP a device must have attained a CE mark (or equivalent), be within the remit of a NICE evaluation programme, be new or a significant modification of a previous technology, and have clear benefits for patients or the NHS. The scope for MTAC's own guidance was eventually defined in June 2010: medical technologies guidance will deal exclusively with products "*...for which the case for adoption in the NHS or social care is based primarily on improvements in the efficient use of resources*" (NICE 2010d).

The concerns of industry have played an important role in MTEP's development, which is evident in the Process and Methods guides (NICE 2011b). For example in section 2.3 of the Methods guide, the characteristic innovation process and limited clinical data for devices are acknowledged, as well as issues relating to the context of trial setting. As a result, the evidence requirement compared with the TA programme is reduced, and includes consideration of observational trials and expert advice (Medilink UK Review 2009;NICE 2011b). Additionally, the prevalence of co-existing versions of certain devices is acknowledged: *'The specific recommendations on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages'* (Campbell 2011;NICE 2012c).

The creation of MTEP and the form it has taken has attempted to be sensitive to industry-related issues. Another major stakeholder in devices, however, is the NHS, and it is perhaps for this reason that medical technologies guidance deals specifically with cost saving/cost neutral devices. This remit has not always been so clear. When the pathway was first announced, guidance was to be issued on 'clinically effective' technologies (NICE 2009c); the more discriminatory criterion was not even discussed at the plenary session for the new pathway at NICE's 11<sup>th</sup> annual conference in December 2009. The selection criterion for medical technologies guidance is now explicit: only a technology which will *'provide equivalent or enhanced clinical outcomes for equivalent or reduced cost'* will be considered (NICE 2012b). With the economic downturn and huge public debt as a backdrop, the NHS must now invest in treatments that are not only cost-effective, but also cost-saving. Cost-consequence analysis rather than the cost/QALY approach will therefore be used to issue guidance on technologies that have the potential to dominate current practice. Those that offer patient benefits but at an additional cost (not offset by the release of other NHS

resources) will be directed to another NICE programme. This is in contrast to the diagnostic technologies routed to DAP, for which a comprehensive cost-benefit analysis will be undertaken.

### *3.5.3 (i) Potential Impact of MTAC*

As the programme is still relatively young, it is difficult to predict its effect on manufacturers and the speed of NHS adoption. The first pertinent question to consider is: What is the benefit of submitting a product to MTAC—does it increase uptake? Whilst NICE does issue reports relating to guidance compliance within the NHS (NICE 2011a), at the time of writing no implementation uptake reports had been produced for guidance produced by MTAC. NICE medical technologies guidance only applies to England, and recommended technologies are not subject to mandatory funding (NICE 2010f). So, whilst the ramifications of a positive (or negative) MTAC recommendation are not yet fully known, this section provisionally assesses the degree to which the pathway might achieve what it set out to: (a) simplify access to evaluation, (b) speed up the process, and (c) increase evaluative capacity for devices within NICE.

To notify a medical technology to NICE for evaluation does appear straightforward. Sponsors complete a short pre-specified form covering general information about the technology along with the claimed patient benefit and cost implications (NICE 2012d). Although medical technologies guidance is unequivocal in only considering devices that are cost-saving or cost-neutral and at least as beneficial to patients, ascertaining clinical equivalence is not a simple task, and industry may have difficulty in providing data on the cost-saving potential of their products (Hogan 2009).



The premise of the pathway is to provide a ‘fast track’ to evaluation for those products which dominate current practice. In comparison with NICE’s single technology appraisal guidance (NICE 2011d), the production of medical technologies guidance seems no quicker (both around 38 weeks), so it is perhaps the (presumably shorter) 10 week ‘routing/selection’ process duration, and the increased capacity where the real benefit will lie. Nevertheless, a total time of 48 weeks is almost two-thirds of the average product’s lifecycle<sup>8</sup> and, given the need for a CE mark prior to notification, the clock is already ticking at this point.

The review of NICE TAs (in section 3.4.2) demonstrated the underrepresentation of medical devices in the national evaluation process. The intended capacity of MTAC is not clear. One source indicates that NICE is expected to handle 50 device and diagnostic submissions per year (Yeo 2009). The target number of assessments to be published in MTAC’s first year was 15, with capacity expected to rise in future years (NICE 2010g). Only four were published in the first year of MTAC<sup>9</sup>, and six in the second. Within the context of such a large market, this clearly is still just the tip of the iceberg. Additionally, it is probable that the new appraisal system will continue to attract only a narrow subset of devices: mainly implantable and other class III devices (though it may be argued that this is appropriate, given their greater attributable risk and larger cost and outcome implications).

As very few medical devices were appraised by the previous TA system, the industry will be keen to understand the benefit of subscribing to the MTEP process; the programme is expected to publish evidence on the impact of guidance on uptake in due course.

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<sup>8</sup> Arguably, the lifetime of the sorts of product that would be submitted to MTAC may be longer, given the implicit requirement that the technologies submitted to the committee are novel and represent more than a minor modification to current practice.

<sup>9</sup> Here, I consider the first year to start from the meeting date in which MTAC discussed specific technologies for the first time (NICE 2010e): June 2010 to June 2011.

### 3.6 Summary

This chapter has attempted to set medical device innovation within the context of the wider social and economic landscape of the sector. Whilst the new evaluation pathway represents an important step in the direction of fair assessment for devices, some provisos have been explored. The current economic landscape explains the committee's focus on cost-saving technologies. However, some may question whether this is the best long-term strategy. The commentary and criticism that fed into Lord Darzi's Next Stage Review (Department of Health 2008a) was slow uptake, underuse of new technologies, and preference for short-term savings over long-term gains. The cost-saving criterion of MTAC guidance therefore has the potential to undermine the review's key recommendations, particularly if capacity for device evaluation in the TA work stream is not increased simultaneously.

The adoption and diffusion of new health technology within the NHS is still regarded to be inexcusably slow (Department of Health 2011a). Looking forward, there will be many organisational changes within the decision-making structures of the NHS taking place over the next few years, the impact of which is difficult to predict. For example the more advisory role which was demanded of NICE in the NHS White paper issued in 2010, which detailed non-mandatory funding of technologies with positive TA decisions (Department of Health 2010b; Department of Health 2010c), has since been overturned. In fact, in order to reduce variation in care across the NHS, the importance of NICE guidance implementation is now being emphasised, and the Department of Health will implement a 'NICE compliance regime' to safeguard the funding direction attached to TAs (Department of Health 2011a) (there is no indication that MTAC recommendations will be made mandatory in the future). Value based pricing will be adopted for pharmaceuticals by 2014 (Department of Health 2010c), though

the exact form of this has yet to be determined. Additionally, the remit of NICE will be extended beyond health to include social care (Department of Health 2011a).

In this chapter I have described and linked the characteristics of the health technology industry and innovation with the national evaluation of devices, and by doing so, have implied that this is an important link to make. However, how important is economic evaluation for the success of medical technologies and their manufacturers? It has already been shown that very few devices are actually evaluated by NICE. Even for those technologies that are appraised, the implications of an approval are not well understood.

In studying the use of economic evaluation in NHS decision-making, Williams et al. (2008) find that, at a local level, committees consider clinical benefit and cost implications separately. This is consistent with the literature which notes that, whilst NICE is able to evaluate cost-effectiveness by adopting a removed, holistic stance, at the local level the inflexibility of budgets distorts this motive for efficiency (Buxton 2006). Those that have explored the implementation of NICE guidance specifically have generally found implementation to be patchy (Moore 2005; Sheldon et al. 2004), probably due to the local-decision-making context noted above (Spyridonidis & Calnan 2011).

Despite the reservations outlined, NICE is still recognised internationally as a pioneer in the incorporation of health economics into decision-making. As in any economic model, the only assumption that can be made is that decision-makers are rational, and it is on this basis that the headroom method incorporates the NICE decision-making framework into the consideration of potential value.

Table 3.3 summarises the main elements of this narrative, and how they relate to each other.

Table 3.3 Summary: Innovative medical devices and their evaluation

The Medical Device Landscape: what makes devices different?	Obstacles identified (relating to technology appraisal)	Response: Medical Technologies Evaluation Programme
1. Process of Innovation	<ul style="list-style-type: none"> <li>• Short product lifecycle: TAs quickly outdated</li> <li>• Many similar devices</li> <li>• Lower spend on R&amp;D</li> </ul>	<ul style="list-style-type: none"> <li>• Faster turnaround of guidance and greater capacity</li> <li>• Notification by manufacturers</li> </ul>
2. UK Market composition	<p><u>Supply</u></p> <ul style="list-style-type: none"> <li>• Principally SMEs, with limited financial capacity</li> </ul> <p><u>Demand</u></p> <ul style="list-style-type: none"> <li>• Budget impact lower and more delayed than pharmaceuticals</li> <li>• Slow adoption by NHS</li> </ul>	<ul style="list-style-type: none"> <li>• Improve accessibility to the evaluation process</li> <li>• Accelerate the uptake of innovative technologies within the NHS</li> </ul>
3. Providing evidence	<ul style="list-style-type: none"> <li>• Difficult to identify the ‘gold standard’ treatment comparator</li> <li>• Lower regulatory hurdle: rigorous evidence not required for market approval</li> <li>• Third party administration: confounding factors and the ‘learning curve’ phenomenon</li> <li>• Recruitment and drop out</li> <li>• ‘Blinding’ often impossible</li> </ul>	<ul style="list-style-type: none"> <li>• Willingness to consider evidence from non-RCT sources (i.e. not based on levels of evidence required when evaluating drugs)</li> <li>• Encourage collaborative research (help manufacturers to make links with academic groups to generate the required data)</li> </ul>

The new MTEP seeks to clear the pathway to the NHS for new and cost-efficient medical devices, an important objective not only for industry and patients, but also to help the NHS make the £20 billion of efficiency savings it needs to by 2014. As MTAC is still in its first few years of operation, it is impossible to tell exactly how the new programme will affect manufacturers and the procurement landscape; processes and expectations are likely to adapt with experience, and according to the wider social context. The increased speed, capacity and accessibility of device evaluation and increased uptake of new technologies within the NHS are commendable goals, and success of the programme must be judged on this merit.

With 60% of medical device manufactures being micro firms (fewer than 10 people), the majority of companies can neither afford costly investment in health economic expertise, nor can they afford to lose money on the development of products that will not find a place on the market. The headroom method aims to provide a simple approach to ensuring that funds are directed to those products for which the chance of reimbursement is most likely.

It has been suggested that the early application of economic evaluation is even more important for devices given their short life cycles, making it crucial for assessments of likely cost-effectiveness to be early and rapid (Vallejo-Torres et al. 2008). Additionally, the nature of innovation for devices, as described in this chapter, demonstrates their particular applicability to the headroom method, which requires an estimation of potential impact on patient outcome and NHS resource implications. This is likely to be better predicted for a new device, having been developed from an engineering process rather than a discovery and whose interaction with the patient is physical rather than pharmacological. Furthermore, the literature review demonstrated a focus of early evaluation methods on pharmaceuticals, meaning that there is a larger contribution to be made for exploring this in the context of the device sector, which is the faster growing of the two industries.

The objective of this chapter was to set the scene for device innovation within the wider market context. It also described how national evaluation is adapting to meet the needs of the device industry, to ensure that the NHS is making the most of the industry's output. Moving forwards, the emphasis is on the inverse relationship. The next chapter, which describes the headroom method in detail, explains how the method offers a way by which industry may adapt their behaviour to suit the demands of the NHS, in turn ensuring sensible and informed development decisions.

## **CHAPTER 4 THE HEADROOM METHOD**

### **4.1 Introduction**

The previous two chapters have set this project within its wider context: first academically, and then in relation to the medical device marketplace. The literature demonstrates the notable development of health economics as a topic over the past 50 years and the increasing maturity of its application. The embedding of these principles into the commercial, supply-side of the market is less well advanced, particularly for medical devices. The previous chapter provided some explanation for this, describing an industry landscape which is dominated by small enterprises that may lack the resources, time and expertise to spend on long and costly decision-making processes. Combined with the short period over which development costs can be recovered, the potential benefit of a simple health economic tool which could distinguish between good investments and bad becomes clear.

The headroom method aims to embed the principles of health economics into an innovator's development decision. Therefore, the first section (4.2) of this chapter outlines the methodological basis of health economic reimbursement decisions. Section 4.3 describes the method, and also explains how it can be extended to consider plausible levels of development costs. Section 4.4 describes the specific framework of the method's application in this thesis, before a summary of the chapter is presented.

### **4.2 NICE's decision-making framework**

Although most medical devices will not be appraised by NICE, the institute's concept of value should, in theory, extend to any rational decision-maker. At the very least, their concept

of 'value' provides solid grounds to justify the worth of a new product (for example for marketing purposes). NICE's decision-making framework therefore forms the basis of the headroom approach, which is explained in section 4.3. The following describes the theoretical underpinning of economic evaluation, and outlines the main schools of thought in this area.

#### 4.2.1 Welfarism versus extra-welfarism

Economic evaluation offers a framework to manage the trade-off between costs and outcomes. How this trade-off is optimally applied is a matter of judgement, and can vary according to ideological stance. Two major schools of thought prevail: welfarist and extra-welfarist. Welfarists contend that utility should be measured in its broadest sense (i.e. not restricted to health-related utility / outcome), and that this is best captured by individual WTP (Hutton 2012) (this would allow for a direct CBA). This is also called a *Paretian approach*, and is ruled exclusively by questions of economic efficiency (Sugden & Williams 1978). Whilst this approach is intuitive, individual WTP alone offers no practical means of making allocation decisions within a centrally funded decision-making scenario, where one group of patients may be treated at the expense of another (Coast, Smith, & Lorgelly 2008). The Paretian approach therefore employs the compensation principle, first described by Kaldor and Hicks (Hicks 1939; Kaldor 1939), which asserts that a global improvement is achieved where those individuals benefiting could compensate those who lose out, and still be better off (a *potential* pareto improvement). Of course, this transaction would not actually take place in the healthcare scenario, but would still be consistent with welfare maximisation by achieving a net social benefit.

Arguments against the Paretian approach are similar to those against the free-market provision of healthcare: as well as the impracticality of basing healthcare resource allocation

decisions around individuals' valuations, there are many reasons why these valuations may not optimally reflect social benefit (for example the merit goods argument, externalities, the influence of ability to pay, etc). Accordingly, the extra-welfarist argues for a *decision-making approach*, whose objective is to maximise health (and/or some other measure of well-being that is not strictly utility), and where the relevant outcomes may be compared across people and across programmes (Brouwer, Culyer, van Exel, & Rutten 2008;Culyer 1989). The decision-making approach is therefore guided by optimisation theory, the criticisms of which revolve mainly around the credibility of a decision-makers' objectives, which may be self-serving (Sugden 2008). Welfarists face a similar optimisation problem, the difference being that the decision-making approach assumes that someone (other than the economist) has the ethical authority to stipulate the objective of a system, for example to base provision on need (Culyer 2008). Whilst accepting this approach to be a form of management consultancy, Williams (1972) insists it to be as scientific an endeavour as any analytic aid, and that it should be carried out systematically and transparently, with the objective of helping the client to conceptualise its problem in order to assist choices (rather than to make them) (Williams 1972).

#### 4.2.2 The decision-making approach

NICE's approach to economic evaluation is consistent with the decision-making approach: a pragmatic method to consider the efficiency of healthcare spending in relation to the health-related outcomes it generates. For conventional CBAs the trade-off between costs and benefits (both measured in monetary units) is straightforward, as is the comparison of net benefit between alternative uses of that money. This is more complicated in a setting where 'health', a much less tangible concept than money, is the outcome of interest. Given the wide distribution of health afflictions and the diverse objectives of healthcare interventions,



allocation decisions must be based on a universal measure of health: enter the QALY. For NICE, ‘the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and HRQL effects’ (NICE 2008b, p. 33), and is used to ensure consistency.

The assertion that the QALY (in its current form) provides the best measure of health outcome is contested by many. For example, its failure to reflect equity issues has been noted as an important omission of the current evaluative framework (Culyer & Bombard 2011; Nord, Enge, & Gundersen 2010; Williams & Cookson 2006), along with issues around the relativity of time (for example whether extra value should be placed on the final moments of life) (Chochinov 2011) and its narrow interpretation of health (Coast, Smith, & Lorgelly 2008). These are all important concerns, some of which have been acknowledged in NICE evaluation practices, for example by extending the threshold cost/QALY range for end of life treatments (NICE 2009a). However, arguably the bigger controversy, which may be more difficult to resolve, is the appropriate way to determine value for money in paying for QALY improvements.

#### 4.2.3 The cost-effectiveness threshold

Constrained optimisation theory allows economists to maximise output in relation to a fixed input (Pemberton & Rau 2001). For NICE, the *decision-maker*, the objective function is to maximise health (measured in QALYs) subject to a fixed health budget (set externally by Government: the *client*). Mathematically, the optimisation problem for just two healthcare interventions (1 and 2, used for  $x_1$  and  $x_2$  number of patients), spending on which is set to exhaust income ( $m$ ), would be as follows, where  $p_1$  and  $p_2$  are their prices and  $U$  is the (health-related) utility resulting from their implementation:

$$\text{Maximise } U(x_1, x_2) \text{ subject to budget constraint } p_1x_1 + p_2x_2 = m \quad (\text{Eq. 4.1})$$

A Lagrangian function can be employed to solve this problem:

$$L(x_1, x_2, \lambda) = U(x_1, x_2) - \lambda(p_1x_1 + p_2x_2 - m) \quad (\text{Eq. 4.2})$$

Where  $\lambda$  (lambda) is the Lagrange multiplier, and represents the marginal value of the constrained resource (money). In order to solve for the point of maximum utility, the first order conditions (differentiating with respect to  $x$ ) would be equated zero, and thus solved for  $x_1$ ,  $x_2$  and  $\lambda$ . Equations 4.1 and 4.2 demonstrate that the optimum choice for  $x_1$  and  $x_2$  is a function of  $p_1$ ,  $p_2$  and  $m$ : the prices of both healthcare interventions, and the overall health budget. The Lagrange multiplier, lambda, represents the opportunity cost of spending at the margin (Gafni & Birch 2006; Weinstein & Zeckhauser 1973), also referred to as the ‘shadow price’ of the NHS budget constraint (Claxton et al. 2006; Sugden & Williams 1978; Williams 2004). Lambda therefore provides the theoretical foundation of the threshold ICER. Equivalently, this threshold ICER can be conceptualised as follows: if a list was compiled of all technologies available to the NHS in order of efficiency (with that generating the most health per pound at the top), the threshold ICER would be equal to the cost per QALY of the last technology on that list before the health budget is used up (Culyer et al. 2007). The threshold ICER would therefore be set so that, at the margin, any adopted technology would have a more favourable cost-effectiveness ratio than that of any technology that is not adopted, or that is displaced as a result (Buxton 2006).

NICE employs a threshold ICER *range* by which to judge the cost-effectiveness of a treatment:

*‘Below a most plausible ICER of £20,000 per QALY gained, the decision to recommend the use of a technology is normally based on the cost-effectiveness estimate and the acceptability of a technology as an effective use of NHS resources. [...] Above a most*

*plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources'*

*(NICE 2008b, pp. 58-59)*

The explicit setting of this threshold range implies that NICE believes it to represent the approximate opportunity cost of NHS spending on one QALY.<sup>10</sup> The main controversy becomes apparent when considering the parameter inputs required to determine the optimal ICER threshold ( $\lambda$ ), as demonstrated in Eqs. 4.1 and 4.2. To consider the true opportunity cost of resources for the whole NHS would require an understanding of the cost and health implications of all current and potential interventions (Birch & Gafni 2006). Additionally, such a threshold should theoretically be dynamic, as the opportunity cost of investment is never constant given the ever-changing budget and basket of interventions (a basket which would change every time a new decision is made).<sup>11</sup> Whilst this partly explains the adoption of a threshold range rather than a definitive threshold ICER, no particular justification has been given for the value of this range, which is said to have been based on the '*collective experience and knowledge of the Committee*' who felt that it was a '*reasonable, defensible threshold*' (NICE 2009e, p. 12).

Although NICE does not set the healthcare budget, affordability cannot be completely dissociated from the matter. To consider the 'opportunity cost' of healthcare spending at the margin is meaningless if that 'opportunity' is not in fact foregone. There has been no real attempt by NICE to *disinvest* in cost-ineffective practices (Culyer et al. 2007;McCabe, Claxton, & Culyer 2008;Towse & Pritchard 2002), which has caused an upward pressure on

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<sup>10</sup> The range also offers more discretion for the committee to bring other considerations into the analysis where appropriate. For example, for ICERs between £20,000 and £30,000 the committee consider in detail the certainty around the ICER, the adequacy of HRQoL measurement, and the innovative nature of the technology (NICE 2008b).

<sup>11</sup> One strong criticism is that the threshold should surely at least have risen with inflation (Ubel, Hirth, Chernew, & Fendrick 2003), which rose 40% between 1999 and 2007, with the NHS budget having risen 90% in the same time frame (Raftery 2009).

spending, seen as a major shortfall of the current appraisal system (Birch & Gafni 2006). Bryan and colleagues (2007) conducted a qualitative study of NICE decisions by interviewing members of the appraisal committee. Whilst finding economic analysis to be of central importance to the decision-making process, many committee members claimed to feel uncomfortable with the threshold, expressing concerns regarding both its theoretical foundation and its affordability implications for the NHS (Bryan, Williams, & McIver 2007). Some argue that the threshold is too low (Towse 2009; Ubel, Hirth, Chernew, & Fendrick 2003), blaming it for damaging the biotechnology industry and innovation (Moran 2009). However, the general consensus suggests it to be too high (Raftery 2009; Williams 2004), implying that NICE guidance may lead to the displacement of more cost-effective technologies. Some authors have tried to estimate the actual (implemented) threshold empirically, by trying (albeit unsuccessfully) to observe PCT-level investment and disinvestment decisions (Appleby et al. 2009), or using a discrete choice analysis of NICE's appraisal results (finding the threshold to be somewhat higher than the stated range) (Devlin & Parkin 2004). Others have shown the relationship between a product's cost-effectiveness ratio and its likelihood of rejection (Rawlins & Culyer 2004).

Whilst imperfect, NICE's decision-making approach is pragmatic, transparent, and evidence-based and—theoretically at least—represents the framework of any rational decision-maker within any healthcare system (though the appropriate threshold will differ according to budget size and current healthcare activity). Before showing how this framework is translated by the headroom method into the conceptualisation of development decisions, it seems appropriate to outline the difference between CE-, CU- and CB-analyses. I believe their often interchangeable use within the literature to be as illuminating as it is

confusing; by outlining their differences and similarities, it is hoped that some clarity will be imparted.

#### 4.2.4 CEA, CUA and CBA: What's the difference?

In health economics textbooks, the line between these three approaches to economic evaluation is clear, and relates to the outcome of interest: CEAs consider outcomes in natural units (e.g. number of hospital days avoided or number of cured cases), a CUA considers utility, and CBAs value benefits in monetary terms so that these may be compared directly with costs (Drummond, O'Brien, Stoddart, & Torrance 1997). This sounds intuitive, but with NICE being referenced (according to the source) as performing all three, it seems useful to outline why. According to NICE:

*'For the reference case, cost-effectiveness (specifically cost–utility) analysis is the preferred form of economic evaluation. This seeks to establish whether differences in costs between options can be justified in terms of changes in health effects. Health effects should be expressed in terms of QALYs.'*

(NICE 2008b, p. 33)

In these terms, CUA is seen as a sub-set of CEA, where health units are measured in QALYs. The employment by NICE of this terminology may reflect its desire to appear pragmatic, not wishing to be perceived as attempting to grasp overall utility.

Can NICE's approach be construed as a CBA in any way? It is understandably unpopular for NICE to be considered as placing a monetary value on human life. By describing the premise of the cost-effectiveness threshold, it was shown that the decision-maker—whilst making implicit value judgements about the *relative* social value between healthcare interventions—makes no judgement about the overall social (monetary) value of health in relation to other goods and services in the economy. Rather, by facing an exogenously determined healthcare budget, the decision-maker's task is simply to maximise the value

derived from it. To argue that the appropriate ICER threshold for NICE should be based on actual social value, as reflected by individuals' WTP (the welfarist approach), is to contend that NICE should have the power to set the healthcare budget. These arguments have led Culyer and colleagues (2007) to appropriately label NICE a 'threshold searcher' rather than threshold setter.

Despite the decision-maker in this scenario being detached from making an explicit health valuation, the government, in setting the healthcare budget, reveals its valuation of health implicitly (Sugden & Williams 1978). The threshold ICER thus represents a postulated value of the QALY (albeit by the government presumably on behalf of the citizenship, rather than the decision-maker), and therefore '*can be regarded as a form of cost-benefit analysis*' (Sugden & Williams 1978, p. 193). Hence, although it is a two-step process, the same outcome is achieved by conceptually using the threshold ICER to value the QALY. It is for this reason that the ICER is often labelled (both within this thesis and the wider literature) as the 'willingness-to-pay', and why the headroom method uses this directly to inform the demand function for a new product, by attaching this monetary value to potential QALY gains. This CBA approach is supported by NICE's own words: '*...expected net monetary or health benefits can be presented using values placed on a QALY gained of £20,000 and £30,000.*' (NICE 2008b, p. 45), as well as the imminent move to VBP for pharmaceuticals.

By framing the decision-maker's objective as the assessment and comparison of costs and health benefits, both valued in monetary terms, a reformulation of the cost-effectiveness problem has been proposed, so as to generate a 'net-benefit' or 'net-monetary-benefit' value (Hoch, Briggs, & Willan 2002). The net-benefit to the decision-maker is simply calculated by

subtracting the extra cost of an intervention from the extra health that it generates (valued in pounds). This is entirely equivalent to standard considerations of a product's ICER, but has been proposed to overcome some statistical difficulties in handling uncertainty (Briggs, Sculpher, & Claxton 2006). This type of re-organisation of the ICER equation, to suit the needs of the user, will be shown to closely relate to the formulation of 'headroom'.

#### **4.2.5 A summary of NICE's 'reference case'**

To ensure consistency of their technology appraisals, NICE provides a 'reference case' in its methods guide, describing the most appropriate parameter inputs. The preferred measure of HRQoL (the quality adjustment for a QALY) is one described by the patient, but considered by a representative sample of the public using a choice-based method of valuation (e.g. the time trade-off method) (NICE 2008b). This contrasts with the welfarist ideal which would consider the individual to be the best judge of their own welfare. The EQ-5D (EuroQol 2012c), a standard instrument which has been validated by many patient populations, is the preferred method of quantifying HRQoL. Costs are considered relevant if they relate to NHS and personal social services (NICE 2008b). Both costs and health effects are discounted at a rate of 3.5%.

### **4.3 The headroom method**

In the same way as demand-side economic evaluations, the objective of the headroom method is to maximise the efficiency of spending: to ensure that investments are only directed towards products that could generate returns for the company (or, where there are competing product ideas, that those with the highest likely value are pursued). This section describes the headroom method, and section 4.4 provides details of its application in this thesis.

In short, the headroom method offers a simple way for manufacturers to investigate the commercial viability of a new medical device, by applying the principles of health economic evaluation early on—ideally when the product is first conceived. Clinical data verifying effectiveness is absent at this stage, but the innovator’s ideas around what the device *could* mean for patients (impact on health) and the NHS (cost impact for services) can be used to estimate its potential reimbursement prospects. Thus, the method uses early predictions of potential impact (which should be optimistic but plausible) to estimate what the NHS should be willing to pay for the device if it works as well as hoped. This places a ceiling on the reimbursement opportunity.

The method re-arranges the standard ICER formula:

$$\text{ICER} = \frac{\text{Cost}(2) - \text{Cost}(1)}{\text{QALY}(2) - \text{QALY}(1)} \leq \text{£}20,000 \quad (\text{Eq. 4.3})$$

For ease of illustration I take here the lower bound of NICE’s threshold range, which is consistent with the interpretation that £20,000 represents the actual ‘threshold’, above which other factors must persuade the buyers (McCabe, Claxton, & Culyer 2008). In the forthcoming headroom case studies, the £20,000 threshold is generally used for the headline headroom estimate, but calculations according to a WTP of £30,000 are also presented.

Equation 4.3 can be re-written as:

$$\text{Maximum WTP} = \text{£}20,000 = \frac{\Delta \text{Cost}}{\Delta \text{QALY}} \quad (\text{Eq. 4.4})$$

Where  $\Delta$  denotes impact (i.e. compared with current practice), and the ‘maximum WTP’ describes what the health service should be willing to pay *up to*. This can be re-arranged to give us:



$$\text{Maximum } \Delta\text{Cost} = \text{£}20,000 \times \Delta\text{QALY} \quad (\text{Eq. 4.5})$$

The right hand side of the equation represents the impact on health (improvement in health utility multiplied by the duration of this improvement in years) multiplied by the WTP threshold, to give us the value of the health improvement. The **Maximum  $\Delta\text{Cost}$**  is the ‘Headroom’, and represents the maximum additional cost (to the health service) of the new technology over the comparator, at which the technology is cost-effective (Cosh et al. 2007). This must include all costs relevant to the NHS, which can be broadly divided into service costs (SC: staff time, hospital bed occupation, etc) and the price (P) of the new or replaced technology. If, based on early estimations of potential effectiveness, the manufacturer deems it feasible to produce the new device at a price which will keep costs to the NHS within this threshold, then development would appear viable (Cosh et al. 2007). If not, then even using optimistic early assumptions, the reimbursement opportunity is not sufficient to warrant development.

#### 4.3.1 Isolating the Maximum Reimbursable Price

In order to be useful for manufacturers, I believe a further iteration must be made: to disaggregate from the equation the *maximum reimbursable price* (MRP) of the new technology. As outlined, the effect on total NHS costs must include service cost impact ( $\Delta\text{SC}: \text{SC}_2 - \text{SC}_1$ ) as well as any difference in price between the new and old device (if there was one) ( $\Delta\text{P}: \text{P}_2 - \text{P}_1$ ). From Eq. 4.5:

$$\underbrace{\text{Maximum } \Delta\text{Cost}}_{\Delta\text{SC} + \Delta\text{P}} = \text{£}20,000 \times \Delta\text{QALY} \quad (\text{Eq. 4.6})$$

The maximum price that the new technology could fetch within this framework ( $P_2$ : henceforth called MRP) is therefore:

$$\text{MRP} = \text{£}20,000 \times \Delta\text{QALY} - \Delta\text{SC} + P_1 \quad (\text{Eq. 4.7})$$

Where  $P_1$  is (where relevant) the price of the current technology that would be replaced (thus representing a disinvestment [saving] for the NHS). The service cost impact would detract from MRP if that impact were positive ( $\text{SC}_2$  greater than  $\text{SC}_1$ ), or add to MRP if it were to introduce a service cost saving. This can be mapped onto a traditional cost-effectiveness plane, where the axes represent QALY and cost impact per unit (device). For example, Figure 4.1 plots a new device (a) which may save service costs and be more effective than a current technology:

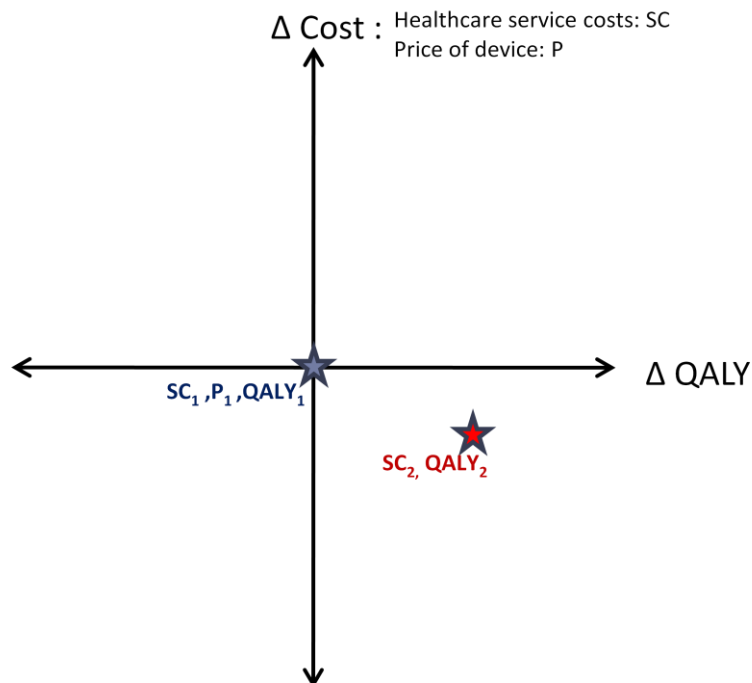


Figure 4.1 Headroom on the modified cost-effectiveness plane for device (a) (1)

In Figure 4.1 the baseline (centre of the graph) represents the current gold standard. The coordinates of technology two (our new device idea) are plotted according to expected health benefit ( $QALY_2 - QALY_1$ ) and expected impact on service costs ( $SC_2 - SC_1$ ). Thus, the only variable left unaccounted for is  $P_2$ : this is what we want to identify the ‘headroom’ for, which will be known as the MRP. First, costs and QALYs must be put onto the same (monetary) scale, for which  $\Delta QALY$  is multiplied by WTP (the threshold ICER)—see Figure 4.2.

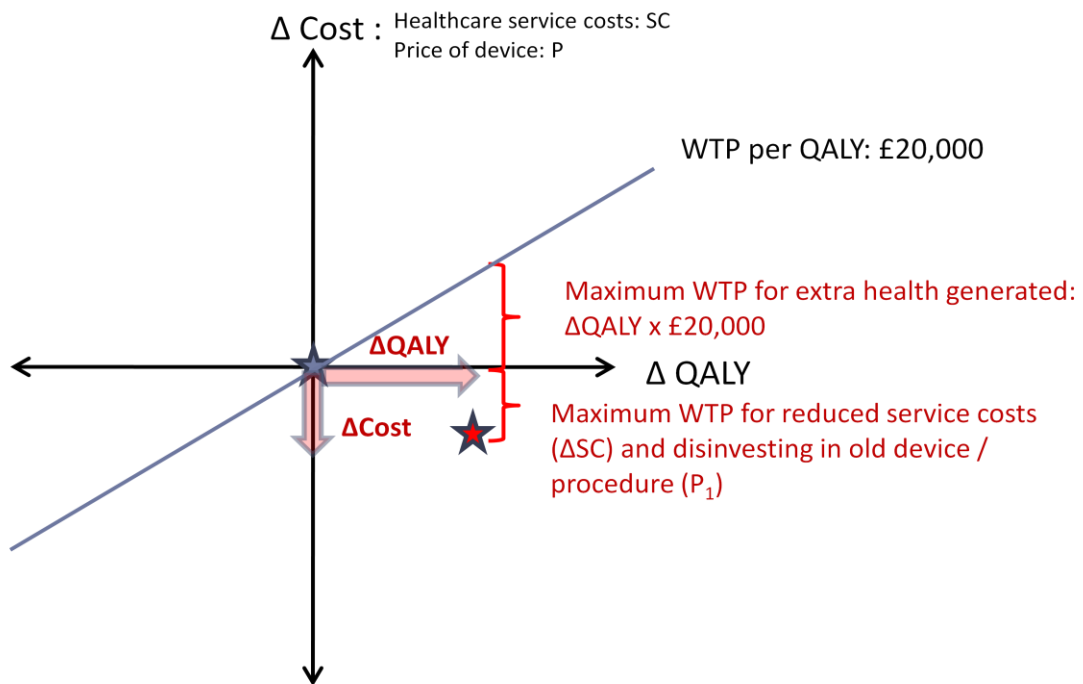


Figure 4.2 Headroom on the modified cost-effectiveness plane for device (a) (2)



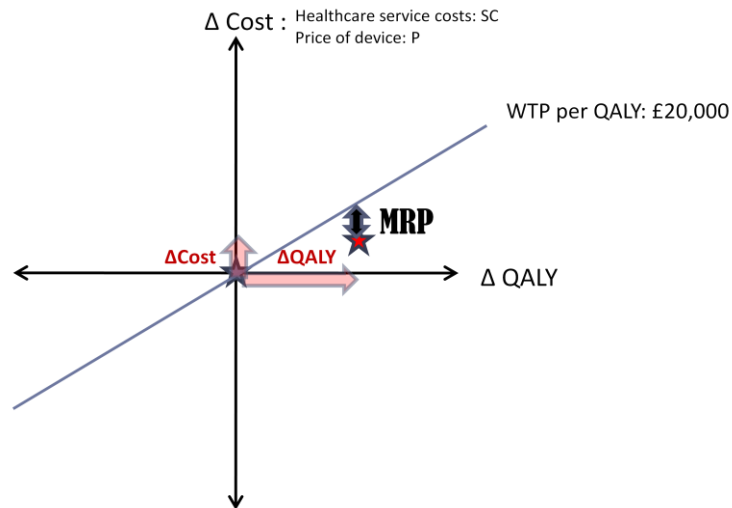


Figure 4.4 MRP for device (b): costs more and improves health

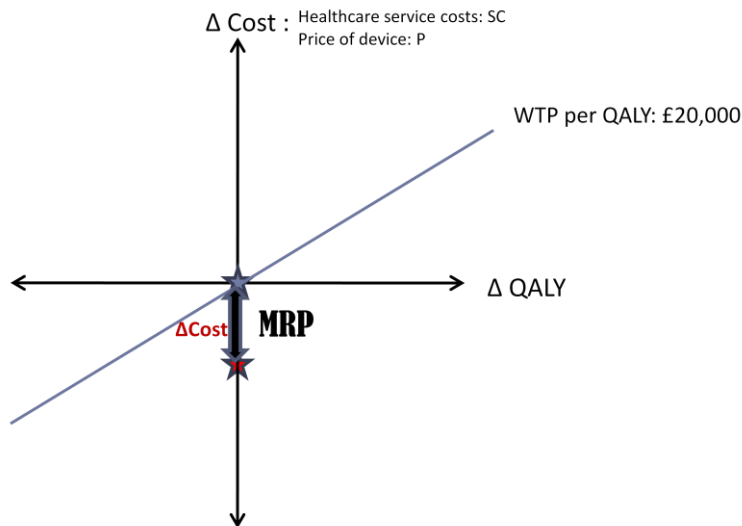


Figure 4.5 MRP for device (c): reduces costs, with no impact on health

This focus on MRP turns the headroom method into a more conceptually useful decision proposition. If the innovator thinks that that device can be developed and produced at a cost which would allow for the price to be within this MRP, then it may present a viable development opportunity. If not, then it is unlikely that the device, once developed, would represent a worthwhile investment for the NHS.

Due to the pre-specified definition of ‘headroom’ in the literature and its corresponding equation (Eq. 4.5), this has been described as the value of the health benefit, and therefore represents the maximum total cost impact to the NHS for a product to be cost-effective. This, of course, is not directly of interest to a device developer, who instead must consider the proportion of that NHS cost impact that may feasibly be allocated to the purchase of the device itself. It is for this reason that ‘MRP’ has been defined and explained as it has above, which essentially represents the headroom for price (or ‘commercial headroom’ (Girling, Chapman, Lilford, & Young 2012)). However, in practice this distinction becomes more fuzzy, as an MRP cannot always be calculated. This may be the case when the full potential impact on service costs cannot be estimated, or where particular characteristics of the device (its longevity, for example) are not known. In such cases, the monetary value calculated cannot be attached directly to the device, as either the value estimation is not complete or is expressed as a value per year or per patient, for example. Therefore, the term ‘MRP’ is used in this thesis when the monetary value calculated relates directly to the device being considered. The term ‘headroom’ (rather than being used only to describe the value of health benefit) is employed as a more general description of the reimbursement gap identified, and is used to label the evaluation output in cases where MRP cannot be identified explicitly.

#### **4.3.2 The headroom method for decision-making: a cost-benefit analysis**

Although the literature provides some examples of the headroom method’s application (Cosh et al. 2007; McAteer et al. 2007), its placement into the decision-making context of the manufacturer has not been explored in much depth. Until now, case studies have simply demonstrated the generation of a headroom figure, followed by an assertion of whether or not this seemed feasible to the developer.

The first step to turning the headroom method into a concrete decision-making framework is (where possible) the isolation of the MRP, as demonstrated above. For the developer, however, this is just half the story, and simply informs the potential future ‘benefit’ of the developer’s own CBA. Put simply, if the expected benefits of a project outweigh the expected costs (to develop and manufacture the device), then the project may be worthwhile. Technically, benefits and costs (both monetary) should be expressed in terms of their present value, which involves discounting these according to the company’s own internal rate. This may be important because much of the cost of development is likely to be incurred early on, whereas the benefit (revenue from sales) may be accrued some years in the future, and thus eroded more by discounting. For a project to be viable, the net present value of the whole project should be greater than zero.

$$\text{NPV} \geq 0 \quad \text{(Eq. 4.8)}$$

$$\text{NPV} = \text{NPV}_{(\text{Benefits})} - \text{NPV}_{(\text{Costs})} \quad \text{(Eq. 4.9)}$$

As the relevant discount rate is likely to vary on a case-by-case basis (depending on the financial position and preferences of the manufacturer), this is left to one side here, and it is assumed that the developer will incorporate consideration of this into their decision.

### 4.3.3 Calculating allowable development costs

The isolation of MRP has been described, and represents the potential unit value of a new device idea. However, potential volume of sales is also an important consideration for business decisions. The relevant market size will directly affect the per unit cost of a device to a manufacturer; the larger the market size, the greater the capacity to spread the costs of development over more units (or to recoup these more quickly), as well as allowing the manufacturer to exploit economies of scale for production. The following analysis will

demonstrate that, if future production costs can be estimated, the developer can use the headroom estimate to determine how much they can afford to spend on development (in order to consider whether this seems feasible).

In keeping with the method’s approach—to estimate the theoretical limits—the value of a development project can be equated to zero in order to determine the maximum viable costs to the developer.

$$NPV = 0 \tag{Eq. 4.10}$$

When combined with Eq.4.9:

$$NPV_{(Benefits)} = NPV_{(Costs)} \tag{Eq. 4.11}$$

There are two major components of total cost (TC): fixed (FC) and variable costs (VC). By introducing volume of sales into Eq. 4.11, we have:

$$\begin{aligned}
 NPV_{(Benefits)} &= MRP * \text{volume} \\
 &= NPV_{(Costs)} \\
 &\quad \uparrow \\
 &\quad TC = FC + VC
 \end{aligned}
 \tag{Eq. 4.12}$$

Table 4.1 defines total, fixed and variable costs.

**Table 4.1 Total costs in the development decision**

<b>TC: Total cost</b>	Total cost for the purposes of this exercise will be equal to total revenue (MRP*vol.) It is the sum of fixed and variable costs.
<b>FC: Fixed cost</b> (development costs)	This is the element of total cost that does not vary with the amount of output produced. Fixed costs may include things like the purchase of machinery, land rent, etc. An important fixed cost is sunk cost of development for devices: the investment in R&D required to get the product ready for market. I will therefore refer to this set of costs as ‘development costs’, but consideration of this must include other such fixed costs as land rent and capital upkeep.
<b>VC: Variable cost</b>	Variable costs are those that do vary with the amount of output produced. This may include raw materials, costs of production, labour, etc.



By estimating the maximum total revenue and thereby assessing the maximum allowable costs for the developer, we can explore the trade-off between development costs and variable costs, where:

$$\text{Maximum total development cost} = \text{TC} - \text{VC} \quad (\text{Eq. 4.13})$$

Where TC is (MRP \* volume) and VC is total variable cost (variable cost per device \* volume). Thus, if the likely variable production costs can be estimated, then the maximum cost of development can be considered. This will be demonstrated in chapter 6 where it is described in relation to the development of a near-patient COPD monitor. It will also show how this analysis can be used to compare target market considerations.

The current literature base for the headroom method lacks a practical focus. The description above therefore places the method within the decision-making context of the manufacturer. However, to calculate ‘headroom’ in the first place requires certain research skills and an understanding of the resources available. With this in mind, the next section outlines an approach to help the user of the method hone in on the important change proposition of the new product, and to extract the relevant information from the literature to furnish these assumptions and quantify their value.

#### **4.4 Finding values for the headroom method**

Through the course of this study, materials have been generated to guide the conducting of a headroom analysis. As well as making its application clearer for a developer, this also allows for a more systematic approach to its application for the purposes of this study.

#### 4.4.1 Pro forma and headroom method template

Although every new device is different in the way it might impact current practice (its change proposition), there are certain questions to be asked and resources to draw upon which allow assumptions to be as informed as possible. For this purpose, a pro forma has been developed, as well as a headroom method template to be used in conjunction with it (see Appendices 1 and 2). The pro forma is divided into seven categories: description of the technology, comparator, market size, health service impact, patient impact, developments in the area (clinical and healthcare context) and research questions. The template breaks these categories down further and outlines the pertinent questions, as well as providing the potentially relevant online resources for each category. This is followed by a more detailed description of some of the categories where identifying the numbers might be difficult, especially for those not used to identifying or manipulating the figures in this way. This includes a description of some relevant databases (e.g. HES Online and NHS reference costs), the provision of particularly useful statistics (costs per hospital bed day, inflation rates, etc) as well as how to adjust for inflation, apply discount rates, approach QALY calculations, and so on.

These materials were compiled through a familiarity with the method and experience gained from the first major case study: the near-patient monitor for COPD. The pro forma and template were developed before the 20 retrospective case studies were undertaken, but extra resources were added to the latter during the work. The documents are not intended as stand-alone material, but can help the user to conceptualise and quantify the potential value of their product. Whilst the identification of costs is reasonably objective (once the appropriate assumptions have been decided upon), QALY estimations are often more difficult due to the paucity of HRQoL data in the literature. In the headroom method template I propose three approaches for this, which are outlined in the next subsection.

#### 4.4.2 Identifying HRQoL weights

Whilst there are many useful resources for identifying HRQoL studies, they are available for only a finite number of health conditions. Therefore, I propose three approaches (in order of preference):

##### **1) HRQoL estimates in the literature**

As mentioned in the summary of NICE's reference case (section 4.2.5), the preferred method of HRQoL estimation is with the EQ-5D questionnaire (to be completed by those affected by the condition), and the use a choice-based method of valuation (such as time trade-off) from a representative sample of the general population (NICE 2008b). HRQoL estimates derived from the EQ-5D therefore represent the first choice (though others are considered by NICE).

The headroom method template, which acts as a resource guide, lists some useful HRQoL resources in the literature. Particularly useful is the CEA registry (TMC Research 2012): a database of CEAs across a wide spectrum of treatments and diseases. Others include the Cochrane library (which has specific search outputs for technology assessments and economic evaluations) (Cochrane Collaboration 2012), the NHS economic evaluation database (CRD 2012), the National Institute for Health Research (NIHR) HTA programme (NIHR 2012), as well as medical journal searches such as Medline and previous NICE technology appraisals.

##### **2) Manipulating the five health dimensions of the EQ-5D questionnaire**

When estimates in the literature do not exist, it may be appropriate to consider the EQ-5D questionnaire directly. This has not been proposed for use in the headroom method before, but seems intuitive in cases where the developer has a clear idea of the product's potential areas of benefit.

The EQ-5D's five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are each divided into three levels: (1) no problems, (2) some problems, and (3) severe problems. There are therefore 243 possible health states. A large survey of a representative sample of the UK population (3,395 participants) was conducted in 1993, through which 42 of these 'health states' were directly valued (Dolan 1997;Williams 1995). Dolan (1997) modelled the results to interpolate values for the remaining 201 states, for which he found the best fit for the data was from a main effects model, which attached a value to each separate deviation from perfect health. This set of national EQ-5D 'tariffs' or 'value sets' have not been updated since, and remain the reference standard for UK QALY valuation (EuroQol 2012a;Karlsson et al. 2011). Table 4.2 summarises the findings of this study, by showing the coefficient values of all possible deviations from 1 ('full health').

**Table 4.2 UK health state valuations for the EQ-5D based on the time trade-off method**

<b>Dimension</b>		<b>Coefficient</b>
<b>Constant</b>		0.081
<b>Mobility</b>	Level 1: No problems walking about	-
	Level 2: Some problems walking about	0.069
	Level 3: Confined to bed	0.314
<b>Self-Care</b>	Level 1: No problems with self-care	-
	Level 2: Some problems washing or dressing self	0.104
	Level 3: Unable to wash or dress self	0.214
<b>Usual Activities</b>	Level 1: No problems with performing usual activities	-
	Level 2: Some problems with performing usual activities	0.036
	Level 3: Unable to perform usual activities	0.094
<b>Pain/Discomfort</b>	Level 1: No pain or discomfort	-
	Level 2: Moderate pain or discomfort	0.123
	Level 3: Extreme pain or discomfort	0.386
<b>Anxiety/Depression</b>	Level 1: Not anxious or depressed	-
	Level 2: Moderately anxious or depressed	0.071
	Level 3: Extremely anxious or depressed	0.236
<b>N3</b>		0.269

Data from Williams (1995)

This information allows us to calculate the value of any single combination of the three levels of the five health states, by subtracting the coefficients presented in Table 4.2, from 1. The ‘constant’ (0.081) should be subtracted from any deviation from full health, and N3 (0.269) should be subtracted from the overall value if one or more health states are in level 3. For example:

$$\text{For health state 11221: } 1 - 0.081 - 0.036 - 0.123 = \mathbf{0.76} \quad \text{(Eq. 4.14)}$$

$$\text{For health state 13312: } 1 - 0.081 - 0.269 - 0.214 - 0.094 - 0.071 = \mathbf{0.271} \quad \text{(Eq. 4.15)}$$

This could be useful in estimating the effect of a one-step change in a particular health parameter. Whilst the potential health implications of many new health technologies is complicated, for particular cases it may be intuitive to attribute the desired effect of a new device idea to one of these categories (see for example the Ulcer Protector in chapter 8). If, for example, a new device could plausibly reduce pain/discomfort from level 2 (some pain/discomfort) to level 1 (no pain/discomfort), then this could be valued at 0.123, and should be multiplied by the time (in years) for which this change is sustained (and then discounted at 3.5%) in order to calculate QALY impact.

The EuroQol group have recently developed a new instrument called the EQ-5D-5L, which will eventually replace that described above, where each of the five health states is split into five rather than three levels (Rabin et al. 2011). However, new value sets (of which there will be 3,125), will take several years to generate. EuroQol provide an estimate of what these values might be, using a ‘crosswalk’ model and existing data for the EQ-5D-3L (EuroQol 2012b). As this five-level instrument has not yet been used for many studies and validated value sets have not been produced, I use those calculated for the three-level instrument, as described above.

Although this strategy should not be considered a substitute for later-stage HRQoL investigations, it could at a very early stage offer some insight into the *potential* value of particular changes in certain HRQoL parameters, in cases where this is intuitive.

### **3) Utility ladder**

Alternatively, HRQoL may be estimated by relating the health state in question to other comparable health states, for which a HRQoL estimate does exist. McAteer (2011) proposes this in her PhD thesis, to overcome problems she encountered in eliciting HRQoL in the absence of literature estimates. By pulling together a range of HRQoL values from various conditions derived from NICE technology appraisals, McAteer places a selection of these on a utility hierarchy ('utility ladder'), which can act as a frame of reference (see Template in Appendix 2 for a visual depiction of these utility ladders).

The solution described above is not completely novel, and other attempts to build such a catalogue of health states date back nearly 20 years. The Beaver Dam Health Outcomes Study predates NICE by around seven years; by providing HRQoL measures for various chronic conditions, the aim was for these to act as reference statistics in a world where there were relatively few HRQoL studies (Fryback et al. 1993). Indeed, one example of its application is in a cost-effectiveness study for a pneumococcal vaccine: '*Because the literature includes no assessments of utility for in-patient and out-patient pneumonia, we estimated them on the basis of comparisons with various health states for which published utility data exist*' (Vold Pepper & Owens 2000, p. 160).

Previous attempts to apply the headroom method in the absence of HRQoL estimates in the literature include an opinion-poll of four urologists, and a survey of 112 members of the

public using a questionnaire (Cosh et al. 2007; McAteer 2011); these methods are time-consuming, resource-intensive, inconsistent with standard utility measures, and above all are unlikely to be feasible for most device developers<sup>12</sup>. The approaches outlined above may help to overcome this, by offering a relatively quick and simple way to make an informed estimate of potential QALY impact. This would appear to be more straightforward, intuitive, and consistent with the framework employed by the decision-makers.

## 4.5 Summary

In order to understand the basis of and the need for the headroom method, it was important to demonstrate the objective function of the healthcare decision-maker. By presenting the headroom method within the framework of a traditional economic evaluation on the cost-effectiveness plane, the direct translation of the demand-side health economic framework into these early decisions by developers is evident. Consideration of the developer's decision as a CBA has clarified how 'headroom' fits into a development decision, as well as allowing the developer to reflect on the allowable development costs of the project. Along with the pro forma and template, these help to make the headroom method and its application more tangible. Section 4.4 demonstrated how the method's application has been made as practical as possible, by providing guidance on navigating the relevant sources of information and outlining pragmatic approaches to overcome information scarcity.

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<sup>12</sup> For example, the headroom analysis for a tissue-engineered substitute of buccal mucosa (cheek lining) to treat a urethral stricture utilised a time trade-off questionnaire distributed to 112 members of the public, which described the pain of buccal mucosa donation and asked participants to specify the time and money they would be willing to sacrifice to avoid this (McAteer 2011). Approach two described above (utility estimation using the EQ-5D questionnaire) could have been employed to very quickly estimate the potential value of avoiding moderate pain for five weeks. This would have rendered a higher disutility estimate: 0.0123 QALYs saved rather than 0.006 estimated by McAteer.

Given the highly competitive nature of the device industry and the short time over which developers can recover costs, it is important that reimbursement potential is considered early on. Of course, actual reimbursement at this threshold level implies that the full value of the innovation would accrue to the manufacturer rather than the NHS which, whilst not socially inefficient, might be a high-risk strategy<sup>13</sup>. However, these considerations are not paramount at such an early stage, and instead the focus should be on the feasibility of containing costs within this theoretical MRP.

Section 4.2 of this chapter explored NICE's approach to decision-making, which for the purposes of the headroom method is considered to be a CBA approach. The headroom method aims to predict the outcome of this late-stage CBA, which can then be used to inform the 'benefit' element of a developer's own CBA for a device development decision. The aim of this thesis is to *evaluate* the headroom method: to consider the **costs** involved (How long does it take? What are the resources required?) and the **benefits** (Is it a good predictor of NHS uptake? Is it useful to manufacturers?) of the headroom method itself. The next chapter describes the methodology employed to tackle this evaluation.

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<sup>13</sup> Girling and colleagues discuss the optimal pricing of medical devices under coverage uncertainty, and suggest that the price should be set to cover production costs and to recover 84% of the anticipated economic surplus (Girling, Lilford, & Young 2011).



## CHAPTER 5 METHODOLOGY

### 5.1 Introduction

A medical device that is developed with no real attempt to study its *effect on* and *compatibility with* patients is arguably of no use. Whilst it may have a sound theoretical justification, real life rarely upholds this perfectly, and with no attempt to test for its actual consequences the device is likely to be left on the shelf. In the same way, a decision-making tool that is not studied in relation to its effectiveness and suitability to the intended user is not well understood. The previous chapter outlined the headroom method and explained its theoretical underpinning and method of application. This chapter sets out how the method is *evaluated* in this research project.

Whilst there are examples in the literature of the application of headroom and other methods of early economic evaluation, these studies fail to evaluate the methods. This omission has been noted by many but addressed by few: *'The field must critically appraise the relevance of early HTA for its stakeholders'* (Ijzerman & Steuten 2011, p. 342); *'Further research, however, is needed to investigate the practicality and likely value of the approach...to medical device companies and the wider healthcare society'* (Vallejo-Torres et al. 2008, p. 463). This project makes the crucial steps from application of the headroom method to an evaluation of it, for which a mixed-methods research design is appropriate.

The review of the literature and market scene-setting chapter alluded to the 'Why' of this research. This chapter outlines the 'How'. In a perfect study the headroom method would be applied to a multitude of new devices at concept stage by the developers themselves, and would be followed up in real time to observe the actual market uptake or cost-effectiveness of the devices studied (or better still, an RCT approach through which the method's employment

would be randomised). Time and resource constraints inhibit this ideal, but the approach outlined here aims to make best use of information that is attainable, and with it to offer a novel insight into the usefulness of the headroom method.

The research questions underlying this project were outlined in the introduction, and were concerned with the method's efficacy and usability. Put simply, I ask: Does the tool facilitate appropriate decisions, and is it applicable in practice?—two questions that remain unanswered by the current literature. These core questions form the basis of my methodological choices, so that a 'chain of evidence' (Yin 1994) can be constructed, allowing each part of the study to be clearly linked to all other parts, and conceptually bound to the original research questions.

The chapter is organised as follows. The first section (5.2) describes the philosophical grounding of the project, and the objectives of evaluation research are presented in section 5.3. The prospective case studies, retrospective case studies and interviews are then outlined in sections 5.4 and 5.5. The overall mixed-methods design of the study is then discussed in relation to the specific research questions (section 5.6). Finally, a summary is offered.

## **5.2 Research Philosophy**

Before describing the evaluation literature, this section briefly introduces the epistemological grounding of this and other types of research. As suggested by Burrell and Morgan (1979), all research is based on a philosophy of science and implicit assumptions about how the world can be investigated. In its widest and most polarised sense, research may ascribe to an objective or a subjective paradigm, hereafter referred to as 'Positivist'<sup>14</sup> or 'Relativist'<sup>15</sup>.

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<sup>14</sup> Also referred to in the literature as scientific, experimentalist, empiricist, traditional and conventional

<sup>15</sup> Also called subjectivist, humanistic, constructivist, anti-positivist and interpretive

These are delineated by several core assumptions concerning what reality is (ontology) and the theory of knowledge (epistemology) (Holden & Lynch 2004).

From an ontological perspective, a positivist believes that the reality to be investigated is a given, objective thing which is external to the individual (Burrell & Morgan 1979). A relativist, on the other hand, believes that reality is a product of individual cognition and of groups who construct their own version of truth, believing there to be no single reality that can be objectively measured (Burrell & Morgan 1979; Clarke 1999). These opposing theories of nature give rise to opposing theories of knowledge. A positivist aims for personal detachment of the researcher from the researched so that knowledge can be gained by measurement and observation, whereas a relativist researcher believes that knowledge cannot be discovered but is subjectively explored (Clarke 1999; Holden & Lynch 2004). These epistemological stances guide evidence generation, the raw material of research, of which there are two main types—quantitative and qualitative—the first of which suits the aims of the positivist, and the second the relativist (Gillham 2000).

Of course, there are standpoints in between these two extremes, the differences between which many authors believe to be overstated (Crossan 2003). Whilst some purists (see for example Guba and Lincoln (1988, pp. 89-115)) believe that methodologies are meaningless if they are not rooted to one (non-divisible) paradigm, others believe that by utilising both paradigms for a particular enquiry, convergences (or divergences) in the stories they tell can be explored, offering a more revealing understanding of the research problem (Greene, Caracelli, & Graham 1989; Kidder & Fine 1987; Patton 1988). I believe the latter perspective to be particularly pertinent to evaluation and to the purposes of this project. Perhaps a more appropriate philosophical stance for this research, therefore, is offered by ‘critical realism’, which sits between the two extremes and believes there to be an independent and objective

reality, but which is critical of our ability to know it with certainty, thus emphasising the importance of multiple approaches (Clark, Lissel, & Davis 2008;DeForge & Shaw 2012;Trochim 2006). I believe that this pragmatic stance most successfully allows the research methodology to be guided by the research questions, and therefore to generate the most useful findings.

### 5.3 Evaluation Research

*'Evaluation is an applied inquiry process for collecting and synthesizing evidence that culminates in conclusions about the state of affairs, value, merit, worth, significance, or quality of a program, product, person, policy, proposal or plan. Conclusions made in evaluations encompass both an empirical aspect (that something is the case) and a normative aspect (judgement about the value of something). It is the value feature that distinguishes evaluation from other types of inquiry such as basic science research, clinical epidemiology, investigative journalism or public polling.'*

(Fournier 2005, p. 140)

Evaluation research tends primarily to address social programmes or policy. However, the object of an evaluation, as demonstrated in the Encyclopaedia of Evaluation's definition presented above, can be almost anything. The various definitions of an evaluation in the literature demonstrate some unifying themes, most notably the necessary 'systematic' nature of evidence generation (Rossi, Freeman, & Rosenbaum 1979;Stufflebeam & Shinkfield 1985), which should relate to an object's 'merit or worth' (Clarke 1999;House 1993;Trochim 2006). The use of the term systematic alludes to the strive for impartiality and reproducibility, whilst the words merit and worth suggest a consideration of efficacy, but in relation to those who have a stake in the object or program. Generally, an evaluation is said to be 'summative' if its aim is to draw conclusions around a program's effectiveness, or 'formative' if the intention is to support the program's improvement (Scriven 1967).

One of the most salient features of an evaluation is its underlying purpose: to influence decision-making. This sets this type of research apart from others, both justifying and guiding its use of multiple approaches. In the early days of program evaluation an experimentalist's approach prevailed, but is argued to have produced poor results with little impact, mainly due to an experiment's incompatibility with non-hard science subjects, and its failure to account for the context of the evaluation and the views of the stakeholders (Pawson & Tilley 1997; Simons 2009). Now, the main body of evaluation literature advocates epistemological and methodological pluralism (Fetterman 1988), stressing that the methods chosen should be determined by the nature of the research rather than pre-existing methodological biases (Chen 1990; Chen & Rossi 1983; Clarke 1999; Weiss 1997).

Although discussed mainly in relation to sociology and criminology, the literature relating to 'realist evaluation' provides some particularly pertinent objectives of evaluation research which chime with the goals of my own evaluation. Realist evaluation was introduced by the seminal work of Pawson and Tilley (1997), who suggest that an evaluation should consider not only whether a programme works, but should also address why, by considering what works, for whom, and in what circumstances. The authors emphasise that evaluation research should be based on hypothesis testing, and stress the importance of context in shaping outcome (Pawson & Tilley 1997; Pawson & Tilley 2004). Whilst not forming the central focus of this study, the realist evaluation approach described briefly here offers some guiding questions which, when it comes to the discussion of results presented in chapter 10, will demonstrate the explanatory power of the evaluation, providing a deeper appreciation of the study results.

The purpose of evaluating the headroom method is to understand its potential to *improve decision-making* by developers: to reduce expenditure on the development of devices which

will ultimately be unsuccessful, and/or to increase expenditure on devices with the potential for health service uptake. This is the ‘outcome’ of interest, and the headroom method’s description in the last chapter set out the theory of why its use by device developers should improve decision-making. The mixed-methods strategy to this evaluation has been designed to test this hypothesis, whilst acknowledging that outcome is likely to be affected by the context within which the headroom method is applied.

As outlined in the introductory chapter, the two key research questions are:

Research question 1: *Does the headroom method ‘work’?*

Research question 2: *Is the headroom method ‘usable’ by device developers?*

The methods employed within this study all aim to address different elements of both of these questions. The way in which the overall mixed-method strategy achieves this is described in section 5.6. First, the individual methods—case studies and interviews—are outlined. However, a detailed account of the precise procedures employed and the implications of decisions made is reserved for the relevant chapters themselves.

## **5.4 Case studies**

The purpose of this section is to briefly outline the procedure of data collection and analysis of the case studies, of which there are two types: prospective and retrospective.

### **5.4.1 Prospective case studies**

Although it has not been possible to interact with developers at true ‘concept’ stage, the two prospective case studies offer a useful insight into the application of the headroom method early on, before major development has taken place.

### *5.3.1 (i) Near-patient monitor for COPD*

The first case study is a near-patient monitor for COPD whose innovator, Professor Monica Spiteri, had initiated the very first stages of product conception and development when we first met in early 2010. The collaboration with Professor Spiteri, a respiratory clinician, was facilitated by a mutual contact who was also involved in the development of the monitor. The sampling technique here was clearly one of convenience, and the Professor's association with an academic institution may have influenced her interest in pursuing the collaboration and understanding the benefit of the research. However, the source of this innovation, having been motivated by the experience of a clinician working in the field, is typical of the device and diagnostic sector, and so offers a unique insight into this type of innovation.

The case study was carried out by independent work that was ongoing for over a year, and whose direction was facilitated by various meetings with the innovator. It involved extensive reference to the literature; the headroom assumptions were generated through both this literature work and discussions with the expert: Professor Spiteri. The process offered an invaluable learning experience in familiarisation with the available literature and resources, in working with the innovator to generate assumptions, and in guiding my understanding of the headroom method at a practical level. Additionally, it is through this case study that the approach to development cost consideration, described in chapter 4, was developed.

This case study (presented in chapter 6), acted as a 'pilot' of sorts, and informed much of the later work. The headroom analysis was time-intensive, which is clearly contrary to the intended use of the method. This therefore inspired the rest of the study and in some ways shaped the whole research design, motivating me to consider the type of evidence required to evaluate the headroom method (rather than simply offering another example of its application). Therefore, whilst not reflecting the intended form of the method's application,

this case study formed an important part of the research process and design, as well as providing an insightful interview opportunity (to be discussed in section 5.5).

#### *5.4.1 (ii) Protective stocking for leg ulcers*

The analysis for the protective stocking for leg ulcers is presented in chapter 8, as it was conducted after the retrospective case studies. The collaboration was facilitated by a mutual contact who had been advising the innovators: two individuals who had set up a new business to develop this device. An appreciation of the proposed product was facilitated by a meeting which took place in November 2011, after which emails were exchanged in order to confirm my understanding of the topic and the feasibility of assumptions drawn. All other work was conducted independently. One additional meeting took place, in which results were presented and discussed (and an interview conducted).

The principal benefit of this case study was to illustrate the prospective application of the headroom method, using the framework and resource set which had been developed during the retrospective case studies. This included the (loosely defined) principle of ‘headroom in a day’. The total time taken for the case study was recorded and reported back to the developers. The application of the headroom method to this particular product type offered additional insight into the method’s use, which is analysed alongside the other elements of the project in the discussion chapter.

Although these case studies were by no means randomly selected, they offer examples of two very different innovation types. As well as demonstrating the method’s early use, they also provided the opportunity to understand the relative merits, disadvantages, and impact of the headroom method in real-life. Additionally, unlike the retrospective case studies described below, these are less biased toward successful or big-impact innovations.



#### 5.4.2 Retrospective case studies

As described, the preferred scenario of following-up case studies to which the headroom method had been applied prospectively (at ‘concept’ stage) is inhibited by the time restraints of this research. Additionally, if headroom results had influenced the development decision, the appropriateness of that influence would not always have been traceable. Therefore, as a surrogate for the prospective application of the method, the method is applied retrospectively to medical technologies that were conceived in the past, but whose success or failure on the market has already been determined.

The source for these case studies was the National Horizon Scanning Centre (NHSC’s) medical technology briefing database, which provides an overview of technologies that are yet to be introduced into clinical practice (see chapter 7 for further details). All briefings produced by the organisation between 2000 and 2009 were considered for inclusion on the basis of clarity, and focus on a specific technology. As explained in chapter 7, of the 83 briefings 54 were excluded, and of those remaining 20 were randomly selected. After the pro forma was developed, and a framework of application designed, the Fibro-Test Acti-Test was used as a pilot study which served to consolidate and refine the approach.

The method was applied on the premise of ‘headroom in a day’, and searches for the relevant data and literature were restricted to mimic as far as possible the information base available to the developer at around its point of conception. After the headroom analysis was undertaken, the technology was followed-up to confirm whether headroom would have indicated a favourable development decision (based on up-to-date information and actual price where available), and the market uptake of the device was identified. In chapter 7, uptake of the medical technology is described to three extents: (a) Evidence of any uptake within the NHS for the specified indication, (b) Evidence of *widespread* uptake within the

NHS for the specified indication, and (c) Evidence of any uptake (globally or for other clinical indications). The headroom method aims to quantify the potential value of a new product to the NHS, for a specific clinical application; therefore, definition of uptake (a) above is used as the main measure of success, to which headroom analyses are compared. However, consideration of the headroom method's performance using the other definitions of uptake will also be explored.

As the headroom method values the gap in the market based on current market conditions and (optimistic) expectations for the technology, the value of this 'gap' may reduce as time goes on (e.g. due to the introduction of new competitors, revision of efficacy expectations etc.) Therefore, it may be reasonable to assume that some devices whose headroom indicated a favourable development decision may in the end be unsuccessful. However, where headroom indicates a no-go decision, and the product turns out to in fact be a successful one, this may imply a problem with the method. It is for this reason that the headroom is primarily suggested as a 'rule-out' method. Results and subsequent analysis considered each case study in terms of the technology type, regulatory class, relationship with current practice, and clinical area, in order to relate these factors to the headroom results.

The limitations of the NHSC database as a source of case studies is clearly important, and the implications for the results are discussed in chapter 7. Most notably, the sample does not include any devices that have been dropped pre-launch, and is likely to be biased toward successful and big-impact products. The headroom method was applied in a systematic way, and the situation of the developer was imitated as far as possible in terms of information availability and likely time restrictions. A significant part of the analysis is found in the 'headroom lessons' that arise from the case studies and their follow-up, such as appropriateness of scope, intrinsic limitations and extra considerations required.

Whilst in the retrospective studies I have tried to some extent to reflect the situation of the developer, I recognise that I, personally, have both disadvantages (limited clinical or in-depth knowledge pre evaluation) and advantages (previous experience and educational background) in applying the headroom method. The pro forma and template, as well as providing the materials to apply the method systematically in this evaluation, also offer the novice health economist (device developers wishing to apply the headroom method) a starting point and a way into the topic. The objective of this research is not to understand how well a PhD researcher can apply the headroom method, but rather to understand its potential application in real life. For this reason, consideration of the context of developers is paramount, and this is the subject matter of the interviews.

## **5.5 Interviews with potential users of the headroom method**

*‘The most important purpose of evaluation is not to prove but to improve... We cannot be sure that our goals are worthy unless we can match them to the needs of the people they are intended to serve’*

(Stufflebeam & Shinkfield 1985, p. 151)

The goal of this research study is to improve the decision-making practice of medical device developers. As well as exploring for whom the method may be most useful / appropriate, the interviews with stakeholders facilitate an understanding of its usability and in what way it has the potential to impact decision-making in real life.

Whilst the case studies consider the causal potential of the headroom method, it must be recognised that outcome is contingent upon the contextual conditions and attitudes of the method’s user. It is for this reason that information and insight are sought from the potential users of the method. Participants were selected based on a purposive sampling technique, and

were identified through either ready-established contacts made through the course of the project or through colleagues. Twelve participants were interviewed through the course of seven interviews, and interviewees covered a wide range of potential users, including a start-up business, a large multi-national medical technology company, business and design consultants, a clinician, an academic, and an NHS innovations manager. The semi-structured interviews were transcribed and thematically analysed.

## **5.6 A mixed-methods evaluation of the headroom method**

The main perceived benefit of a mixed-methods research design derives from the recognition that all individual methods have error and are susceptible to bias (Trochim 2006; Williamson 2005). Moreover, by employing a mixed-methods approach, the strengths of each approach can be exploited and their combined results can provide a wider and more informative exposition of the issues (Creswell 2009; Yin 1994). The combining of methods has risen in popularity both within evaluation research and more widely, reflecting the development in legitimacy of many different approaches, as well as the recognition that each contributes a distinct and useful perspective (Clarke 1999; Creswell 2009). The philosophical grounding of adopting a mixed-methods approach was set out in section 5.2, along with the rationale for its use within this particular enquiry.

Greene and colleagues (1989) provide a useful outline of the various purposes of a mixed-method strategy to evaluation: triangulation, complementarity, development, initiation and expansion. These five distinct purposes are explained in chapter 9, where the methodological contribution of the qualitative interview investigation to the overall study design is described in more detail. Triangulation in particular is regularly stressed in the literature to be an

important output of mixing methods. A term originally deriving from nautical navigation, triangulation refers to the establishment of location (or meaning in this case) using inferences obtained from various methods or measurements (Stake 1995). This allows for the improved validation of research results by exploring the convergence in findings from the various methods (Campbell & Fiske 1959; Simons 2009; Stake 1995).

### 5.6.1 Study design

The first most obvious criterion for the headroom method's assessment is its ability to discriminate between good projects and bad. This addresses method efficacy, and is dealt with primarily by the 20 retrospective case studies and their follow-up. The word 'efficacy' has been chosen purposefully here as it refers to the ability of something to produce the desired effect or outcome under controlled conditions (e.g. within a clinical trial), as opposed to effectiveness which considers the effect of an intervention in practice (Osterholm, Kelley, Sommer, & Belongia 2012). Although this contribution is novel (the outcome of the headroom method's use has not previously been investigated), an understanding of efficacy alone is insufficient to appreciate the potential effectiveness of the method.

As described in the literature review, current studies of early HTA methods for developers lack an evaluative approach (Bartelmes et al. 2009). McCabe and Dixon (2000) acknowledge the desirability of identifying the predictive value of economic models, whilst noting that their validity cannot be determined exclusively on that basis; the value of a model should be assessed in relation to the decision-maker for whom it is intended (McCabe & Dixon 2000). Usability is explored primarily through the stakeholder interviews, although both methods are designed to address both research questions in different ways. The implicit assumptions of the headroom method must also be addressed. For example, by assuming that the headroom method could improve decision-making, we implicitly assume that health economics is not

currently incorporated into development decisions, or is done so sub-optimally; this must be investigated. The ways in which each method contributes to the evaluation is summarised in Table 5.1, which breaks down the primary research questions further into contributory research questions.

Table 5.1 The elements of study design contributing to each research question

Research Questions	Subsidiary Research Questions	2 x Prospective case studies	20 x Retrospective case studies	Interviews
<b>Does it work?</b>	(i) Is it novel?			The method may only <i>improve</i> decision-making if it adds to current practice. This is investigated in the interviews.
	(ii) Is it a good predictor of market uptake?		Follow-up of the retrospective headroom analyses allow the implied development decision to be matched with later market uptake. Given the diverse characteristics of the study sample, patterns may be sought.	
	(iii) What is left out of the analysis?	Later interviews with the developers of the prospective case study devices offer a unique insight into their views on the completeness of the analysis, and the usefulness of its output.	The headroom analyses and follow-up allow for pertinent omissions (that had an impact on future market uptake) to be noted. These are presented in chapter 7 as 'headroom lessons'.	Interviewees are asked to discuss any important omissions from the headroom approach, which may be as / more important at development decision stage.
<b>Is it usable by device developers?</b>	(i) Can it be utilised at 'concept' stage?	These case studies demonstrate the method's application in real time to devices in the very early stages of development.	Information searches are date-restricted to mimic the concept stage of the developer.	Headroom should be related to expected costs in order to inform the development decision. Interviewees are asked whether costs can be conceptualised at such an early stage.
	(ii) Can the method be applied by device developers?		A pro forma and resource template offer non-specialists a framework to follow in applying the method.	Interviews investigate whether the method is understandable and what the biggest barriers might be to its application.
	(iii) Could it practically be incorporated into decision-making?		Time spent per headroom analysis is guided by 'headroom in a day'.	Practical barriers are explored, including time available and expertise, and how barriers may vary according to the user.

The break-down of method choice and design presented in Table 5.1 demonstrates the multiple ways in which efficacy and usability of the headroom method are considered in this research. The strategy employed for the evaluation is aligned most clearly with what Creswell (2009) describes as a ‘sequential explanatory design’. Rather than the methods being applied concurrently, I first analyse the case studies (which represents a quantitative-leaning method), which then informs the secondary qualitative data collection. This allows for the interview questions to build upon (and sometimes make reference to) the results or output of the initial stage of research. It is important to note that the weight attached to each phase of the research need not be equal, and in fact a sequential explanatory design normally places priority on the initial, quantitative stage (Creswell 2009).

This section has described the merits of a mixed-methods approach to evaluation, and has introduced my own research design in relation to these.

## **5.7 Summary**

The practical focus of the research design described in this chapter has at its core the desire to understand the potential impact of the headroom method on decision-making in the medical device industry. This is the novel contribution of this research methodology, which is grounded in the need to critically evaluate the headroom method in relation to its consequences and its viability; the review of the literature showed this to be absent from the current literature base.

The consideration of philosophical paradigms is important for a research project, both allowing the researcher to open their mind to other possibilities, to explain the approach chosen, and also to *‘enhance their confidence in the appropriateness of their methodology to*



*the research problem which, in turn, enhances confidence in their research results'* (Holden & Lynch 2004, p. 406). I have shown that I take a sequential explanatory mixed methods approach, and by doing so increase the strength of the overall study by approaching the research questions from various angles. This triangulation will enrich the synthesis of results presented in the discussion chapter, enhance the conclusions drawn, and improve the validity of the overall study.

This chapter has sought not to provide precise detail of each research method, but rather to tie up the whole thesis and frame it within its stated objective: to evaluate the headroom method. By assessing the method in this way, an improved understanding of its potential impact is sought, thereby providing the foundation for recommendations concerning its appropriate use. The chapters that follow provide a sequential account of the work undertaken.

# CHAPTER 6 HEADROOM ANALYSIS FOR A NEAR-PATIENT MONITOR FOR COPD

## 6.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a far-reaching and costly disease for the NHS. The innovation under consideration, which proposes to improve patient care and streamline services, is a near-patient monitor for COPD. This portable device for point-of-care management (for use by patients in their own homes) would combine a biosensor which would detect levels of COPD-relevant biomarkers in saliva, with symptom-related health question responses. This would facilitate a record of progression and detect the onset of acute inflammation / infective episodes (exacerbations), to allow for prompt treatment.

This case study acts as a foundation for the approach taken in ensuing case studies, and demonstrates some opportunities as well as difficulties associated with early economic evaluation using the headroom method. It also introduces and demonstrates further functions of the method, for example in assessing different scenarios or target markets, and considering the costs of development. Section 6.2 provides the background, explaining the current model of COPD care and how the near-patient monitor might change this. Using this information as a platform, section 6.3 presents the headroom analysis based on three clinical scenarios. Possible interpretation of the analysis is then provided, followed by a summary which outlines the relative strengths and omissions of the study.

## 6.2 Background

This section describes COPD and its care in the UK. After outlining the key characteristics of the disease and the way it affects patients and the NHS (section 6.2.1), the current model of care is described, alongside the deficiencies in this model that the near-patient monitor could address. The third sub-section (6.2.3) presents the device and its change proposition in more detail, before the relevant data and literature are outlined, setting the scene for the headroom analysis that is presented in section 6.3.

### 6.2.1 COPD: Prevalence and Relevance

This section briefly outlines the clinical and economic burden of COPD in the UK.

#### 6.2.1 (i) Definition

COPD is a lung disease characterised by airflow obstruction which interferes with a patient's breathing.<sup>16</sup> The disease is progressive in nature and is not fully reversible, and symptoms include breathlessness and chronic cough. Predominant causes include smoking and occupational exposures (smoking is the cause of 85% of COPD deaths (NICE 2010a)). COPD is associated with a significantly impaired QoL and can cause premature death (NICE 2010a;WHO 2010a). Although unable to reverse the disease, treatment is important in controlling symptoms and avoiding or ameliorating exacerbations (a flare-up in symptoms), which are associated with increased inflammation in the airways and are mainly triggered by respiratory viruses and bacteria (Wedzicha & Seemungal 2007). Exacerbations cause significant QoL loss, and can trigger further irreversible damage to lung function, often causing disease severity to have progressed when the patient returns to their 'stable' state.

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<sup>16</sup> COPD is the term now used for patients with airflow obstruction of the lungs, and includes patients who would previously have been diagnosed with chronic bronchitis and emphysema.

Therefore, patients with more frequent exacerbations tend to exhibit worse health status and quicker disease progression.

#### *6.2.1 (ii) Burden of disease*

COPD is the fourth most common cause of death worldwide, and is predicted to become the third by 2020 and to rank fifth in terms of worldwide burden of disease (Burney 2006;Rabe et al. 2007). Within the UK, COPD causes approximately 30,000 deaths each year. Around 900,000 people in the UK are diagnosed with COPD (accounting for around 1.5% of the population in 2007/08), though the actual number affected is more likely to be around 3 million (Healthcare Commission 2006;NICE 2010a). Prevalence is significantly biased towards older patients, and there is a strong association with level of deprivation (Burney 2006;NICE 2010a).

#### *6.2.1 (iii) Economic burden*

As well as its important clinical impact, COPD is a very costly disease for the NHS. Total direct healthcare costs are estimated to be over £800 million per year, which excludes the huge productivity loss associated with the disease, said to be 24 million working days or £2.7 billion per annum (Department of Health 2004). The disease accounts for 1.4 million consultations in primary care each year. Exacerbations experienced by COPD patients represent the second most common cause for emergency admission to hospital in the UK, accounting for around one million hospital bed days per year (Burney 2006;Lung & Asthma Information Agency 2003;NICE 2010a). Over half of the total direct costs of COPD are attributable to these hospital admissions (Burney 2006;NICE 2010a). This means that recognising the early signs of an exacerbation and treating symptoms before they escalate is crucial, not only for the health of the patient but also in reducing resource use. The average cost per patient is highly dependent on disease severity (NICE 2010a), as is quality of life,

implying that any treatment or disease management strategy that could slow the progress of the disease would be hugely beneficial.

### 6.2.2 Current care for COPD patients: 'Standard practice' & national initiatives

In response to the high impact of the disease, there have been a number of national schemes and initiatives which encourage improvements in COPD patient care: the Chief Medical Officer's report '*It takes your breath away: The impact of COPD*' (Department of Health 2004); the Healthcare Commission's national study of COPD '*Clearing the air*' (Healthcare Commission 2006); a new National Strategy for COPD from the Department of Health (2010d); and also an updated NICE clinical guideline (NICE 2010a). All of these initiatives aim to make care more responsive to patients' needs. This section briefly explains current best practice for diagnosis, day-to-day management, patient follow-up, and exacerbation response, and is mainly guided by NICE's clinical guideline for COPD (NICE 2010a). The deficiencies of current care in reality (informed by both the reports listed above and Prof. Spiteri)—deficiencies which could potentially be addressed by the proposed near-patient monitor—are presented in boxes alongside the relevant text.

#### 6.2.2 (i) *Diagnosis*

Diagnosis should be considered in patients who: are over 35, smoke (or have another risk factor) and who present symptoms such as chronic cough, breathlessness, or regular sputum production (NICE 2010b). Airflow obstruction is confirmed by spirometry which measures lung volume (forced expiratory volume in one second FEV<sub>1</sub>) which, combined with clinical judgement, determines the diagnosis. Airflow obstruction is categorised by severity as shown in Table 6.1.

**Table 6.1 Definition of COPD severity stages**

<b>FEV<sub>1</sub> % predicted* (Post bronchodilator)</b>	<b>COPD severity**</b>
≥80%	Stage 1- Mild
50-79%	Stage 2- Moderate
30-49%	Stage 3- Severe
<30%	Stage 5- Very severe***

\*Measured FEV<sub>1</sub> of the patient, as a percentage of the average FEV<sub>1</sub> in the population for similar age, sex, etc.

\*\*Note that this classification system differs to that used in NICE 2004 guidance, of which CG101 is an update.

\*\*\*Or FEV<sub>1</sub> < 50% with respiratory failure

Under-diagnosis is mainly due to patients ignoring the symptoms of mild COPD, dismissing the warning signs as a smoker’s cough and not seeking medical help. Early, proactive diagnosis is therefore a feature in all the national guidelines for improved care (often labelled ‘finding the missing millions’).

### 6.2.2 (ii) Day-to-day management (for stable COPD)

All patients are encouraged to stop smoking and to be vaccinated against illnesses that could aggravate symptoms, e.g. the annual influenza vaccination. To treat symptoms, NICE recommends the prescription of short-acting bronchodilators as needed in the first instance, followed by long-acting bronchodilators and potentially adding inhaled corticosteroids according to severity. Medications are scaled up according to treatment response.

Whilst this progressive prescription of drugs is necessary to gauge the level of treatment required for each individual patient, and to tailor their management accordingly, analysis of the response to a patient’s initial management plan can be difficult and somewhat subjective. This is because ‘response’ to treatment may not be based on improved lung function, but on symptom improvement. Additionally, there is no clear timeframe for the treatment plan.

#### Box 1 Difficulties measuring treatment response

Patients are encouraged to undertake pulmonary rehabilitation. Lung volume surgery and transplantation are only considered for severe COPD patients who do not respond to ‘maximal medical therapy’.

Delivery of care should be by a multidisciplinary team of experts who ensure that the patient receives the right treatment at the right time.

In reality, COPD care is patchy across the country. More effort is needed to make care consistent and available to all those that need it. This equity concern is highlighted in the Chief Medical Officer's report (Department of Health 2004) which demonstrates the large national variations in the re-admission rate to hospital, average length of stay, specialist staff numbers, and mortality rates.

**Box 2 Inconsistent care**

**6.2.2 (iii) Follow-up and review**

Patients with mild, moderate or severe manifestations of COPD should be followed-up in primary care at least once a year to assess symptom control, and very severe patients at least twice a year. Regular hospital review is not normally required, but preparations should be in place to allow for rapid hospital assessment when necessary. Measurements to be taken in primary care consultations include FEV<sub>1</sub>, forced vital capacity (FVC), body mass index (BMI) and dyspnoea score, plus SaO<sub>2</sub> (arterial oxygen saturation) for very severe patients.

Much of the recommendation for follow-up is based on expert opinion rather than research studies, due to the lack of evidence in this area. Response to treatment is difficult to measure, and having year-long gaps between reviews can mean that the need for incremental treatment is not recognised early enough. This is why patient education and self-management strategies have been emphasised in all of the national initiatives to improve care. For example:

- Recommendation 16 in the COPD strategy document (Department of Health 2010d);
- The provision of integrated care recommendations within the healthcare commission report (Healthcare Commission 2006, p.32);
- The emphasis on patients taking control of their own care in the CMO report (Department of Health 2004), and;
- A persistent emphasis on self-treatment strategies in NICE's clinical guideline 101 (NICE 2010a).

**Box 3 Unresponsive care**

### 6.2.2 (iv) Exacerbations

A timely response to the early signs of an exacerbation (worsening of breathlessness, cough and sputum production) is very important, and includes the use of corticosteroids, antibiotic therapy if sputum is purulent, and adjusting bronchodilator therapy. Recovery should be monitored and follow-up or home care should be arranged for those admitted to hospital for the exacerbation.

The initial signs of an exacerbation are often ignored by patients, meaning that they do not receive crucial treatment which can prevent the episode from progressing. The National COPD audit found that before admission to hospital for an exacerbation, two thirds of patients (68%) indicated having suffered a respiratory infection or flu-like symptoms in the month leading to admission, and 57% noted a change in phlegm (colour/volume) within the week prior to hospital admission (RCP 2008c). Additionally, the report on COPD by the Healthcare Commission (2006, p. 38) noted a large variability in hospital admission rates, suggesting that many admissions are avoidable. The following quotation is drawn from Report 4 of the National COPD Audit 2008 (Patient Survey), and highlights the opportunity for earlier identification and treatment of exacerbations:

*‘The results suggest that the lead-in, or pro-dromal, phase of exacerbation is quite long and imply there is ample opportunity to make earlier interventions to prevent hospital admission in a selected group of patients who exacerbate frequently. There is also a need for improved self-management and the value of personal COPD plans should be explored in this context’*

(RCP 2008c, p. 6)

Self-management and providing patients with the means to recognise and react to early symptoms is therefore at the top of the agenda for all national initiatives.

#### Box 4 Delayed treatment of exacerbations

Section 6.2.2 has provided a brief summary of current care guidelines for COPD patients and some shortfalls in current practice. The recurrent themes in many of the national COPD studies/ recommendations are that: (a) care is currently reactive rather than proactive, with a structure of care which treats patients when things have already gone wrong; (b) care is inconsistent across the country; (c) treatment should be tailored to individual patients; (d) acute episodes should be dealt with in a timely manner, and; (e) patients should be



empowered to self-manage. The following section describes an innovation for the monitoring of COPD, and demonstrates its potential to tackle all of these issues.

### 6.2.3 Smart Biosensor: A near-patient monitor of COPD status

The near-patient monitor would be a portable handheld device which would provide the patient and their healthcare team with a clear and comprehensive picture of COPD status and progression over time, in the form of patient-driven bio-clinical profiling. The home-use device would capture and combine subjective clinical metrics (from self-reported wellbeing scores) and the objective measurement of COPD relevant biomarkers in the patient's saliva (using lab-on-a-chip technology). Results (which would ideally be generated daily) would be telecommunicated to the patient's clinic, thus alerting the healthcare professionals to any sudden changes. The headline advantages of the innovation are threefold: (1) it acts as a personalised monitor of COPD status with respect to the patient's own baseline, (2) it allows for better, more objective and more sensitive monitoring of response to initial management plans, and (3) it can act as an early warning for exacerbations, ensuring prompt treatment.

These proposed advantages would optimise the delivery of care, and improve clinical outcome by doing so. A key economic driver would be the reduction in hospital visits, resulting from the earlier recognition and treatment of acute episodes. Additionally, the device could differentiate between the viral or bacterial cause of a COPD exacerbation, ensuring antibiotics are prescribed more intelligently. Table 6.2 provides a summary of patient management best-practice, shortfalls in current care, the key recommendations made by the national initiatives discussed, and alongside these how the near-patient monitor might improve patient care in these areas.

Table 6.2 Near-patient COPD monitor and how it could improve patient management

Aspect of patient management	Current 'best practice' (what should happen)	Shortfalls of current practice	Comments/ recommendations in the various national initiatives	How the near-patient monitor addresses these issues
<p style="text-align: center;"><b>Day to day management for stable COPD</b></p>	<p>Treatment, aimed at alleviating COPD symptoms, is prescribed progressively.</p>	<p>Analysis of response to the patient's initial management plan can be difficult /subjective.</p>	<p>- PCTs must ensure that COPD patients receive structured and personalised care (Healthcare Commission 2006). -Clinicians should be supported locally with an appropriate team and the right tools and evidence to do their jobs (Winter 2010).</p>	<p>Allows for treatment to be guided specifically by patient's own health. Step-up in medication can be informed by regular data on patient wellbeing and objective biomarker observation (changes in which precede alterations in physiological measurements and patient symptoms).</p>
	<p>Response to treatment is monitored, and medication is adjusted accordingly.</p>	<p>There lacks a clear timeframe to monitor response, and review meetings are infrequent.</p>	<p>-Care should be integrated and more personalised with better information to guide changes in treatment (Winter 2010).</p>	<p>The device acts as a tool for clinicians to personalise management, and as a record of temporal changes in symptoms and biological indices. These can thus be picked up and acted upon quickly.</p>
	<p>Delivery of care should be by a multidisciplinary team of experts.</p>	<p>Care is inconsistent and not available to all those that need it. Access to specialists varies greatly across the country.</p>	<p>-Care should be standardised (Department of Health 2010d). -Optimal care requires partnership between the COPD patient and the healthcare professional associated with regular review (Department of Health 2010d).</p>	<p>Allows all COPD patients, regardless of location, to be monitored and managed according to their own needs. Provides a means of communication and understanding between patient and healthcare professional.</p>
	<p>Patients should receive the right treatment at the right time.</p>	<p>Patients contact the health service when things have already gone wrong.</p>	<p>-The current model of care is reactive (Department of Health 2010d;Healthcare Commission 2006). -Care should be more accessible and closer to home (Winter 2010).</p>	<p>Offers a means to make care proactive. By monitoring their own progress, patients are empowered to manage their condition and take control of their treatment. This is in keeping with the general shift away from care in hospital and into the home. Fewer hospital and primary care contacts also complement NHS sustainability drive.</p>

<p><b>Follow-up and review</b></p>	<p>Follow-up consultations in primary care recommended annually, or bi-annually for very severe patients. Treatment should be reviewed and assessed for adequacy.</p>	<p>Long gaps between reviews can mean that the need for treatment changes is not recognised early enough.</p>	<p>-COPD patients should be empowered to self-manage (Department of Health 2010d;Department of Health 2004;Healthcare Commission 2006;NICE 2010a;Winter 2010).</p> <p>-Care should be supported by actionable data, that is clinically owned (Winter 2010).</p> <p>-Regular review should reduce the demand for unscheduled care (Department of Health 2010d).</p>	<p>The near-patient monitor acts as a <i>tool for self-management</i>. It would allow patients to monitor their health, and critically would also provide advice on self-treating. By combining data from biomarkers and self-reported indicators of wellbeing, the device will alert the patient and healthcare team to the need of a change in treatment. By making the patient part of this process and allowing review to be consistent rather than periodical, treatment can be better targeted and effective.</p>
<p><b>Exacerbations</b></p>	<p>The best way to avoid an exacerbation is to ensure that the patient is adequately managing symptoms. A patient should react immediately to the early signs of an exacerbation, by treating with a step-up in current medication, or the use of corticosteroids or antibiotics, as appropriate.</p>	<p>Initial signs of an exacerbation are often ignored by patients.</p> <p>Many current hospital admissions for COPD are avoidable (due to lack of recognition of early signs, or lack of knowledge/means to self-treat).</p>	<p>-Exacerbations are associated with a significant worsening of prognosis and very high costs. Timely and appropriate treatment is important for reducing the impact of acute episodes (<i>all reports listed above</i>).</p> <p>The number of people admitted to hospital should be reduced, by:</p> <ul style="list-style-type: none"> <li>- Better identification of exacerbations(Department of Health 2010d, Recommendation 17);</li> <li>- Providing patients with the means to self-treat in response to an acute episode (Department of Health 2010d).</li> </ul>	<p>By identifying abrupt changes in longitudinal data (based on patient’s own baseline), the biosensor can alert the patient to the early signs of an exacerbation and provide advice on what to do about it.</p> <p>The device will facilitate the early identification and treatment of acute exacerbations. The patient may then administer the treatment which could prevent the episode from progressing, thus reducing its impact in the:</p> <ul style="list-style-type: none"> <li>- <i>Short term</i>- exacerbation is less severe if treated early</li> <li>- <i>Long term</i>- slows the rate of progressive lung function decline</li> </ul> <p>Lowered costs to the NHS would result from fewer hospitalisations and slower disease progression.</p> <p>The treatment of episodes that do require hospitalisation could be made more efficient if a consistent and comprehensive picture of a patient’s health status over time is readily available.</p>

There is clearly room for improvement in the management of COPD patients, a gap which the headroom analysis to follow in section 6.3 aims to value. Along with the national reports already outlined, Table 6.3 provides details of additional initiatives in the UK (both for COPD specifically and more widely), which illustrate not only the demand for the type of improvements that the biosensor could generate, but also the demand for this specific format of management.

**Table 6.3 Additional justification for the near-patient monitor and its specific mode of delivery**

<b>Topic</b>	<b>Description</b>
<b>Salivary diagnostics</b>	Interest in the use of saliva as a non-invasive means to monitor health status, progression and treatment outcome is rising (see (Li et al. 2005)).
<b>Health Innovation Challenge Fund (HICF)</b>	<p>The HICF, an initiative set up by the Wellcome Trust and Department of Health to stimulate innovation (Wellcome Trust 2010), issues thematic calls for proposals. At the time of analysis (2010), this call was for innovative technologies addressing the <i>'monitoring of chronic illness in the home and remote settings'</i>. This illustrates the current relevancy of this topic.</p> <p>The following 'desirable qualities' were expressed (Wellcome Trust 2010):</p> <ul style="list-style-type: none"> <li>- <i>'Methods that engage the patient on an ongoing basis and motivate the patient to take the appropriate self-management action. Methodologies that prevent the patient escalating to the next care level are particularly important'</i></li> <li>- <i>'Systems that offer improved front-end data capture'</i></li> <li>- <i>'Achieving optimal balance between the amount of face-to-face care and remote monitoring by health professionals'</i></li> </ul>
<b>NHS White Paper</b>	<p>Within the NHS White Paper there is a strong emphasis on focusing care around patients' needs, and empowering them to take control of their own care (Department of Health 2010b). In particular, they emphasise:</p> <p><i>'...increased self-care and the use of new technologies for people with long-term conditions'</i> (Department of Health 2010b, p. 47)</p>
<b>Lung Improvement Programme</b>	<p>The Lung Improvement Programme supports local improvement of respiratory services (NHS Improvement 2010). They identify <i>'four winning principles of transforming inpatient care'</i> which, for lung cancer care, have lowered hospital admissions, reduced length of stay, and encouraged earlier discharge, and which should be applied to the management pathway of COPD (Duncan 2010):</p> <p>(1) Daily decision-making; (2) Encourage self-management; (3) Defined inpatient pathways; (4) Assessment prior to admission.</p>
<b>COPD Strategy: case study</b>	<p>The Department of Health's (2010d) recommendation no.16: <i>'People with COPD should be encouraged to learn how to manage their condition themselves...'</i> (p.80) includes a case study of a telehealth project. The benefits of remote monitoring are highlighted, and are similar to those attributable to the near-patient monitor.</p>

The near-patient monitor seems to chime well with key national objectives in COPD care. Having presented how the innovation fits in with current practice, it was demonstrated how such a device would make care more proactive, patient-centred and efficient. The focus now shifts to the practical areas of benefit that might be valued using a headroom analysis. In any economic evaluation, the proposed technology is compared with current practice by assessing its impact on health and resource use. For a medical device that will directly replace another, this comparison is relatively straightforward. For this innovation, the anticipated improvement would result from altering the care pathway, rather than changing the model of treatment per se. This makes valuing its impact more challenging.

Figure 6.1, below, provides a visual summary the natural progression of COPD, and how the near-patient monitor may affect this.

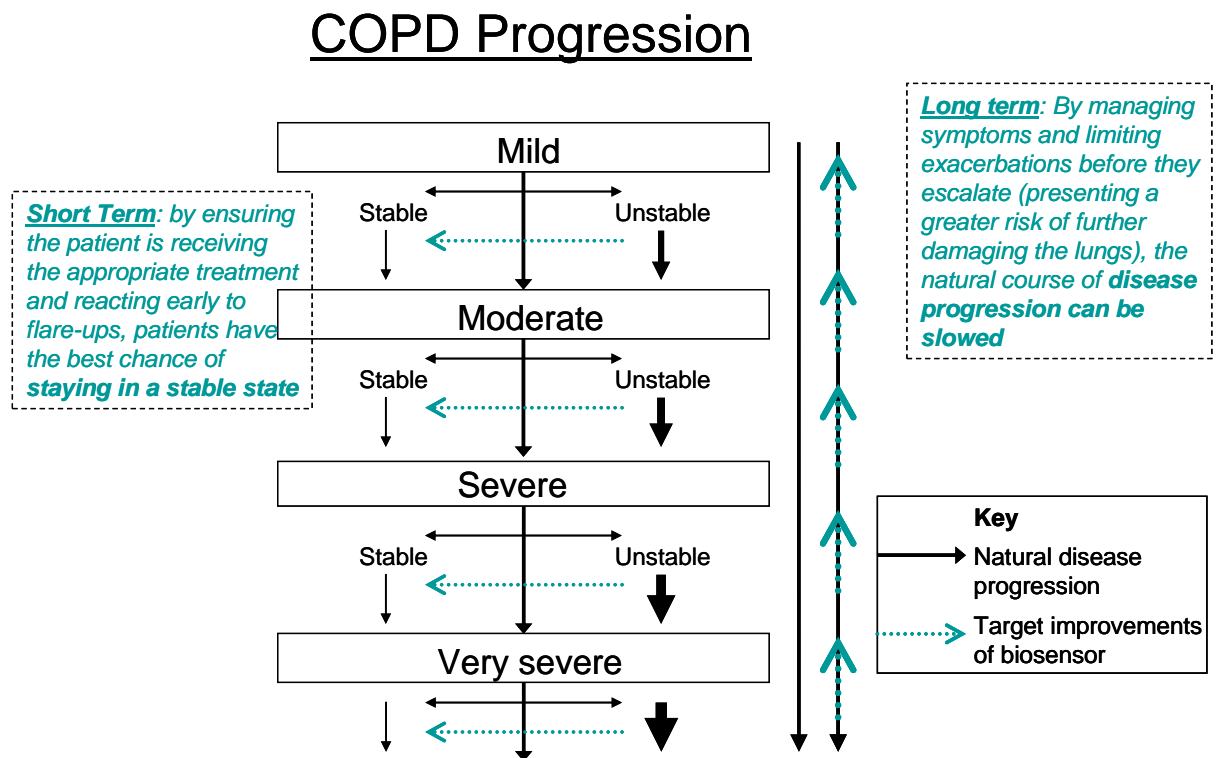


Figure 6.1 Diagram of COPD progression

COPD's progressive nature is represented in the diagram. At any level of severity, patients may be in either a stable or an unstable condition. The unstable state (which may manifest as an exacerbation) poses a greater risk of generating further irreversible damage to the lungs, thus progressing to a higher severity category. This risk of exacerbation and reduced lung function becomes progressively greater (as represented by the thickening of the transition arrows). The paler dotted arrows represent the target improvements of the near-patient monitor, aiming in the short term to maintain stability of symptoms, and thereby in the long term reducing the pace of disease progression. As more severe manifestations of COPD are associated with higher morbidity and increased resource use, having a greater control of the disease's progression would improve both quality of life prospects and NHS costs.

To economically evaluate these suggested improvements fully would require a complex Markov model, for which cost and QALY estimates would be attached to each disease state, along with transition probabilities and estimates of how these would be affected by the near-patient monitor. The approach taken for the headroom analysis is explained in section 6.3, which necessarily involves a simplification of this scenario. Before this, the pertinent statistics which are relevant to this clinical problem are outlined, along with the literature which provides evidence for the relationships that are either assumed in the headroom analysis, or not quantified in the model but which should be considered to understand the wider potential impact of the device.

#### 6.2.4 Data and the literature

##### 6.2.4 (i) *Data*

The data presented in Table 6.4 and Table 6.5 describe the current clinical and economic landscape for COPD care in the UK. Whilst not all of the data will be used specifically in the

subsequent headroom calculations, they highlight the room for improvement in current care and may be beneficial at a later stage when clinical data for the near-patient monitor are available and a more complex model could be built. All data can be found in the full NICE clinical guideline (NICE 2010a).

**Table 6.4 Data: Clinical context**

<b>People affected</b>	3 million	
<b>Diagnosed</b>	900,000 (1.5% population)	
<b>Mortality</b>	30,000 deaths each year in UK	
<b>Inpatient mortality rate (2008)</b>	7.7%	
<b>Leading cause of death</b>	5 <sup>th</sup> in UK, 4 <sup>th</sup> worldwide	
<b>Number of patients on the practice list for the average GP (who cares for 7,000 people)</b>	200 COPD patients per practice	
<b>GP consultations per year</b>	1.4 million	
<b>Healthcare contact for patients admitted to hospital, and exacerbation history</b>	<b>In the month prior to admission</b>	<b>In the 12 months prior to admission</b>
	74% make contact with GP 31% have 3 or more contacts	Median of 12 contacts with GP Median of 3 exacerbations 51% have no contact out-of-hours
<b>Symptoms before admission</b>	68% reported respiratory infection/flu-like symptoms in the month prior to admission 57% noticed change in colour/volume of phlegm, of whom: <ul style="list-style-type: none"> <li>• 46% 2-5 days before</li> <li>• 26% 6 or more days before</li> </ul>	
<b>Emergency admissions to hospital</b>	Though representing a small proportion of the COPD patient population, hospitalized COPD patients account for: <p><b>1 in 8</b> emergency admissions (130,000 per year), which represents:</p> <ul style="list-style-type: none"> <li>• The second largest cause of emergency admission;</li> <li>• One of most costly inpatient conditions treated by NHS;</li> <li>• More than one million 'bed days' each year in UK (2<sup>nd</sup> only to pneumonia)</li> </ul>	
<b>Median length of stay in hospital</b>	5 days	
<b>Within 3 months after admission</b>	34% re-admitted to hospital 14% die	
<b>Mean age of admission</b>	73 (men) 72 (women)	
<b>Patient occupancy</b>	90% live at home (36% on their own) 39% receive care at home (whether paid or unpaid)	
<b>Lung capacity</b>	Median predicted FEV <sub>1</sub> = 38% (for those with spirometry recorded in the last 5 years)	

Source of data: NICE (2010a) Clinical Guideline 101

**Table 6.5 Data: Economic impact**

<b>Total cost to NHS (2000/1)</b>	£491,652,000 direct healthcare costs
<b>Total cost to NHS (2004)</b> (according to CMO report (Department of Health 2004))	'Over £800million' direct healthcare costs (more than half of which relates to provision of care in hospital)
<b>Average cost per patient p.a. (2000/1)</b>	£819.42, of which: <ul style="list-style-type: none"> <li>• 54.3%- inpatient hospitalization</li> <li>• 18.6%- treatment</li> <li>• 16.4%- GP and specialist visits</li> <li>• 5.7%- A&amp;E visits and unscheduled contacts with GP/specialist</li> <li>• 5%- laboratory tests</li> </ul>
<b>Indirect costs of COPD p.a. (2000/1)</b>	24 million working days lost per annum Total direct and indirect costs: £982,000,000

Source of data: NICE (2010a) Clinical Guideline 101

Of note from the data presented, there is a clear time window between the initial signs of an exacerbation and subsequent hospitalisation. High readmission rates indicate suboptimal community care after an acute episode, which will become especially important as hospitals start to be penalised for re-admissions. The high economic impact indicates a strong case for measures to prevent exacerbations.

#### 6.2.4 (ii) *The Literature*

The literature base for COPD care is vast, especially relating to new drug treatments. The key themes from this evidence base are outlined in this sub-section, which is divided into exacerbations, self-management, quality of life, and finally evidence around biomarkers. These will substantiate claims made or relationships inferred in the headroom evaluation.

#### **Exacerbations**

Due to the significant role of exacerbations in COPD management, these play a big part in the economic evaluation described in the next section. Table 6.6 provides a summary of the main assertions from the literature, accompanied by the reports or investigations that explicitly verify or quantify these themes.



**Table 6.6 Literature for exacerbations**

<b>Assertion</b>	<b>Sources</b>
Exacerbations cause un-recoverable impairment of health status. Strategies that extend a patient's time free of exacerbation by recognising and reacting to exacerbations early are crucial.	Miravittles (2005); Anzueto (2010); Wedzicha & Seemungal (2007).
Exacerbations, especially those requiring hospitalisation, lead to quicker lung function decline (decline in FEV <sub>1</sub> ).	Cote, Dordelly & Celli (2007); Anzueto (2010); Anzueto, Leimar & Kesten (2009); Donaldson et al. (2002); Silverman (2007); Spencer et al. (2004); Soler-Cataluña et al.(2005); Almargo et al. (2002); Celli et al. (2008); Miravittles et al. (2000); Quint et al. (2008)
Higher exacerbation rates are associated with a significantly worse patient quality of life.	Osman et al. (1997); Spencer & Jones (2003); Seemungal et al. (2000); Miravittles et al. (2004); Miravittles et al. (2007); Kessler et al. (2006); Doll & Miravittles (2005); Haughney et al. (2005); Wang & Bourbeau (2005); Connors et al. (1996); Anzueto (2010); Seemungal et al.(1998); Quint et al. (2008); Budweiser (2008); Llor et al. (2008)
Many exacerbations go unreported, and therefore untreated. These 'ignored' exacerbations have a very detrimental impact on patient health, so strategies to increase recognition and early treatment of these exacerbations is paramount. Prompt treatment of an exacerbation is associated with improved recovery, reduced hospitalisations and greater quality of life.	Seemungal et al.(1998); Xu et al. (2010); Koff et al. (2009); Langsetmo et al. (2008); Wilkinson et al.(2004); Wedzicha & Donaldson (2003); Paggiaro (2004)
The cause of an exacerbation is difficult to determine, and could be either bacterial or viral. A means to differentiate between the two would limit the over-prescription of antibiotics, along with the associated costs and health risks of unnecessary usage.	Stolz et al. (2007); Brusse-Keizer et al. (2009)

### **Moving care to the patient**

The literature contains many investigations into the benefits of more proactive care. Table 6.7 is split into three parts, which present the main conclusions of studies investigating (1) home hospitalisation, (2) self-management strategies, and (3) remote monitoring devices. The ambitions of the near-patient monitor relate to all three of these.

Table 6.7 Literature for self-management and home care initiatives

Assertion	Sources
<p><b>Home hospitalisation offers equivalent or improved outcomes and reduces costs.</b></p> <p><i>[Home hospitalisation: treatment of exacerbation at home, or early discharge from hospital. Patients are usually supported by home-visits or phone consultations]</i></p>	<ul style="list-style-type: none"> <li>• <i>Puig-Junoy et al. (2007)</i>: The magnitude of cost saving increases with the patient's disease severity. For the 'average' patient, a <b>36% reduction in cost</b> was associated with home hospitalisation.</li> <li>• <i>NICE CG101 (2010a, p. 365)</i>—Recommendation 138: 'Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of caring for patients with exacerbations of COPD'.</li> <li>• <i>Ram et al. (2004)</i>: Readmission rates and mortality are not significantly affected, but the hospital at home scheme reduces health service costs (<b>about 50% reduction in cost</b>).</li> <li>• <i>Hernandez et al. (2003)</i>: Home care intervention is cost-effective, leading to better outcomes and at lower costs than conventional care (<b>38% lower cost</b>).</li> </ul>
<p><b>Patient self-management and integrated care improves outcomes and reduces costs</b></p> <p><i>[Self-management: patients are given education (and sometimes medicines) to react to changes in symptoms]</i></p> <p><i>[Integrated care: individually tailored care and coordination among care teams]</i></p>	<ul style="list-style-type: none"> <li>• <i>Effing et al. (2009)</i>: Self-treatment of exacerbations incorporated into a self-management program leads to fewer exacerbation days and lower costs (<b>23% fewer exacerbation days</b>).</li> <li>• <i>Bourbeau et al. (2003)</i>: Self-management compared with standard care resulted in: <b>39.8% fewer hospital admissions</b> for exacerbations, <b>41% fewer A&amp;E visits</b>, <b>58.9% fewer unscheduled physician visits</b>, and greater quality of life.</li> <li>• <i>Gadoury et al. (2005)</i>: Provision of education in self-management leads to significant reduction in hospitalisations (<b>26.9% reduction in all-cause hospitalisation</b>).</li> <li>• <i>Casas et al. (2006)</i>: Integrated care lowers hospitalisation rate</li> <li>• <i>Garcia-Aymerich et al. (2007)</i>: Integrated care reduces hospital readmissions.</li> </ul>
<p><b>Remote monitoring systems foster the earlier detection and treatment of exacerbations</b></p>	<ul style="list-style-type: none"> <li>• <i>Koff et al. (2009)</i>: The 'Health Buddy' was given to the 'proactive integrated care' (PIC) arm of the trial, which combined disease-specific education, self-management techniques, enhanced communication and remote home monitoring (measuring daily symptoms, oxygen saturation, FEV<sub>1</sub> and exercise capacity). Compared with the control group, patients experienced both improved QoL, and reduced healthcare costs (not statistically significant).</li> <li>• <i>Alonso (2004)</i>: A Spanish pilot of the 'e-Vital' project, which monitors patients' vital signs to detect symptom deterioration. Early results are encouraging: fewer emergency visits, improved QoL and lower costs.</li> <li>• <i>Sund et al. (2009)</i>: A feasibility study investigating patient compliance for remote daily monitoring of COPD patients, by means of an electronic diary and portable spirometer. The results were favourable: on average 77% of total study days had recordings, and COPD-related hospitalisations were significantly reduced compared with the previous year (<b>57% reduction</b>). However, the sample size was small.</li> <li>• <i>Trappenburg et al. (2008)</i>: A non-randomised study on the effect of a home based telemonitoring device, offering daily symptom surveillance. Hospital admission rates and exacerbations were reduced, as were hospital days (no significant changes in HRQoL).</li> <li>• <i>COPD National Strategy case study (Winter 2010, p. 79)</i>: The case study involved a telephone-based self-management service for people with chronic conditions (including COPD). The trial reported high patient satisfaction, and "substantial savings".</li> </ul>

Although the remote monitoring systems described above have produced positive results, the use of salivary diagnostics by the near-patient monitor would have the capacity to *predict* acute flare-ups before these are reflected in a patient’s symptoms, thus providing earlier warning and facilitating prompter treatment.

### Quality of Life

A search of the CEA registry (TMC Research 2012) was undertaken to identify utility weights associated with COPD. See Appendix 3 for details of all studies found in this search. The most commonly cited utility weights are those originally reported by Borg et al. (2004), summarised in Table 6.8.

**Table 6.8 Utility weights according to disease severity**

Mild (GOLD* I)	Moderate (GOLD II)	Severe (GOLD III)	V. Severe (GOLD IV)
0.897	0.755	0.748	0.549

\*GOLD: The Global Initiative for Chronic Obstructive Lung Disease

For utility loss during an exacerbation, the most frequently cited estimates are those originally reported by Paterson et al. (2000) and Spencer & Jones (2003), as described in Table 6.9.

**Table 6.9 Utility loss during an exacerbation**

	Utility loss
Moderate exacerbation*	15% drop in utility
Severe exacerbation**	50% drop un utility

\*An exacerbation requiring systematic corticosteroids and/or antibiotics

\*\*An exacerbation requiring hospitalisation

Sin and colleagues (2004) report a quality of life loss of 0.32 per acute episode, with mild episodes lasting one week, moderate two weeks, and severe four weeks.

## Biomarkers and COPD management

Three biomarkers are to be targeted by the biosensor. For the near-patient monitor to accurately *anticipate* the onset of an exacerbation pre-symptoms—distinguishing it from other remote monitoring devices—there must be a direct and established link between pathological changes reflected by the selected biomarker levels (as measured with the device), and a subsequent acute episode. This relationship will be directly investigated in clinical trials in due course, but the literature, outlined in Table 6.10, provides some indication of its feasibility.

**Table 6.10 Literature for biomarkers associated with COPD**

<b>Author</b>	<b>Observation</b>
Jones & Agusti (2006)	Discussion of biomarkers and their use as a marker for COPD and disease progression.
Cazzola et al. (2008)	A summary of the pulmonary biomarkers to have been associated with COPD in the literature. The author emphasises the need to elicit more information on the reproducibility and relevance of such measurements.
Christ-Crain et al. (2006)	Results are presented for an RCT in which procalcitonin concentration (a biomarker which is elevated in the presence of bacterial infections) in the blood is used to guide antibiotic prescription for patients with community-acquired pneumonia. Procalcitonin guidance (compared with the control group which received antibiotics according to usual practice) reduced total antibiotic exposure, prescriptions, and treatment duration. Outcomes in both groups were similar.
Stolz et al. (2007)	Results are presented for an RCT which compares standard antibiotic treatment of patients admitted to hospital with a COPD exacerbation, with procalcitonin-guided therapy (guided by serum procalcitonin levels, as above). Procalcitonin guidance significantly reduced antibiotic prescription and exposure. Clinical outcome was similar in both groups.
Yamamoto et al. (1997)	The results of this cohort study indicate that interleukin-8 (IL-8) concentration in sputum is closely associated with degree of airflow obstruction in COPD patients, so may serve as a marker for airway inflammation.
Nadel (2000)	This paper discusses Neutrophil elastase (ELA2) and its important role in the pathogenesis of COPD and its exacerbation.
Barczyk et al. (2004)	A study in which two markers—IL-8 and neutrophil activation marker myeloperoxidase (MPO)—are measured in induced sputum to investigate why inhaled glucocorticosteroids may decrease exacerbations.
Broekhuizen et al. (2006)	An investigation into C-reactive protein (CRP) levels as a clinical marker for acute systematic inflammation.
Vignola et al. (1998)	A study which shows that airway inflammation in chronic bronchitis and asthma is associated with high levels of active elastase.
Man et al. (2006)	This paper shows that (Serum) CRP measurements provide greater prognostic information for COPD patients than traditional markers alone (e.g. smoking, FEV <sub>1</sub> etc).

The headroom analysis that follows is based on the optimistic (but plausible) beliefs of the innovator, which support the predictive capacity of the near-patient monitor.

### 6.3 Identifying the 'Headroom' for development

The headroom method considers the economic case for an innovation, by comparing it to current practice in terms of its cost implication to the health service and its health benefit (to which a monetary value is attached by using NICE's cost-effectiveness threshold). By considering the net effect of these two parameters, the potential reimbursement value of the innovation is estimated. This can, however, be an iterative process. It is possible to initially consider the cost saving effect of a device in isolation, to observe whether this generates sufficient 'headroom'. This seems appropriate in this instance for three reasons:

1. The key economic and clinical driver of this innovation is the **reduction in emergency admissions**, achieved by monitoring health status and reacting early to flare-ups. Exacerbations treated in hospital make up over 50% of the overall economic burden of the disease, so shifting treatment to an earlier stage where events can be treated at home would offer significant savings.
2. The device could provide cost-savings and health benefit both in the short term (reducing the impact of exacerbations) and long term (slowing disease progression). Whilst important, the long term effects are less immediately tangible, and are likely to be realised a long time into the future. Therefore, it is perhaps more pertinent for today's decision-maker with today's budget and today's cohort of COPD patients, to take a more **short-term perspective**.

3. Thirdly, the current climate surrounding NHS procurement is that of tightened budgets and cautious spending. Therefore, justifying the case for the **cost-saving** potential of a device (coupled with equivalent or improved health outcomes) will be important. That health outcomes would be at least equivalent by using the device is easily justifiable, as it simply provides more information on which to base treatment decisions.

The following analysis thus considers the short-term cost-saving potential of the device from the reduction in emergency hospital admissions, to see whether this generates sufficient ‘headroom’ to justify development.

As the near-patient monitor does not represent a simple replacement of a current technology, the potential scale of distribution is not clear-cut; despite resonating well with current ideals for change within COPD care, it would likely represent a significant shake-up in the pathway. Therefore, headroom is considered under three scenarios of deployment. The first two scenarios consider the headroom for the near-patient monitor based on a reduction in hospital visits: in scenario one the device is distributed according to yearly exacerbation rate, and in scenario two according to average yearly *hospitalised* exacerbation rate. This is followed by the more aspirational scenario three, where the device is rolled-out to all those diagnosed with COPD, the value of which is explored in terms of savings in primary care resources as well as hospital care.

The analysis is split into three sections. The first presents the data which inform the base-case assumptions for all forthcoming scenario evaluations. Section two provides the analysis for the three scenarios described. Where previous applications of the method have stopped at the headroom calculation, section 6.3.3 ‘Headroom: The Decision’ extends the analysis by interpreting the headroom output, considering, for example, the trade-off between development and production costs, and presenting further analysis of distribution strategies.

### 6.3.1 Data: Base-case assumptions

The data used for headroom calculations are summarised in Table 6.11, and described below.

**Table 6.11 Summary of base-case assumptions for COPD patients in the UK**

<b>Number of diagnosed COPD patients</b>	<b>900,000</b>
<b>Average number of exacerbations per year per patient</b>	<b>1</b>
<b>Proportion of exacerbations that are hospitalised</b>	<b>20%</b>
<b>Cost of an exacerbation</b>	<b>£36 – Non-hospitalised</b> <b>£2,539 – Hospitalised</b>
<b>Breakdown of average cost per patient (for Scenario 3)</b>	<i>See Table 6.13</i>

- **COPD patient population (diagnosed): 900,000**  
(Healthcare Commission 2006;NICE 2010a)
- **Average yearly exacerbation rate: 1**

Based on the data presented in Table 6.12 and the opinion of the clinical expert, this is suggested to be an appropriate (and conservative) initial estimate.

**Table 6.12 Exacerbations per year across disease categories**

<b>Source</b>	<b>Mild (FEV<sub>1</sub>≥80%)</b>	<b>Moderate (FEV<sub>1</sub> 50-79%)</b>	<b>Severe (FEV<sub>1</sub>30-49%)</b>	<b>V. Severe (FEV<sub>1</sub>&lt; 30%)</b>
Spencer et al. (2005)	0.79		1.22	1.47
	<i>Notes: This study uses slightly different disease stage categorisation (given here are their 'mild, moderate and severe' exacerbation estimates: mild: ≥50%, moderate:35-49%, severe: &lt;30%.</i>			
Quint (2010)	2	2.16	2.52	2.73
	<i>Notes: Quint describes baseline characteristics of a cohort of 356 COPD patients.</i>			
Calverley et al. (2007)	1			
	<i>Notes: This figure represents the baseline average exacerbation rate in the previous 12 months prior to screening (self-reported) over all treatment groups in the TORCH study<sup>17</sup>. This is cited frequently in the literature (NICE 2010a;Wedzicha &amp; Seemungal 2007). Average FEV<sub>1</sub>%predicted in this study was around 44, indicating that the average patient in this cohort falls within (the less serious end of) the 'severe' category.</i>			

<sup>17</sup>This was the 'Towards a Revolution in COPD Health (TORCH) trial: a double-blinded RCT which compared combination therapy of salmeterol and inhaled fluticasone propionate, with usual care.

- **20% of these exacerbations are hospitalised**

In describing the baseline characteristics of participants in a large COPD trial (the ‘TORCH study’), Calverley et al. (2007) find an average of 0.2 exacerbations per year per patient requiring hospitalisation, representing 20% of the average annual exacerbation rate. This source is also used to populate NICE’s CG101 cost-effectiveness model (NICE 2010a, p. 566).

Hospitalisation rate estimates elsewhere in the literature are inconsistent. In reality this rate will vary between patients, as the severity of an exacerbation is strongly associated with disease staging (Almagro et al. 2002; Miravittles et al. 2000). From the information available at the time of writing, this 20% estimation seems the most validated and cited estimate.<sup>18</sup>

- **Cost of an exacerbation: £36 (non-hospitalised) or £2,539 (hospitalised)**

The source of these estimates is the NICE clinical guideline for COPD (NICE 2010a), inflated using UK healthcare inflation indices to 2009/10 prices (last indices available at the time of analysis)<sup>19</sup>. The cost estimate for non-hospitalised exacerbations was based on a UK costing study, whereas that for a hospitalised episode was a weighted average for all categories of COPD hospitalisations, principally using 2007/8 NHS reference costs (see Appendix M of the NICE guideline for more details (NICE 2010a, p. 576)).

- **Breakdown of the overall costs for the average COPD patient**

This data (source: (NICE 2010a)) will relate to scenario three—the community roll-out—which considers the ‘average’ COPD patient and their cost of care. There are 1.4 million GP consultations for COPD every year (about 1.5 per patient) (Healthcare Commission

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<sup>18</sup>Note: Spencer et al. (2005) report a hospitalisation rate for exacerbations of only 10% for severe patients and lower for those with less severe COPD.

<sup>19</sup> The Hospital & Community Health Services (HCHS) Pay & Prices Index (PSSRU 2010) is used to inflate to current prices throughout this evaluation



2006;NICE 2010a), but a reliable and consistent estimate of their cost has been difficult to obtain. Britton (2003) provides a useful breakdown of costs which is used in the NICE COPD clinical guideline (NICE 2010a). These data are summarised in Table 6.13, presented in their original form (in 2000/1 prices), alongside their adjustment to 2009/10 prices (all rounded to nearest pound).

**Table 6.13 Breakdown of cost per patient attributable to particular services**

Average cost per patient per annum	Breakdown	Percentage representation	2000/1	2009/10
£819 (2000/1 prices) <b>£1,132</b> (2009/10 prices)	a) Inpatient hospitalisation	54.3%	£445	£615
	b) Treatment	18.6%	£152	£211
	c) GP and specialist visits	16.4%	£134	£186
	d) A&E visits and unscheduled contacts with GP / specialist	5.7%	£47	£65
	e) Laboratory tests	5%	£41	£57

### 6.3.2 Headroom analysis

Using the base-case assumptions outlined, the headroom offered under three distribution scenarios is considered.

#### 6.3.2 (i) Scenario 1: Distribute according to number of exacerbations per year

The value of the near-patient monitor will vary according to its user. Table 6.14 describes the exacerbation-related costs for the ‘average’ COPD patient, who experiences one exacerbation per year (thus representing the ‘base-case’).

Table 6.14 Base-case cost of exacerbations for ‘average’ COPD patient

	Average exacerbations per year	Cost (£)
<b>Non-hospitalised</b>	0.8	£36
<b>Hospitalised</b>	0.2	£2,539
	Average cost per patient	£537
	Total cost of exacerbations (based on a COPD population of 900,000):	£482,940,000
	Total cost of <i>hospitalised</i> exacerbations:	£457,020,000

The total cost of hospitalised exacerbations (£457 million) provides some reassurance that these base-case estimations are feasible; hospitalisations represent just over half of total COPD healthcare costs (Burney 2006;NICE 2010a;Soler-Cataluña et al. 2005), which in 2004 was around £800 million (Department of Health 2004)—£935 million when inflated to 2009/2010 prices.

The headroom analysis is based on one main assumption: **the near-patient monitor will halve hospitalisations**. By treating flare-ups earlier, 50% of acute episodes will be treated at home rather than in hospital. This was thought by the innovator to be a realistic consequence of the device’s proactive patient management approach, considering also that full compliance would not be achieved. The literature presented in section 6.2.4 included studies of specific education programs or management schemes, which reported reductions in hospitalisation rate or cost that ranged from 23% to 57%. Although most estimates were below 50%, it is thought that the added predictive capacity of this technology makes this assumption feasible.

The device may, in addition, make hospital care more efficient, by providing richer patient data and thereby allowing treatment to be more timely and appropriate.<sup>20</sup> By also improving patient supervision in the community (allowing for earlier hospital discharge), hospital length of stay (LOS) should be significantly reduced. As a result, a 50% reduction in the average cost of a hospital episode was initially considered to be a reasonable expectation. However, this could involve double-counting; if hospitalisations are reduced by half, then the cohort of exacerbators still attending hospital will be the more serious (and more costly) patients. Therefore, halving the cost of hospitalisations implies cutting LOS by much more than half (the ‘average’ LOS of those still attending hospital will be higher than the average of the previous, larger cohort). By assuming that the average cost of a hospitalised exacerbation remains constant, we are indicating a (more feasible) reduction in LOS for those more serious patients with whom we are left.

## Results

Table 6.15 Cost of exacerbations *with* device for ‘average’ COPD patient

	Average exacerbations per year	Cost (£)
<b>Non-hospitalised</b>	0.9	£ 36
<b>Hospitalised</b>	0.1	£2,539
	Average cost per patient	£286
	Total cost of exacerbations:	£257,670,000
	% of original cost	53%
	<b>Headroom (£):</b>	<b>£225,270,000</b>
	<b>Headroom per person or device (£ / year)</b>	<b>£250</b>

<sup>20</sup> Currently, very little clinical data are available to clinicians treating patients in hospital for a COPD exacerbation. The National COPD Audit 2008 found that only 55% of those admitted to hospital had spirometry results recorded in the last 5 years (RCP 2008b).

The average headroom per device (per year) is £250 when distributed to all 900,000 COPD patients. Of course, its value will be higher when used by patients who experience more frequent exacerbations. Table 6.16 provides the headroom per patient based on their yearly exacerbation rate:

**Table 6.16 Headroom based on number of exacerbations per year**

<b>Base-case</b>				
No. of exacerbations per year	Non-hosp (£36)	Hosp (£2,539)	Total cost per person	
1	0.8	0.2	£537	
2	1.6	0.4	£1,073	
3	2.4	0.6	£1,610	
4	3.2	0.8	£2,146	
<b>With device (hospitalisations halved)</b>				
No. of exacerbations per year <sup>21</sup>	Non-hosp (£36)	Hosp (£2539)	Total cost per person	<b>Headroom per device (£/year)</b>
1	0.9	0.1	£286	<b>£250</b>
2	1.8	0.2	£573	<b>£500</b>
3	2.7	0.3	£859	<b>£750</b>
4	3.6	0.4	£1,145	<b>£1,000</b>

These figures represent the headroom (per device per year) generated for each group individually. However, a real decision-maker is likely to offer the device to those with a yearly exacerbation rate of *X or more*. To calculate the cost saving effect of this strategy (which would be a weighted average), one would require the distribution of exacerbation rates in the target population. Due to the strong regional differences in COPD severity, this would

<sup>21</sup> There will obviously be some patients who experience zero exacerbations per year. As the device would imply no cost saving for these patients, this is omitted from the table. The ‘average of one exacerbation per year’ scenario described initially, includes these patients.

be more appropriately considered locally (Department of Health 2004;Healthcare Commission 2006;NICE 2010a).

It should be noted that illustrating ‘headroom’ by patient subgroup predicates perfect price discrimination. In reality this is unlikely, and the price may be based on the subgroup with the fewest exacerbations (further discussion of this is reserved for section 6.3.3).

### **Rationale for this approach**

The most obvious way to categorise COPD patients is by disease severity (lung capacity based on FEV<sub>1</sub>% predicted); the literature finds severity to be strongly associated with (a) frequency of exacerbations and (b) severity of exacerbations (see literature section 6.2.4 (ii)). The analysis presented here, however, divides the patient population according to their predisposition to experiencing exacerbations. Despite the strong association between lung capacity and exacerbations, a large observational trial<sup>22</sup> presented by Hurst et al. (2010) demonstrates that the most important predictor of frequent exacerbations is a history of exacerbations, indicating there to be an ‘exacerbation-susceptibility phenotype’ that may be independent of underlying disease severity. This should be reflected in how interventions that target exacerbations are directed (Hurst et al. 2010). The trial also finds exacerbation frequency to be relatively stable, further complementing the approach taken.

#### *6.3.2 (ii) Scenario 2: Distribute according to number of hospitalised exacerbations per year*

Given the huge costs attributable to hospitalised COPD episodes, commissioners will be keen to limit these. However it may be appropriate (at least initially) to focus resources on patients who place the largest financial burden on the health system: those who regularly have

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<sup>22</sup> The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECCLIPSE).

exacerbations requiring hospitalisation. Three situations are explored: a) 100% of hospitalisations are avoided, b) 75% avoidance and c) 50% avoidance (turning these episodes into non-hospitalised exacerbations, for which there is a significantly lower cost).

As in the previous scenario, it is assumed that the cost of an ‘average’ hospitalised episode remains constant.

## Results

**Table 6.17 Headroom based on number of hospitalised exacerbations per year**

	A patient's current number of <b>hospitalised</b> exacerbations per year	a) 100% avoidance	b) 75% reduction	c) 50 % reduction
Headroom per device (£/year)	1	£2,503 *	£1,877	£1,252
	2	£5,006	£3,755	£2,503
	3	£7,509	£5,632	£3,755
	4	£10,012	£7,509	£5,006

\*Example of calculation: **£2,539** (cost of avoided exacerbation) - **£36** (cost incurred of a non-hospitalised exacerbation) = **£2,503**

Table 6.17 displays the headroom per device per year according to a patient's yearly hospitalisation rate, and the degree to which these admissions are reduced. This differs from scenario one only in that the COPD patients being considered are those who are more regularly hospitalised. Whilst this strategy generates much higher headroom per device, the fixed costs of development must be spread between fewer units. Consideration of this trade-off is presented later.

## Rationale for this approach

The literature suggests that the lead-in phase of an exacerbation provides sufficient opportunity to treat early and avoid admissions. The value of this will be higher for those patients who are currently hospitalised more regularly.

It should be noted that for scenarios one and two, value is calculated based on the number of exacerbations a patient would experience in the next year. Clearly the device cannot be assigned retrospectively, but as described previously, exacerbation rate is strongly associated with previous exacerbations.

### 6.3.2 (iii) Scenario 3: Community Roll-out

Improving self-management is likely to reduce demand of both primary and secondary services. The community roll-out strategy is an extension of scenario one which considered the ‘average’ COPD patient (assuming full distribution), but widening the perspective beyond hospitalisations. Whilst inpatient hospitalisation poses the most substantial economic burden within COPD, A&E visits and unscheduled contact with GPs or specialists also represent important contributors to the cost of unscheduled emergency care. Additionally, the data from a national COPD audit suggest ‘*frequent exacerbation and high usage of primary care health resources in the 12 months leading up to admission*’ (RCP 2008a, p. 11). 74% of patients hospitalised for an exacerbation within the audit period had made contact with their GP in the month prior to admission; 31% had made three or more contacts in that time.

The break-down of costs for the ‘average’ COPD patient (as presented in the NICE clinical guideline) is used as the base-case for this scenario (see Table 6.13 on page 129). It suggests that 16.4% of the COPD budget is attributable to GP and specialist visits, 5.7% to A&E visits and unscheduled contacts with GP/specialist, and 5% to laboratory tests. The near-patient monitor could reasonably create savings in all of these areas, particularly for unscheduled healthcare visits. However, due to the paucity of information on the regularity of (scheduled) GP contacts across the whole COPD population, estimating potential impact on these would be too speculative (though the innovator believes that GP/specialist visits *would* be reduced, due to the constant monitoring and more informed GP-patient interactions).

Treatment costs are presumed to remain constant.<sup>23</sup> The following assumptions are made for the community roll-out scenario:

- Reduction in hospitalisation costs associated with COPD by half;
- Elimination of A&E visits and unscheduled contacts with the GP / specialist (or to be reduced by 75%);
- Significant reduction in the need to send samples for laboratory tests (generally diagnostic in nature), resulting in negligible lab costs, or a reduction by 75%.

## Results

**Table 6.18 Headroom based on Community Roll-out**

	Base-Case	With Device: 100% cut in emergency contacts / lab tests	With Device: 75% cut in emergency contacts / lab tests	<i>Costs relating only to hospitalisations (as in scenario 1)</i>
a) Inpatient hospitalisation (costs cut by 50% with device)	£615	£308	£308	£308
b) Treatment	£211	£211	£211	£247*
c) GP and specialist visits	£186	£186	£186	£186
d) A&E visits and unscheduled contacts with GP or specialist	£65	£0	£16	£65
e) Laboratory tests	£57	£0	£14	£57
Average cost per patient p.a	£1,132	£704	£734	£863
<b>HEADROOM per person per year</b>	-	<b>£428</b>	<b>£398</b>	<b>£269</b>

\*£36 added for incurred treatment cost for treating exacerbation at home as in scenario 1

<sup>23</sup> Although earlier treatment at home may increase ‘Treatment’ expenditure, this may be cancelled out by the reduced spending on antibiotics where these are not appropriate. The cost of a non-hospitalised episode used for the last scenario is not used here, as no assumptions about frequency of exacerbation are made in this case, and inconsistency in data sources may invalidate the analysis.



Table 6.18 describes the savings associated with the community roll-out scenario based on 100% or 75% cuts in the cost of unscheduled primary / secondary care visits and lab tests, which generate £428 and £398 of 'headroom' (per device per year) respectively. Presented alongside this is a re-estimation of the model assumptions for scenario 1. That the headroom figures derived are relatively similar (£269 versus £250) provides some assurance in the two sources of data.

### **Rationale for this approach**

The community roll-out scenario represents most comprehensively the advantages developed in section 6.2 of such a technology. The Primary Care Respiratory Society (previously the General Practice Airways Group) outlined three key aspects of optimal exacerbation management, all of which are addressed in scenario three (GPIAG 2008):

1) The key cost-contribution of those exacerbations requiring unscheduled care is noted, which includes GP visits, out-of-hours visits and A&E attendance, as well as hospital admission.

2) *'...reducing the frequency and severity of an acute exacerbation of COPD by adopting a proactive approach centred on the patient will have benefits not only to the patient but also makes good financial sense.'* (GPIAG 2008, p. 1).

3) A 'proactive' approach should be managed in primary care, and should aim to reduce the frequency of exacerbation, provide self-management advice, assess and manage the exacerbation, and ensure appropriate follow-up post-exacerbation.

The strategy also fits in with the imminent changes to the NHS which will force hospitals to become leaner and to transfer services into the community (Department of Health 2010b).

### 6.3.3 Headroom: The Decision

Table 6.19 summarises the headline headroom figures, based on the most conservative of the assumptions considered in each scenario.

**Table 6.19 Summary of headroom figures under three scenarios**

Scenario	Key assumptions	Headroom per person (device) per annum	
		Exacerbations p.a	Headroom
1. Distribute according to number of exacerbations	Cost-saving based on avoided hospitalisations alone. Hospitalisations halved	1	<b>£250</b>
		2	£500
		3	£750
		4	£1,000
2. Distribute to those who exacerbate regularly in hospital	Cost-saving based on avoided hospitalisations alone. Hospitalisations halved	Hospitalised exacerbations p.a.	Headroom
		1	£1,252
		2	£2,503
		3	£3,755
4			£5,006
3. Community Roll-out (This is the extended version of scenario one's 'average' patient)	Distributed to all 900,000 patients diagnosed with COPD. Break-down of spending on 'average' COPD patient as estimated in the NICE CG101 Device allows a) hospitalization costs to be halved, and b) A&E visits, unscheduled contact with GPs/specialists, and lab costs to be cut by 75%	£398	

To support a favourable development decision, headroom must exceed total costs to the manufacturer. These must include manufacturing costs, any consumables, and making back the fixed costs in its development and production. For all three strategies described, headroom has been presented as a monetary value per patient (or device, assuming individual use) per year. By accounting for the expected device lifetime, we can consider the headroom per *device* (thus estimating the MRP under the assumptions utilised).

The innovator expects the device to last around five years. The present value (PV) of the cost saving (applying a discount rate of 3.5%)<sup>24</sup> for scenario one's 'average' patient is therefore:

$$PV \text{ cost saving} = \text{£}250 + \frac{\text{£}250}{(1 + 0.035)^1} + \frac{\text{£}250}{(1 + 0.035)^2} + \frac{\text{£}250}{(1 + 0.035)^3} + \frac{\text{£}250}{(1 + 0.035)^4}$$

$$= \text{£ } 1,168$$

Table 6.20 presents a summary of headroom figures per device, representing the (discounted) value over five years for each scenario.

**Table 6.20 Headroom per device under three scenarios**

Scenario	Headroom per device (life expectancy: 5 years)	
1. Distribute according to number of exacerbations	Exacerbations p.a.	MRP
	1	£1,168
	2	£2,341
	3	£3,509
	4	£4,678
2. Distribute to those who exacerbate regularly in hospital	Hospitalised exacerbations p.a.	MRP
	1	£5,851
	2	£11,697
	3	£17,547
	4	£23,393
3. Community Roll-out	£1,860	

Whilst in the literature the analysis ends here, this section explores the potential interpretation of these results and some specific trade-offs that can be considered. The decision of if / under what circumstances the device should be developed must include the following considerations:

1. *How many people will you give it to?* This will be important because the size of the target market will represent the number of units over which the fixed costs of

<sup>24</sup> The NICE "reference case" stipulates that cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. The annual discount rate should be 3.5% for both costs and benefits (NICE 2008b).

development / production can be shared. The more serious the condition of a patient the greater the headroom per device, but the more limited the scope for sharing sunk costs and making use of economies of scale.

2. *Expected device costs.* This must include the expected cost of the near-patient monitor itself once in ‘full’ production, and also the annual cost of consumables.

If the reimbursement potential is sufficient to cover costs, a favourable decision for development can be justified. If not, then it must be considered by how much the reimbursement need falls short of the projected MRP for the application considered. If this were the case, further quantification of additional value may be sought by considering improvements in quality of life and slowing disease progression, to see whether these would turn the project into a viable investment.

### *6.3.3 (i) Decision-making for manufacturers: Some economic analysis*

Although savings within primary care services are anticipated, these are less easily quantified than the effect of reduced hospitalisations alone. The roll-out of such a device (in any of our scenarios) will incur additional costs within primary care, for example from providing patient training in its use, and monitoring its output which may additionally require some re-organisation of services. Even though these additional costs are expected to be more than offset by reduced GP visits (scheduled and unscheduled), these are difficult to quantify at this stage. Therefore, the analysis below considers the simpler scenarios one and two, where the impact on primary care services is overlooked and it is assumed hospitalisations are halved. Firstly, the potential trade-off between fixed and variable costs at different levels of headroom is outlined. This is followed by a value-based pricing exercise, considering headroom to represent the NHS’s WTP and thus constructing a demand curve.

## Mapping 'headroom' in terms of its component costs

The approach to exploring the trade-off between the fixed costs of development and the variable costs of production was outlined in chapter 4. By equating the MRP to the maximum total cost per device, the NPV of the project would be zero. This therefore represents the maximum cost to the manufacturer per device for its development to be feasible, and must cover both the variable costs of production (materials, production, labour, selling costs etc. once in full production) and also the fixed development costs (including land rent, capital upkeep, and crucially the costs of development<sup>25</sup>).

At such an early stage, there will clearly be uncertainty around these costs, but as an exercise it is possible to map the relationship between the two. By inputting various potential levels of variable cost, Table 6.21 considers the maximum allowable development cost of the device under scenario one (device is given to a 900,000 COPD population who has on average one exacerbation per year, with 20% of these being hospitalised; headroom: £1,168 per device)<sup>26</sup>.

Table 6.22 considers scenario two, where the device is distributed according to hospitalised exacerbation rate. Unfortunately, patient numbers stratified by hospitalisation rate were difficult to obtain, so I use the assumptions described in scenario 1 to estimate total number of hospitalised exacerbations ( $1 \times 0.2 \times 900,000 = 180,000$ ), and assume these all represent different patients (one hospitalised exacerbation per year; headroom: £5,851 per

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<sup>25</sup> At this early stage, investment in R&D can be considered a fixed cost to the manufacturer, which only becomes sunk at launch (and must therefore feature in the decision to develop).

<sup>26</sup> As explained, the headroom figure of £1,168 has been calculated by adding the discounted value accumulated over the 5 year lifetime of the device. Although this represents the value of the device to the buyer when they purchase it at time 't', using this to represent the future monetary benefit to the manufacturer now (at time t-1) may be misleading, as these benefits are to be accrued later than the development costs incurred at t-1. This means that relatively more weight should be attached to the sunk costs of development; although the headroom figure should therefore be discounted at an appropriate rate—the internal rate of return of the company—this will vary according to the developer, and therefore is not attempted here.

device). This is clearly a simplification as among those admitted will be repeat hospitalisations, implying a market size of less than 180,000. However, for illustrative purposes, a comparison of these two scenarios is presented.

**Table 6.21 Headroom1: Distribute to all COPD patients**

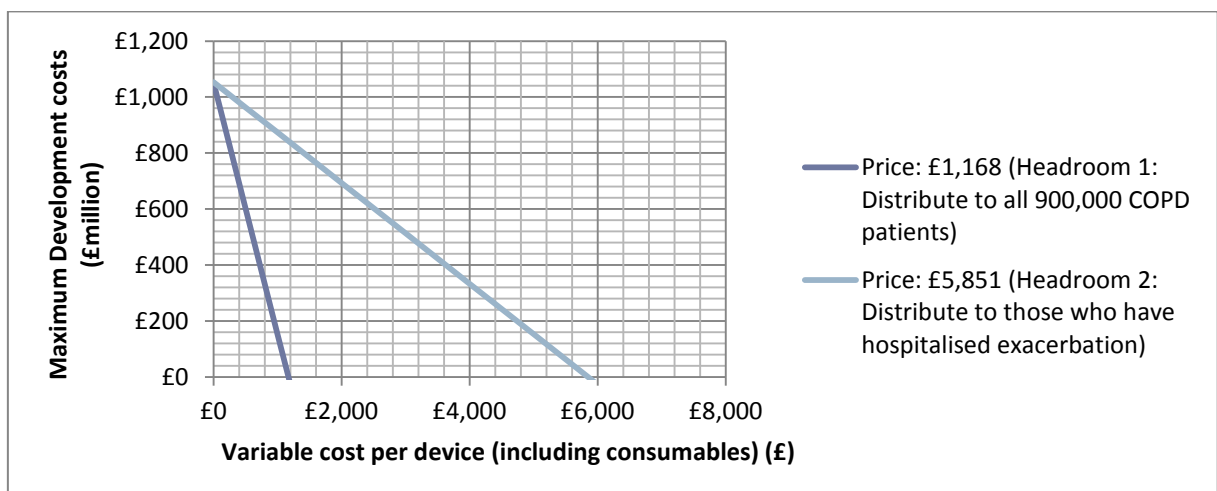
Headroom (per unit per year): £250 Headroom over 5 year expected device lifetime [MRP]: £1,168 Number of patients: 900,000		
<b>Total cost per unit (TCPU)</b>	<b>Variable cost per unit (VCPU)</b>	<b>Maximum development costs</b> Total fixed costs= TC [TCPU*900,000] – TVC [VCPU*900,000]
£1,168	£0	£1,051,200,000
£1,168	£100	£961,200,000
£1,168	£250	£826,200,000
£1,168	£500	£601,200,000
£1,168	£750	£376,200,000
£1,168	£1,000	£151,200,000
£1,168	£1,168	£0
£1,168	£1,250	- £73,800,000
£1,168	£1,500	- £298,800,000

**Table 6.22 Headroom 2: Distribute to those who experience a hospitalised exacerbation (one per year)**

Headroom (per unit per year): £1,252 Headroom over 5 year expected device lifetime [MRP]: £5,851 Number of patients: 180,000		
<b>Total cost per unit (TCPU)</b>	<b>Variable cost per unit (VCPU)</b>	<b>Maximum development costs</b> Total fixed costs= TC [TCPU*180,000] – TVC [VCPU*180,000]
£5,851	£0	£1,053,180,000
£5,851	£500	£963,180,000
£5,851	£1,000	£873,180,000
£5,851	£2,000	£693,180,000
£5,851	£3,000	£513,180,000
£5,851	£4,000	£333,180,000
£5,851	£5,000	£153,180,000
£5,851	£5,851	£0
£5,851	£6,000	- £26,820,000

A result of the simplification made for scenario 2's population size is that both scenarios actually consider the same population of exacerbators, the difference being that scenario 2

involves supplying the device to this group only (and charging a higher price to reflect its higher value), and scenario 1 involves supplying the device to everyone and charging its average value. This means that permissible development costs given a zero variable cost (this is also equal to total revenue: price\*quantity) should be the same for both scenarios (the reason they are not must be due to rounding in the calculation of prices). If better information were available on the population size for scenario 2, it would be evident that restricting the target market would increase headroom but limit the ability to share the fixed costs of development, and the optimum strategy would depend on the variable costs of production. However, given the assumptions made above (and that the price is set at the theoretical MRP for both groups) scenario 2 is more attractive: for any given variable cost, what's left over for development (or future profit) is larger. Figure 6.2 depicts this graphically.



**Figure 6.2 Relationship between variable cost per device and maximum allowable development costs (assuming NPV=0)**

The wide distribution strategy lies everywhere below the second scenario, meaning that for any given variable cost, the maximum allowable development cost is greater for ‘Headroom 2’ than ‘Headroom 1’. If, for example, the developer believes that the variable cost per device once in full production will be £1,000, this allows for development costs of £151 million for

scenario 1 and £873 million for scenario 2. This assumes full uptake (unrealistic in reality), a revision of which would simply pivot the curves in Figure 6.2 downwards, implying lower allowable development costs for any given variable cost.<sup>27</sup>

## 6.4 Summary

Assuming that the near-patient monitor will allow for the accurate monitoring of a patient's symptoms and pathological changes, the literature suggests that this would improve patient prognosis. In its exacerbation-predicting function, the device may be viewed as a diagnostic test. The analysis has implicitly assumed sensitivity and specificity to be 100%, but the impact of false positives (patients taking extra medication unnecessarily), and false negatives (being assured no action is needed when the patient should in fact receive medical treatment) should be considered in the future when clinical data are generated. Compliance issues should also be explored.

The second crucial assumption was that hospitalised exacerbations would fall by 50%. As well as being supported by the literature, the innovator believed this to be realistic based on her experience treating COPD patients within the current care pathway (the baseline). One issue, however, is the possibility of a changing baseline. The positive results from other studies demonstrate the magnitude of work being undertaken in the area that could lead to real benefits in the system. Although these initiatives are currently not widespread, developments may eventually alter the baseline, in which case the 'headroom' for the near-patient monitor may be reduced.

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<sup>27</sup> As an exercise, one could calculate the additional QALYs required to make the reimbursement potential equal for both scenarios. For example, if the variable cost were £1,000 and we assume a WTP of £30,000 per QALY, then for scenario 1 to fill the reimbursement gap (so that the allowable development costs are equal to scenario 2) the wider distribution strategy would have to generate 24,066 *extra* QALYs.



Throughout the scenarios presented in section 6.3.2, headroom was expressed per patient (or device) per year, in terms of the value created for the NHS and therefore the maximum reimbursement opportunity, which should include any net change in service costs. In subsequent analysis where development costs are considered (section 6.3.3), the headroom is considered to be maximum reimbursable *price* of the device itself. However, if extra service costs associated with the device (e.g. maintenance, training, safety checks, a clinical member of staff to monitor results, etc.) exceed primary care cost savings (e.g. from fewer GP contacts), then this may not be appropriate, and the net effect of these should be considered alongside the ‘headroom’ in order to isolate price. In the analysis these two effects were implicitly assumed to be of equal magnitude; this will require further research when more is known about the technology, its exact form, and how disruptive it would be to the current pathway.

The final section of this chapter considered distribution strategies, and how targeting different subgroups would impact MRP and allowable development costs. From June 2014 value based pricing (VBP) will come into effect; evaluating bodies for new pharmaceuticals will stipulate the price at which they would buy a new drug, based on the value it creates for the NHS (Department of Health 2010a). Price will therefore be set at the maximum WTP—the parameter that the headroom exercise aims to predict. Indeed, the VBP literature explores the concept of cost-effectiveness differing by patient subgroup, and the possibility of manufacturers being able to choose a level of coverage which would maximise revenue (Claxton 2007). The distribution exercise performed above was illustrative only, as altering the market size assumptions would alter the results. Additionally, although distribution scenario 1 was intended to be illustrative of an inclusive strategy, 100% market capture is very unlikely. As well as the near-patient monitor representing a complex example of the

headroom method's application—posing a change in the whole clinical pathway rather than a simple exchanging of treatments—this may also present a potential barrier to adoption, requiring a large shake-up in service provision.

The potential 'scenarios' are extensive, and it would be unreasonable to attempt to quantify them all. One high-value application may be its use as a tool for GPs or specialists to monitor patients during visits. This could be especially important considering the imminent changes to the NHS, where care is moving out of hospitals and into the community. Specialists will travel to local surgeries, making high-tech equipment (easily on hand in a hospital setting) less accessible. The value per device in this scenario, which would no longer be on a per-patient basis, could be very high.

Largely ignored by this analysis is the QoL impact of ameliorating exacerbations. The summary of the literature showed that these benefits are likely to be positive and tangible, and so should contribute to the case for the near-patient monitor (and possibly be quantified later on). However, this case study demonstrated that a complete analysis may not be necessary to support an investment decision; there was no need to extend beyond the initial simplified scenario, as (according to the developer) sufficient headroom was identified to warrant development when considering costs alone. Other factors omitted from the analysis, being currently outside the remit of healthcare decision-makers, include the wider benefits to society (e.g. fewer lost working days, less burden on carers, etc.).

COPD is a notoriously difficult disease to assess in terms of the potential cost-effectiveness of treatments. The headroom analysis dealt only with the short-term cost-saving prospects of the near-patient monitor. A much more complicated modelling approach would

be required to consider the long term effects of slowing disease progression.<sup>28</sup> Mapel and Roberts (2012) provide a recent review of the literature, finding half of the cost-effectiveness studies identified to be based on observational data, a quarter on RCTs, and the remaining quarter to be modelling studies. A substantial problem identified by the authors in relation to modelling in COPD is the use of FEV<sub>1</sub> severity stages to model disease progression; due to the heterogeneity within disease state populations, in particular relating to propensity to exacerbate, dividing the population in this way could be misleading (this has now been acknowledged in the 2011 GOLD strategy: '*FEV<sub>1</sub> is an unreliable marker of the severity of breathlessness, exercise limitation, and health status impairment.*' (GOLD 2011, p. vii)). The literature fails to provide many good alternatives to markov modelling for COPD; although patient-level simulation may provide the best way to model outcomes (as this can incorporate a patient's history of events), this would require a huge data input.

The analysis provided in this chapter presents a (necessarily) very simple model of potential cost savings, which only deals with the short term. The headroom method aims to tap into the reimbursement opportunity, and the (sub-optimal) reality is that purchasers can be by nature at least somewhat short-sighted. As evidence for the technology accumulates, assumptions and estimates may be updated in order to paint a more accurate picture of its impact. However, by presenting an initial estimate of the reimbursement potential, development may be informed by this value.

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<sup>28</sup> Rutten, van Mólken and Lee provide a review of COPD-related economic models (Rutten, van Mólken & Lee 2006). At that time, there had been five studies using cost-effectiveness models in COPD, all of which were Markov models: Sin, Golmohammadi & Jacobs (2004), Borg et al. (2004), Spencer, Briggs, Grossman & Rance (2005), Oostenbrink, Rutten, van Mólken, Monz, & FitzGerald (2005), and Hoogendoorn et al. (2005).

In relation to her own projected costs, the innovator believes the headroom analysis to provide a favourable case for development. The utility of the method, its scope, and the impact it has had for the innovator is discussed in the interviews chapter 9.

This case study was in some ways exploratory, both illustrating the application of the method to a complex pathway-changing device early on, as well as exploring possible interpretations of headroom. The ensuing case studies benefit from the experience gained in this one, in: approaching the literature, the data sources utilised, and the consideration of the wider context of the new device. This headroom analysis also had an important impact on the research direction, in particular shaping the need for and the design of the retrospective case studies that are presented in the next chapter.

## CHAPTER 7 RETROSPECTIVE CASE STUDIES

### 7.1 Introduction

The aim of this chapter is to shift the paradigm from *application* of the headroom method to its *evaluation*. There are three principal novelties to this retrospective case study investigation: a large sample, a systematic approach, and the ability to follow-up headroom decisions. Given the huge range of products encompassed by the term ‘medical device’, any lessons drawn from the headroom method’s application may be specific to the type of device under evaluation. By evaluating 20 case studies, the range of different perspectives and outcomes these individual examples contribute can be capitalised. The approach to each case study aims to be as systematic, informed, and transparent as possible, which is assisted by the use of a pro forma, a template of resources, and a rough time limit for each case study. Furthermore, until now the ramifications of favourable or unfavourable headroom in terms of subsequent uptake have not been explored. The headroom method is applied to the case studies retrospectively, by basing calculations on primitive expectations for the device and information from the literature that would have been available at the time the idea for the device was conceived.

The chapter is set out as follows. After describing the database used to identify case studies, the selection strategy is outlined. The strategy of evaluation is presented in the methods section (7.3). The results of each case study are then summarised in section 7.4, along with the principal messages that can be taken away from each in terms of the method’s applicability. Section 7.5 considers the overall findings, and relates the products’ characteristics to the analysis and results, in order to identify relationships and to draw firmer conclusions around the headroom method’s potential value.

## **7.2 The database: National Horizon Scanning Centre**

As described previously, the ideal strategy for evaluating this decision-support tool would be to: (1) elicit early expectations for a new product idea in real time; (2) calculate headroom and consider its adequacy for development; and (3) follow-up the device and observe its success or lack thereof. The COPD case study offers an example of the first two steps, but to follow this up to an eventual reimbursement decision would require a time-frame beyond that of a PhD. However, for a decision-support tool not to be related to the potential implications of that decision seems amiss, and whilst the question ‘does the headroom method work?’ cannot be answered definitively in this academic setting, there is certainly more to be learnt about the method by exploring this path.

The use of retrospective examples, whilst associated with inherent limitations that will be discussed, offers an opportunity to tackle this time constraint. The National Horizon Scanning Centre (NHSC) provides technology briefings on emerging health technologies that may have a significant impact on NHS healthcare provision (NHSC 2012b). Funded by the NIHR, the centre’s remit is to provide timely information to policy and decision-makers within the NHS. These short briefings (which can be found on their website) describe: the technology, the related patient group, current treatment alternatives, suggested impact, and any early evidence. From 2000 until the close of 2009, the NHSC produced 83 medical device and diagnostic briefings (2009 was chosen as an end point to allow adequate opportunity for follow-up). These were all considered for inclusion, according to the selection strategy described in the next subsection.

Of course, the selection strategy of the NHSC itself completely defines the sample of medical technologies available to evaluate, even before these are filtered further for inclusion

in this study. The NHSC's identification process is designed to pick up new technologies across a wide spectrum of clinical areas, which are evaluated for urgency and impact. Their selection criteria reflects the remit described above, and explicitly excludes any minor or incremental developments, and products that would not be purchased by the NHS (NHSC 2012a) (though as the analysis will demonstrate some of these seem to have slipped through). This is indicative of their role, which has often been to alert NICE of relevant new technologies.<sup>29</sup> Although briefings are intended to be broad in topic coverage, the obvious caveat is that only technologies with high impact potential are considered. Those that represent only minor changes or additions to current options, or those with a small cost impact, are likely to have been excluded; as discussed in chapter 3, these represent an important portion of the medical devices sector. Also, given the timing of the briefings (around the time of launch) the sample contains no examples of devices whose development was aborted somewhere between 'idea stage' and launch. The implications of this are discussed further in the chapter's discussion.

### 7.2.1 Selection strategy

It was decided that 20 case studies would provide a good range of examples and subsequent insights, while being manageable within this PhD study. All 83 medical technology briefings were considered for inclusion, according to criteria that developed organically from the process of reading and summarising all briefings. Table 7.1 provides a list of the exclusion criteria.

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<sup>29</sup> More recently, the NHSC have started to produce 'news briefs' for medical devices rather than full technology briefings. These are shorter, simpler, and directed at NHS commissioners, health professionals, hospital and community care providers, and patient groups. This shift in emphasis is a result of the new Medical Technology Evaluation Programme within NICE, which no longer wishes to be notified of new technologies by the NHSC, preferring instead to receive technology submissions directly from manufacturers (NHSC Associate Director 2011).

Table 7.1 Case study exclusion criteria

Reason for Exclusion		Number of devices excluded on this basis
1	Its application or advantages are not clearly set out. For example, the relevant patient population is not well specified, or benefits over current practice not clearly expressed.	22
2	The briefing is on a general topic: it incorporates multiple devices, or is applicable very broadly.	9
3	It is very similar to a previous briefing.	8
4	It represents a complex change in the clinical pathway with no estimate of overall impact on patients (e.g. screening test).	5
5	The report is a technology 'note' rather than a 'briefing'. Notes are very short, quite general, and have no real detail.	4
6	More of an evolving technique. No developers indicated.	3
7	It is likely to be a patient purchase.	2
8	NICE guidance was issued on the procedure in the three years prior to the briefing. It is not clear if/how the procedure involved for this device is any different.	1
		Total Excluded: <b>54</b>

It is worth considering what these exclusion criteria reveal about the headroom method.

Every attempt was made to ensure that exclusion was not based on the likely difficulty of the case study, by ensuring the criteria for exclusion were functional rather than preference based; not doing so may mean missing some potentially important caveats of the method. The vast majority of devices were excluded on the basis of insufficient information on which to base assumptions. This was pertinent for criteria 1, 2, 5, 6 and 8 in Table 7.1, which represented 39 cases of exclusion (72%). The information provided for these examples was either unclear or not specific; headroom analysis would therefore have been too speculative. Whilst this implies that the method's application requires a good understanding of the technology, this has more to say about the design of this investigation (a briefing note cannot be interrogated). Eight cases were excluded in order to maintain breadth of examples (criterion 3). Five were excluded on the basis of complexity (criterion 4); this was especially problematic for screening tests. Whilst this highlights a potential deficiency of the method, the COPD case study illustrated that it is possible to reduce a complex change in the clinical pathway to a simple proposition of impact. The expert insight required to make such simplifications was



not available for these retrospective case studies. The remaining two exclusions were due to the device not being relevant for health service purchase (criterion 7)<sup>30</sup>.

A total of 54 devices were excluded, leaving 29 for consideration. To investigate the possible implications of the selection process, Table 7.3 and Table 7.4 summarise the headline characteristics of those selected and excluded. The availability for each of NICE guidance for follow-up is also indicated. First, Table 7.2 outlines the categories used to describe the type of innovation: ‘relationship with current practice’.

**Table 7.2 Definition of terms: Relationship with current practice**

<b>Relationship with current practice</b>	<b>Explanation</b>
Incremental Development (ID)	These could fit into the ‘replacement’ category, but relate specifically those that represent a small or straightforward change to an existing device that is used in current practice.
Another Option (AO)	The new product represents another option for the treatment of patients within a specific clinical area.
Replacement (R)	Whilst there is some overlap with AO, replacement innovations refer to those that will displace current practice, even if this is for a specified subset of the patient population.
Addition (A)	The new medical technology will be used alongside / in conjunction with current clinical practice.
New Indication (NI)	There are currently no treatment options for technologies that address a ‘new indication’. No current clinical practice or procedure is displaced by the introduction of NIs.
Mix (M)	This label is for those new medical technologies that fit into more than one of these categories.

**Table 7.3 Comparing the characteristics of those selected and excluded: devices and diagnostics**

	<b>Total number</b>	<b>Devices (%)</b> [Total:45]	<b>Diagnostics (%)</b> [Total:38]	<b>For which there is NICE guidance for follow-up (%)</b>
<b>Selected</b>	29	20 (44%)	9 (24%)	12 (41%)
<b>Excluded</b>	54	25 (56%)	29 (76%)	11 (20%)

<sup>30</sup> Despite being itself an exclusion criteria of the NHSC, a small number of NHSC briefings related to technologies that were not likely to be NHS purchases. Although these were excluded from this investigation, it transpired after starting to evaluate one device (the ‘SpeechEasy’) that this would be a consumer purchase. The case study was left in the sample in order to illustrate the difficulties encountered when applying the headroom method to those devices that would not be offered reimbursement by the health service.

**Table 7.4 Comparing the characteristics of those selected and excluded: Relationship with current practice**

	<b>Total number</b>	<b>Selected (%)</b>	<b>Excluded (%)</b>	<b>For which there is NICE Guidance (%)</b>
<b>Incremental Development</b>	6	6 (100%)	0 (0%)	0 (0%)
<b>Another Option</b>	23	3 (13%)	20 (87%)	7 (30%)
<b>Replacement</b>	13	10 (77%)	3 (23%)	5 (38%)
<b>Addition</b>	18	2 (11%)	16 (89%)	2 (11%)
<b>New Indication</b>	7	5 (71%)	2 (29%)	5 (71%)
<b>Mix</b>	16	3 (19%)	13 (81%)	4 (25%)

Aside from the exclusion criteria themselves, a closer look at the characteristics of those selected and excluded—and how they differ—is revealing. A much larger proportion of diagnostics were excluded from the sample than devices. Most technologies selected represent a more straightforward change in clinical practice, such as incremental developments or replacement technologies. The majority of those developed for a new indication were selected. On the other hand, most of those representing another option, an addition, or a mix, were excluded. This may be because their fit within clinical practice was less clear. This is in contrast to the other three categories for which the comparator is much clearer: a specific product (IDs and Rs) or ‘nothing’ (NIs).

The headroom method is simply a manipulation of the NICE framework of economic evaluation, applied early. This strong association is emphasised by the availability of NICE guidance for follow-up, which is double for those selected compared with those excluded. The category for which proportionally there is most NICE guidance is new indications, followed by replacements. Unsurprisingly, there is no guidance for those that represent an incremental development.

The 29 technologies that were left after the exclusion process were placed in a random order and the first 20 selected for review.

## 7.3 Methods

As far as possible, the design of this investigation aspires to reflect the context of the method's intended use: by the device developer. This includes consideration of the time available to conduct such an analysis, which is unlikely to be akin to the months of work involved in the COPD case study. Therefore, a guiding policy of 'headroom in a day' was employed (though not always achieved), and time taken was recorded for each case study. The methods employed are explained below; by outlining the significant potential problems with the study, I describe how the design of this investigation seeks to overcome these problems and minimise their influence on the results.

### 7.3.1 The problem of 'too much information'

As the medical technologies under examination were conceived in the past, it is important that the retrospective application of the headroom method does not profit from any information that has become available more recently.

NHSC medical technology briefings are generally produced in the six months pre-launch to six months post-launch window<sup>31</sup> (NHSC Associate Director 2011). The NHSC team contact developers directly with a pro forma (see Appendix 4), which is then supplemented by a limited literature search (NHSC 2012a). The potential impact of the technologies reported in the briefings is therefore guided by the developer's own expectations.

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<sup>31</sup> This differs from NHSC briefings for pharmaceuticals, which are produced two to three years pre-launch.

The time it takes to develop a device is clearly variable, depending among other things on the type of device and the situation of the developer. Dixon and colleagues (2006) estimate mean development time to be 24 to 34 months. Conservatively, I take a date restriction for information searches of three years before the NHSC briefing publication (or three years before launch date if this is known to predate the briefing); that is to say, any information utilised must have been available three years prior to the briefing's publication date. This is scaled down to two years for incremental developments, for which development time is likely to be shorter. Any data or information provided either within the briefing or in the wider literature whose source postdates this restriction is ignored (this includes any clinical trials outcomes which are sometimes reported in the briefings). Any deviation from this rule in specific cases is explained in the headroom pro forma. Although the date restriction limits the information searches significantly, this is important in making the headroom analysis as realistic as possible. As well as excluding any information relating to the performance of the device itself, it is appropriate to reflect the state of knowledge in the general literature, which may be more limited before significant technological advances generate considerable research in a clinical area.

### 7.3.2 Removing the researcher from the research

To test a tool that is meant for device developers, it is important to set out a scheme that could be followed by someone other than an academic researcher. The approach to the headroom analyses—described below—is therefore set out explicitly, which should make the 20 case studies as systematic and repeatable as possible, as well as accessible to others.

#### 7.3.2 (i) *Template*

The template was designed as an overview of the steps required to calculate headroom, along with useful resources to furnish these. This is supplemented by further specific reference to

sources of information on market size data, cost data, and patient QoL elicitation, along with guidance on the appropriate ways to manipulate these figures (discounting, inflation rates, etc). The framework was designed before the commencement of the case studies, but the resources were built upon throughout the study (see Appendix 2).

### *7.3.2 (ii) Pro forma*

The template is to be used alongside the pro forma (see Appendix 1), which is completed for every case study. The pro forma helps to tease out the necessary information to estimate headroom: an explanation of the product and disease area, a description of the comparator, an estimate of market size, the likely impact on health service costs, the effect on patient health, a description of developments or changes in the area (clinical and healthcare context), and research questions that the analysis has inspired.

As far as possible, the headroom assumptions were based on an interpretation of the aspirations for the technology expressed in the briefing notes, combined with an appreciation of the relevant literature in order to judge what might reasonably be expected from the new technology. Depending on the level of information provided, some required more speculative assumptions than others.

### *7.3.2 (iii) Headroom calculations*

‘Headroom’ represents the maximum incremental cost to the health service of a new intervention (per unit), up to which point it would provide value for money. More conceptually useful to the manufacturer, as explained in the headroom method chapter, would be an MRP which requires one further iterative step: netting the headroom of the relevant cost impact to the health service. Many potential sources for eliciting healthcare costs are

provided in the template, but in the absence of implementation information (not always offered in the briefing notes) it was not possible to turn all headroom estimates into an MRP.

The output is calculated according to the following formula, as explained in chapter 4:

$$\mathbf{MRP} = [\mathbf{WTP} \times \mathbf{\Delta QALY}] - \mathbf{\Delta SC} + \mathbf{P}_1 \quad \mathbf{(Eq. 7.1)}$$

The output is expressed as ‘headroom’ rather than MRP in cases where service cost implication is missing or incomplete, or where the headroom value identified could not be matched directly with the device (e.g. expressed as a yearly value when longevity is not known or as a per patient treated value in cases where the number of units required to service the relevant population was unknown). The headroom or MRP output is presented in the results tables for each case study as a range, according to a WTP of £20,000 and £30,000.

Where the appropriate assumptions required for the headroom analysis are not clear, a range of values is presented according to various scenarios, which are explained. Where possible, development cost decision analysis is presented, as in the COPD case study. These are presented in graphic form in the full case study documentation provided in the Appendix.

### 7.3.3 Headroom: Decision Outcomes

Although confirmation from the developer would be required to know for sure whether the level of headroom estimated would have been perceived as adequate, this can often be gleaned intuitively by comparing headroom with actual cost or price where this is available (e.g. where subsequent price is set below MRP, it seems likely that headroom would have indicated a favourable development decision). The development decision analysis can then be compared with evidence of uptake. This information is elicited from the current (up-to-date) literature, information available from the internet, and attempts to contact the relevant companies or interested parties. The strategy for follow-up is presented in Appendix 5. It

must be noted that the declaration of a favourable/unfavourable development decision, whilst as informed as possible and explained in the analysis, is still speculative and should be read as such.

#### 7.3.4 Presentation of results

Each case study is presented individually in section 7.4, in which the main properties of the devices are outlined, a summary of the results and follow-up presented, and pertinent lessons described. Due to space constraints, explanations behind the assumptions made and details of the data used (including references) are not presented in the main text. This information is provided in the full case study documentation, attached in Appendix 6. For each case study, the time perspective for the ‘description’ and ‘headroom analysis’ is that from which the headroom analysis was conducted (usually three years prior to launch). This perspective shifts to 2012 for the ‘follow-up’ and ‘headroom lessons’ sections.

These case studies explore the feasibility of conducting an early economic evaluation using only the information available at concept-stage and the most preliminary of expectations for the product (as deduced from the NSHC briefing). By following these case studies up to the present day, the degree to which the headroom analysis reflected actual market opportunity can be explored. All these elements of the analysis and results are then considered together in section 7.5, which reflects on what has been learnt about the headroom method and its application.

## 7.4 Case study results: The Data

### 7.4.1 FibroTest-ActiTest — BioPredictive

#### *Description*

The FibroTest-ActiTest<sup>32</sup> is a non-invasive alternative to liver biopsy for assessing fibrosis (liver damage) in people with hepatitis C. The test evaluates biomarkers from a blood sample, and a patented algorithm predicts the level of fibrosis and necroinflammatory activity in the liver. This can assess disease staging prior to antiviral treatment. The current gold standard for assessment of fibrosis is an invasive liver biopsy.

**Table 7.5 Summary of headroom analysis and follow-up for FibroTest-ActiTest**

Key characteristics:	Clinical area	Liver Disease (HepC)
	Technology type	In Vitro Diagnostic.
	Relationship with current practice/ comparator	Replacement
	Relationship with current company portfolio	n/a
Analysis:	Time perspective taken	2001
	Market size (per year)	3,600
	Service cost impact*	£438 [saving]
	QoL Impact*	0.005 QALYs
	<b>Headroom</b> (per test)	<b>QoL impact included: £538 - £588**</b> <b>QoL impact not included: £438</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>Adequate sensitivity and specificity will be key.</li> <li>There may be a gradual move away from routine testing (currently with biopsy) prior to treatment for Hep C. This could limit the potential market.</li> </ul>
	Allowable development costs calculated?	Given the variable and consumable cost per test is likely to be small, the maximum allowable development cost is huge (in the millions of £s).
	Time taken for headroom	6 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom indicative of <i>favourable</i> development decision.
	Is the device used in the UK or the rest of the world?	(Limited) availability in UK identified. Laboratories performing the test are located globally.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

<sup>32</sup> As noted in the methods chapter, this case study acted as the pilot, through which the approach and resources compiled were refined. No specific changes were made following/as a result of this case study.



### *Headroom analysis*

FibroTest-ActiTest could directly replace biopsy in 90% of cases, and accuracy is presumed to be equivalent to biopsy. Headroom (per person or test) is the average cost of a liver biopsy (£438), plus the value of disutility saved from avoiding invasive biopsy (0.005 QALYs); both parameters were elicited from the literature. Insufficient information was provided to estimate the likely service costs involved in providing the test. The figure presented is a 'headroom' (per test): between £438 and £588.

### *Follow-up*

The unit cost to the NHS per FibroTest-ActiTest performed would be £70, indicating that the headroom would have presented an attractive proposition for development. The test is offered by three UK laboratories and in 49 countries across the globe. FibroTest-ActiTest has been recommended for reimbursement in France as first-line fibrosis assessment, but I have found no evidence of its systematic use across the NHS. Cost-effectiveness studies indicate that FibroTest-ActiTest may be cost-saving but at the expense of reduced diagnostic accuracy (sensitivity, specificity and accuracy are 84%, 87% and 86% respectively). In the UK biopsy remains the reference standard, but increasingly is not considered necessary before initiating treatment (NICE 2006); this has reduced the demand for disease-staging tests.

### *Main lessons learnt*

Given its low price compared with its estimated (headroom) value, FibroTest-ActiTest should have achieved wide-spread adoption across the NHS. The main factors to have impeded this are: diagnostic accuracy, a change in clinical practice, and the prevalence of direct competitors (these were all identified as potential threats in the headroom analysis).

## 7.4.2 Molecular adsorbent recirculating system (MARS®) — Teraklin Ltd.

### Description

MARS is a mechanical blood detoxification system which would offer liver support therapy to patients with acute and chronic liver failure (much like dialysis for renal patients), potentially acting as a bridge to transplantation. Liver transplantation is currently the only option once supportive measures have failed. By considering NHS organ donation statistics, I estimate that an extra 10% of the approximately 1,000 patients on the waiting list would survive long enough to receive transplantation if all 1,000 have access to the MARS liver-support system in this bridging period. An estimate of 5% was also considered.

**Table 7.6 Summary of headroom analysis and follow-up for MARS**

Key characteristics:	Clinical area	Liver Failure
	Technology type	Device (Equipment <sup>33</sup> ). Class Iib <sup>34</sup>
	Relationship with current practice/ comparator	New Indication
	Relationship with current company portfolio	n/a
Analysis:	Time perspective taken	1997
	Market size (per year)	1,000
	Service cost impact*	-
	QoL Impact*	0.69 (Assumption 1: 10% more survive until transplant) 0.34 (Assumption 2: 5% more survive until transplant)
	<b>Headroom</b> (yearly value per patient)	<b>Assumption 1: £13,800 - £20,700 **</b> <b>Assumption 2: £6,800 - £10,200 **</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>Competitors: research is currently underway into liver-assist systems that also fulfil the <i>metabolising</i> function of the liver.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	12 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom indicative of <i>favourable</i> development decision.
	Is the device used in the UK or the rest of the world?	NICE IPG does not recommend MARS, on the basis of insufficient evidence of efficacy. The system has been used in various UK centres and across the world. In the U.S. it is indicated for the treatment of drug overdose and poisonings rather than for liver conditions.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

<sup>33</sup> Equipment refers to medical technologies that are not used on a per patient basis

<sup>34</sup> Devices have been classified using the rules outlined in the European medical device directive documentation for the classification of medical devices (European Commission 2010).

### *Headroom analysis*

Headroom is presented per patient per year, given the uncertain service provision costs and device longevity. QALY impact is based on the average life years saved per patient treated with MARS, adjusted for HRQoL after liver transplantation (inferred from the literature).

Headroom is estimated to be between £6,800 and £20,700 (see Appendix 6 for explanation).

### *Follow-up*

Considering the £16,000 price tag for MARS, its intended use (for multiple patients) and likely longevity (more than one year), the headroom analysis is likely to have indicated a favourable development decision. One cost-effectiveness study finds a QALY gain from MARS very similar to that estimated above, but in general there is insufficient evidence of clinical effectiveness (NICE 2009b). The device is sold (both in the UK and globally), but has not achieved complete diffusion in the UK.

### *Main lessons learnt*

Some potentially important benefits of MARS were ignored, simply because there was no easy way to estimate, quantify and incorporate these. To estimate health-economic value of equipment requires some understanding of distribution, patient throughput, and device lifetime. These may be difficult to envisage early on, even for the developer. The headroom calculation, which involved a transformation of survival rates into expected life years remaining, may have been difficult for someone with no background in statistics/epidemiology. The assumptions made for this analysis felt particularly speculative, and very open to alternative approaches.

### 7.4.3 SpeechEasy — SpeechEasy International

#### *Description*

The ‘choral effect’ describes the phenomenon that stammering often improves when a person is singing or talking in unison with others. The SpeechEasy is a prosthetic device that fits into the ear (much like a hearing aid), which stimulates this choral effect by providing altered auditory feedback (AAF) of the person’s own voice, into their ear. Other AAF devices exist, but this would be the first wireless AAF device, and thus the least conspicuous.

**Table 7.7 Summary of headroom analysis and follow-up for Speech-Easy**

Key characteristics:	Clinical area	Stammer
	Technology type	Device. Class IIa
	Relationship with current practice / comparator	Incremental Development
	Relationship with current company portfolio	n/a
Analysis:	Time perspective taken	2005
	Market size (per year)	-
	Service cost impact*	[Price of most expensive current model: £1,827]
	QoL Impact*	[0.071 to 0.152 per year]- <i>illustrative and not included</i>
	<b>Headroom/MRP</b>	<b>[£1,827]</b>
	Important extra considerations	This is likely to represent a patient purchase, and so is unsuitable for headroom evaluation.
	Allowable development costs calculated?	-
Time taken for headroom	6 hours	
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	-
	Is the device used in the UK or the rest of the world?	The device is available across the world.

\*Average per person treated

#### *Headroom analysis*

The simple baseline MRP for a device that incrementally develops an existing model is the price of that comparator (£1,827). After seeking information from The British Stammering Association and contacting a local NHS speech and language therapy clinic, it became apparent that, whilst occasionally used within clinics, AAF devices are not provided to

patients by the NHS (see Appendix 6 for further explanation). HRQoL impact was explored using a manipulation of the anxiety level in the EQ-5D, but only for illustrative purposes.

### *Follow-up*

The estimated MRP was £1,827, plus some premium that consumers should be willing to pay for the discrete nature of SpeechEasy. The headroom method provides no means with which to estimate this premium. The actual price of SpeechEasy is £2,450, and is available globally.

### *Main lessons learnt*

Many economic methods exist to elicit the value a consumer would place on particular product characteristics, but this falls outside the scope of a headroom analysis. Whilst the health value of this incremental development was explored, this cannot be used to estimate incremental WTP for SpeechEasy, as the ‘QALY tariff’ (NICE’s ICER threshold) has been designed specifically with the NHS and its inherent budget prospects in mind. Although comments made in the pro forma and the general surface analysis transpired to be pertinent upon follow-up, they are unlikely to have provided additional insight; the headroom method is not applicable to consumer products.

## 7.4.4 SLF Bypass Graft — Tayside Flow Technologies

### *Description*

Peripheral arterial disease (PAD) involves stenosis (narrowing) of a peripheral artery. This leads to insufficient blood supply to muscles and other tissues, causing pain and weakness. Spiral laminar flow (SLF) describes the natural pattern of blood flow through arteries, which is disrupted by stenosis. The turbulent energy caused by this disruption contributes to

restenosis following bypass surgery. An autologous vein graft is the first choice for surgeons, and is the most effective option but is not always available. Where an autologous vein is unavailable, synthetic grafts are used, though these have a lower patency rate (become blocked more frequently). The SLF bypass graft has a flow-inducer at the distal end which restores natural SLF, potentially improving graft patency compared with standard synthetic grafts. I assume that the SLF graft could achieve equivalent patency rates to vein grafts.

**Table 7.8 Summary of headroom analysis and follow-up for SLF Bypass Graft**

Key characteristics:	Clinical area	Peripheral arterial disease
	Technology type	Device. Class IIb
	Relationship with current practice / comparator	Incremental Development
	Relationship with current company portfolio	n/a
Analysis:	Time perspective taken	2006
	Market size (per year)	-
	Service cost impact	- [various estimates presented]
	QoL Impact	- [given the strong possibilities of reimbursement on the cost side alone, and the fact that improved patency could only <i>benefit</i> patients, no attempt to quantify QoL benefit was made.]
	<b>Headroom/MRP</b>	The case for development is intuitive
	Important extra considerations	<ul style="list-style-type: none"> <li>Other innovations in this area were identified, including various direct competitors. If proven effective, these could change the baseline of effectiveness.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	8.5 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	A favourable development decision is indicated.
	Is the device used in the UK or the rest of the world?	The SLF graft is sold in over 20 countries, and is used in some NHS hospitals.

### *Headroom analysis*

The potential value of the SLF bypass graft arises from a reduced burden of restenosis (which must be followed by repeat intervention or amputation). Whilst some relevant literature was identified—one source suggesting that such an improvement in patency could be worth £4,400 per case (Cheshire et al. 1992)—data were scarce and any calculation would be

tenuous. There is a strong indication that the potential reimbursement opportunity would far outweigh the cost of this incremental development.

### *Follow-up*

Headroom indicated an intuitively favourable development decision. The device is sold and marketed across the world (the company confirm that it is used within some NHS hospitals). Early indications of clinical function suggest reduced vessel occlusion following bypass with SLF grafts, but no economic evaluation was identified.

### *Main lessons learnt*

Considering the expectation of improved patency and the straightforward change proposition of this device, the economic case for the SLF graft was a 'no brainer'. It is difficult to say whether the headroom exercise would have been useful, even though it was not incorrect. This case demonstrated that even where the relevant information should be available (the cost implications of two existing options), this was lacking in the literature, highlighting that the headroom method's output is only as informed as the research undertaken by others.

## 7.4.5 Meniett — Medtronic Xomed

### *Description*

Ménière's disease is a pressure condition of the inner ear which can affect hearing and balance, causing vertigo attacks, hearing loss and tinnitus. The Meniett device is proposed as an alternative to current approaches for the treatment of refractory cases: surgery or ablative treatment. Meniett is a non-invasive portable patient-administered device which delivers low pressure pulses into the inner ear via a tympanostomy tube (grommet) which must first be

inserted under local anaesthesia. I assume that Meniett will work as well as current methods of treating refractory cases, but may be better accepted by patients.

**Table 7.9 Summary of headroom analysis and follow-up for Meniett**

Key characteristics:	Clinical area	Ménière's disease
	Technology type	Device. Class IIa
	Relationship with current practice/ comparator	Another Option
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1999
	Market size (per year)	172 – 3,452 per year
	Service cost impact*	£1,474 [saving]
	QoL Impact	-
	<b>MRP</b>	<b>£1,474</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>Local injection as a means of treatment seems to be well supported by the literature; if this becomes more widespread it might displace other treatment options (and is likely to be much less costly).</li> <li>Would there be an improvement in hearing preservation compared with current surgical options?</li> <li>Might the device be a patient purchase?</li> </ul>
Allowable development costs calculated?	For a variable unit cost of between £50 and £550, maximum development costs ranged from £160,000-£250,000 for the lower market estimate (172 patients) to £3.2 million-£5million for the higher market estimate (3,452 patients)	
	Time taken for headroom	9 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Uncertain- possibly unfavourable. Price for Meniett has been set <i>above</i> MRP at £2,000.
	Is the device used in the UK or the rest of the world?	NICE does not recommend the procedure on the grounds of insufficient efficacy and safety evidence. Meniett does not seem to be available on the NHS, and appears to be mainly funded by patients themselves.

\*Average per person treated

### *Headroom analysis*

Health service cost impact is calculated by subtracting the cost of grommet insertion (including one hospital day) from the current cost of surgical treatment (which would be avoided)<sup>35</sup>: £1,474. This is the MRP for Meniett over a patient's lifetime (i.e. price per

<sup>35</sup> Costs were difficult to obtain. In the absence of literature estimates predating 1999, I used the estimates provided in the NHSC briefing. These were not referenced, so I assume were provided by the manufacturer. Given the paucity of cost data predating 1999, I used more recent sources to estimate generic hospital costs (and deflated these, using the HCHS Pay & Prices index). Whilst breaking the date restriction rule, it was surmised that whilst effectiveness / quality of life estimates capture a knowledge base that changes over time (which is important to mimic), costs are objective, and would probably have been identifiable by those in the field.



device, if it lasts a lifetime). HRQoL estimates are not attempted. Development cost analysis produces a wide range of estimates given the large uncertainty in market size.

### *Follow-up*

At launch, Meniett was priced at £2,000, above the MRP. Interventional procedures guidance by NICE finds insufficient clinical evidence upon which to recommend the therapy, and it is not reimbursed by the NHS. As predicted, local injections have become the gold standard, thus reducing the potential headroom. Meniett is mainly purchased by patients, and cheaper devices with similar function have become available.

### *Main lessons learnt*

Although a not-entirely-convincing headroom case was indeed followed by a not-entirely-convincing health service uptake, the product still seems to be viable for Medtronic, mainly from patient purchases. This, and other factors that have affected the market environment, were highlighted in the headroom analysis, and show that the MRP must be considered alongside these other important factors, which can generally be predicted at an early stage.

## 7.4.6 AmpliChip CYP450 — Roche Diagnostics Ltd.

### *Description*

Tamoxifen is the main hormonal treatment for early-stage oestrogen receptor positive (ER+) breast cancer. The AmpliChip CYP450 is a laboratory array-based prediction test that can detect the levels of a certain marker gene thought to influence the rate at which patients can metabolise tamoxifen. The test is proposed to identify poor metabolisers who would not benefit from tamoxifen treatment.

**Table 7.10 Summary of headroom analysis and follow-up for AmpliChip**

Key characteristics:	Clinical area	Early Breast Cancer
	Technology type	In Vitro Diagnostic
	Relationship with current practice/ comparator	New Indication
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	2004
	Market size (per year)	29,500
	Service cost impact	-
	QoL Impact	-
	<b>Headroom/MRP</b>	-
	Important extra considerations	<ul style="list-style-type: none"> <li>• Aromatase Inhibitors have been found by some to be more cost-effective than tamoxifen. If this is proven further, they may in the future replace tamoxifen as first-line adjuvant treatment for early stage ER+ breast cancer.</li> <li>• Some studies indicate that this particular gene in isolation may not be the most useful predictor of tamoxifen metabolic function.</li> <li>• The gene detected by AmpliChip relates not only to the metabolism of tamoxifen, but also other types of drugs. Therefore the commercial opportunity of AmpliChip is likely to be far wider than that investigated here.</li> </ul>
	Allowable development costs calculated?	-
Time taken for headroom	8.5 hours	
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	No headroom was delivered, but significant threats were identified.
	Is the device used in the UK or the rest of the world?	AmpliChip is available in the UK and across the world (at a cost of £200 per test). It is indicated more widely than for breast cancer patients alone—mainly in the area of psychiatry.

### *Headroom analysis*

Although tamoxifen is currently the gold standard, aromatase inhibitors (AIs) provide an alternative chemoprevention method that is more costly but more effective. AmpliChip could personalise chemoprevention, allowing for continued use of tamoxifen for good metabolisers, and identifying poor metabolisers whose treatment can then be modified (e.g. to AIs). The required parameters for a headroom calculation include: the proportion of tamoxifen users that are poor metabolisers, their prognosis, the proportion of AI users who would be good

metabolisers of tamoxifen, etc. The literature provides no estimates of these parameters, inhibiting a headroom estimate. Important considerations are summarised in Table 7.10.

### *Follow-up*

Whilst lacking a monetary estimate of market opportunity, the exercise did highlight some important considerations. NICE now finds AIs to be more cost-effective than tamoxifen (but do not suggest the removal of tamoxifen from clinical practice). The literature includes some favourable results for AmpliChip, but most (including the MHRA, a technology evaluation, and a systematic review) do not recommend genetic testing prior to tamoxifen treatment. Its application to other disease areas has been important for the success of AmpliChip.

### *Main lessons learnt*

This case study demonstrated that sometimes the necessary parameters for headroom cannot be elicited. AmpliChip was a ‘new indication’—there is no other test for poor tamoxifen metabolism—so prevalence estimates do not exist. As AmpliChip is applicable for other indications, to base a development decision on this evaluation alone would have been inappropriate. Although no numbers were presented, the analysis correctly identified the significant barriers to adoption/reimbursement in its use for breast cancer patients.

## 7.4.7 Agento I.C. — Bard Limited

### *Description*

Ventilator associated pneumonia (VAP) is acquired in hospital by mechanically ventilated patients, when the endotracheal tube (ETT) that delivers this ventilation becomes colonised

with bacteria. The Agento I.C is a silver-coated ETT, whose antimicrobial properties may prevent VAP in patients who require prolonged mechanical ventilation (>24 hours).

**Table 7.11 Summary of headroom analysis and follow-up for Agento I.C.**

Key characteristics:	Clinical area	Ventilator associated pneumonia (VAP)
	Technology type	Device. Class IIa
	Relationship with current practice/ comparator	Incremental development
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	2005
	Market size (per year)	62,000
	Service cost impact*	100% reduction in VAP: £3,111 [saving] 50% reduction in VAP: £1,556 [saving] 25% reduction in VAP: £778 [saving] (Max) Price of standard ETT: £55 [saving]
	QoL Impact*	100% reduction in VAP: 0.0005 QALYs 50% reduction in VAP: 0.00025 QALYs 25% reduction in VAP: 0.000125 QALYs
	MRP**	<b>100% reduction in VAP: £3,167 - £3,181</b> <b>50% reduction in VAP: £1,616 - £1,619</b> <b>25% reduction in VAP: £836 - £837</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>Other means of tackling VAP have been found to be effective, e.g. laying the patient in a semi-recumbent position, use of antibiotics, etc. One study found that an educational program for ICU nurses and respiratory care practitioners, on the risk factors and prevention strategies of VAP, reduced VAP incidence by 46%. If in the future recommendations are better implemented, this could reduce the potential impact of the Agento I.C.</li> </ul>
	Allowable development costs calculated?	For the least optimistic scenario (MRP: £836), a variable cost of £0-£250 would allow for development costs in the region of £40-£50 million. For the most optimistic, these reach nearly £200 million. This is based on a market size of 62,000, which may be an overestimate.
	Time taken for headroom	10 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom indicative of a favourable decision (price of Agento IC falls well below the most pessimistic estimate of MRP).
	Is the device used in the UK or the rest of the world?	Based on trial sites, it is available in the U.S. and Spain. The company's UK headquarters confirms that Agento IC is not sold in the UK.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

### *Headroom analysis*

The impact of the Agento IC is estimated according to three scenarios: a 100%, 50%, and 25% reduction in VAP. HRQoL loss is assumed to be 0.15 during a VAP episode (elicited

from the literature<sup>36</sup>), which lasts 11.5 days (the average additional days spent in hospital for VAP patients). MRP ranges from £836 to £3,181, depending on assumptions and WTP.

### *Follow-up*

The price of Agento IC is around £100; the headroom analysis would have indicated a favourable development decision. The product is not sold in the UK. Most trials are located in the U.S. or Spain, the largest of which attributes a 36% relative risk reduction in VAP to Agento IC (Kollef et al. 2008). Some studies indicate that Agento IC is cost-effective (though not to the extent imagined in the headroom analysis).

### *Main lessons learnt*

Although the device appears to be cost-effective, uptake by the NHS has not followed. This may relate to a limited awareness of VAP due to the difficulty in its diagnosis, or the implementation of other recommendations to combat the illness (as identified during the headroom analysis). Most assumptions were based on information from a single source, deemed by me to be the most reliable/consistent. The huge spread of data in the literature means that speculation was required; bias may therefore creep in. Indeed, more recent estimates of VAP cost are more modest but, perhaps unsurprisingly, Bard Ltd. make reference only to the older, more generous estimates.

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<sup>36</sup> This estimate was provided by Vold and Owens “...on the basis of comparisons with various health states for which published utility data exist” (Vold Pepper & Owens 2000). This is strikingly similar to the philosophy behind the ‘health utilities ladder’ put together by McAteer (McAteer 2011).

## 7.4.8 Cool-Cap — Olympic Medical Corp

### *Description*

Perinatal asphyxia is the deprivation of oxygen to a newborn baby, usually resulting from an interruption of blood flow to the brain during delivery. Normal causes include placental infarction, a drop in maternal blood pressure, uterine rupture or umbilical cord complications. Hypoxic-ischaemic brain damage is a serious risk of perinatal asphyxia, which can cause infant death and impair neurological development. 20% of cerebral palsy cases are caused by perinatal asphyxia, which can also cause mental retardation, learning disabilities and epilepsy. The cool-cap would reduce a newborn's core brain temperature, to prevent continuing damage to the brain cells and their environment. Although whole body cooling has been found to improve cerebral outcome, this is not used systematically in clinical practice. The cool-cap provides focal cooling of the head, and is the first commercial product for neonatal cooling.

**Table 7.12 Summary of headroom analysis and follow-up for Cool-Cap**

Key characteristics:	Clinical area	Perinatal asphyxia
	Technology type	Device. Class IIa
	Relationship with current practice/ comparator	New Indication
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1997
	Market size (per year)	600
	Service cost impact	- [assumed to be very high]
	QoL Impact	- [assumed to be very high]
	<b>Headroom/MRP</b>	-
	Important extra considerations	<ul style="list-style-type: none"> <li>The significance of brain temperature on the outcome of cerebral ischaemia is well recognised. The systemic cooling of patients undergoing heart surgery is often employed to avoid ischaemic brain damage. Whilst this confirms the likelihood of improved outcome from the cool-cap, other methods of cooling may be just as effective (e.g. whole body cooling).</li> </ul>
Follow-up:	Allowable development costs calculated?	-
	Time taken for headroom	7.5 hours
	Would the headroom analysis have indicated a favourable development decision?	Headroom analysis is indicative of a favourable headroom decision (intuitive), but should consider the potential change in the counterfactual.
	Is the device used in the UK or the rest of the world?	The cool-cap is used both within the NHS and globally.

### *Headroom analysis*

The NHS cost impact of avoiding even a small percentage of hypoxic-ischaemic brain damage cases would be difficult to quantify, but must be large. Savings may be seen in medical costs, nursing care, physiotherapy, and transportation, as well as limiting pay-outs (in the millions of pounds) for litigation cases where clinician error was the cause. By the same token, QALY gains would be vast. Cooling by other means should be considered, but given the lack of current alternatives, the development case for cool-cap seems obvious.

### *Follow-up*

The high value of the cool-cap indicated a strong case for development, but should be considered alongside the research questions generated, namely: would it be better than whole body cooling? NICE recommends therapeutic hypothermia for hypoxic perinatal brain injury, either by whole body cooling or with a purpose-made cap (all evidence presented for cooling caps pertain to Olympic Medical Corp's product) (NICE 2010c). Both methods of cooling are clinically and cost-effective, and both are used within the NHS.

### *Main lessons learnt*

The cool-cap proposed to commercialise a known therapeutic technique which was not yet part of routine clinical practice. Being the first commercial device for hypothermic therapy gave the product (and its case for development) an advantage. From a health economic perspective, costs and effectiveness alone dictate the preference of one intervention over another. Even though other methods seem more cost-effective, many techniques and products for cooling co-exist in the market, indicating the strong influence of other factors, including personal preference. The commercial opportunity and the external threats identified in the headroom analysis turned out to be pertinent and indicative of the future market opportunity.

## 7.4.9 ChondroCelect — TiGenix

### *Description*

Cartilage damage in the knee can occur spontaneously or from injury, and is associated with knee pain, knee locking, and weakness. ChondroCelect is a somatic cell therapy product, developed from a patient’s own cartilage-forming cells and expanded *ex-vivo* prior to implantation. ChondroCelect (the ‘product’) is administered as part of an autologous chondrocyte implantation (ACI), a ready-established procedure that was appraised by NICE in 2000 (re-visited in 2005) and not recommended<sup>37</sup> (NICE 2005). The proposed advantage over standard ACI is the improved cell culturing technique, leading to more effective cultured chondrocytes. Other treatment options include symptomatic relief, matrix-guided ACI (MACI), microfracture, mosaicplasty, knee lavage and knee replacement. At the time of analysis, microfracture was the standard treatment for cartilage defects.

**Table 7.13 Summary of headroom analysis and follow-up for ChondroCelect**

Key characteristics:	Clinical area	Knee cartilage defects
	Technology type	Advanced therapy medicinal product (ATMP). <sup>38</sup> Includes elements of medicine, surgery and medical device implantation.
	Relationship with current practice/ comparator	Incremental development
	Relationship with current company portfolio	-

<sup>37</sup> Although ACI is not the gold standard in clinical practice, is it the most relevant comparator in this example. As NICE have already produced a technology evaluation on the procedure, it is important to consider ChondroCelect in relation to this, to determine whether it might be possible for the product to warrant a different reimbursement decision outcome.

<sup>38</sup> There is some disagreement around the appropriate classification of somatic cell therapy / tissue-engineered products; from a regulatory perspective, they pose quite different risks issues to devices and medicines. They are officially classified as ATMPs. Within the European Medicines Agency (EMA), the ‘Committee for Advanced Therapies’ will provide scientific advice of ATMPs, and at least two members of this committee must have medical device expertise (Department of Health 2008b). Although products of this nature fit more closely into the ‘medicines’ category, at least from a regulatory perspective (evident from their consideration within the EMA), this was classified by the NHSC as a medical technology rather than pharmaceutical, and was kept within the analysis as it may provide some useful insight into the headroom method. It represents a bit of a special case that is worth exploring, as the procedure contains elements of medicine, surgery *and* medical device implantation, so is representative of complex procedures that involve many elements.



Analysis:	Time perspective taken	2006
	Market size (per year)	900 – 1,200
	Service cost impact*	- [Price of current ACI: £3,710]
	QoL Impact*	- [an estimate was provided regarding what this needed to be]
	<b>Headroom/MRP</b>	-
	Important extra considerations	<ul style="list-style-type: none"> <li>If the ChondroCelect procedure is able to keep its cost to the health service within that of arthroscopic ACI, then in the short term (two years) it would have to show at least 70% better outcomes than microfracture (but there are indications that it might be much more expensive and thus require even greater improvement in outcome). From their technology appraisal, it is clear that NICE will not consider a longer term perspective until clinical data are available (which may require at least 20 years).</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	8 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Potential for reimbursement seems unlikely
	Is the device used in the UK or the rest of the world?	ChondroCelect is reimbursed on a case by case basis in Belgium, Germany, the UK, and soon Finland.

\*Average per person treated

### *Headroom analysis*

Although ChondroCelect may improve the effectiveness of ACI, to estimate the service cost and QoL implications of this is very complex: no headroom was estimated per se. However, as an HTA relating to ACI has been published within the relevant timeframe, some precise qualifications for reimbursement are identified, and outlined in the ‘research questions’ section of the pro forma.

### *Follow-up*

Although I am unable to predict whether the qualifications set out would have appeared feasible to ChondroCelect developers, this seems unlikely due to the extra costs involved over arthroscopic ACI, and therefore the huge improvement in outcome that would be required to make it cost-effective. ChondroCelect is reimbursed in Belgium, Germany, and the UK on a case-by-case basis. Although ACI is not recommended by NICE, TiGenix is ‘working with

*orthopaedic surgeons to obtain Pass-Through Payment<sup>39</sup> from individual PCTs, and also working with private insurance: very positive initial reception from BUPA*' (Meurgey 2010).

Results of clinical and cost-effectiveness studies for ChondroCelect are mixed; a long term time horizon is certainly required before the product may appear cost-effective, and the data required to confirm these longer terms outcomes have still to be generated.

### *Main lessons learnt*

ChondroCelect was the first ATMP to receive European market authorisation. The 'headroom analysis' was simply derived from an HTA that had been produced for ACI just a year earlier. Therefore, nothing novel is likely to have been added to the decision-making process here. Despite its uncertain cost-effectiveness, alternative methods of reimbursement are available for novel and expensive products such as this one. Regenerative medicine products present a particular challenge to health economists, due to the long time horizon required to capture their value, and therefore the difficulty in generating the required evidence. In the closing remarks of a presentation on ChondroCelect, Meurgey (V-P Commercial Development of TiGenix) says: *'Unless national authorities demonstrate willingness to experiment with conditional reimbursement, there is a real risk that regenerative medicine will remain a nice idea without any routine clinical use (or a luxury reserved for the rich)'* (Meurgey 2010).

### *Other headroom analyses*

Helen McAteer (2011) uses ACI as one of four examples in her PhD thesis on the headroom method for regenerative medicine products. ChondroCelect is one of the products considered

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<sup>39</sup> Pass-Through Payments are *additional* payments that can be used to support (reimburse) a particular device over and above the relevant tariff. These are sometimes used to support the use of new products (Pate 2009). Special arrangements for reimbursement are similarly proposed for other countries, being on the 'expensive drugs list' in the Netherlands, and obtaining 'innovative status' in Belgium.

within this thesis. To inform her headroom analysis, all relevant evidence was reviewed and synthesised, producing three models of potential outcome and ‘headroom’. This diverges from the approach taken here in two major ways: firstly, evidence available for the product itself is used to inform its headroom, and secondly, complicated models of potential effectiveness are produced in order to consider the headroom value. Her concluding remarks relate to the paucity and discrepancy in the available data for ACI, and that without long term data evidence-based modelling is impossible. This does not seem appropriate for a tool intended to be integrated into development decisions, and one whose approach is intended to be straightforward. It is also proposed that ‘...supply side analysis has been used to calculate the incremental benefit required if the technology is to cost the same as ACI’ (McAteer 2011, p. 231). The approach taken in this analysis has provided a similar result, but elicits this directly from the literature.

#### 7.4.10 KRYPTOR compact — Brahms AG

##### *Description*

A lower respiratory tract infection (LRTI) can cause symptoms such as shortness of breath, fever, cough and fatigue, and is principally associated with acute bronchitis, COPD and pneumonia. LRTIs can be of bacterial or non-bacterial (viral) cause. Antibiotics are only useful for bacterial infections, but are currently over-subscribed; clinical examination is the only widely used method to distinguish between viral and bacterial causes, and is often unreliable. Levels of the biological marker procalcitonin (PCT), detectable in the blood, can indicate the cause of an infection. The Brahms Kryptor assay (classic version), available since 1997, is a sensitive assay that measures levels of PCT in a blood sample, and is used for various diagnostic purposes (primarily prenatal screening). The Kryptor compact is based on

the same reagent system, but would be smaller, less costly, and easier to maintain. Data for the Kryptor classic (trialled for LRTIs but not used routinely) can inform the headroom of the compact version, assuming that the barriers to uptake for Kryptor classic may be overcome by its compact version.

**Table 7.14 Summary of headroom analysis and follow-up for KRYPTOR compact**

Key characteristics:	Clinical area	Lower respiratory tract infection (LRTI)
	Technology type	In Vitro Diagnostic (Equipment)
	Relationship with current practice/ comparator	New Indication
	Relationship with current company portfolio	Incremental Development
Analysis:	Time perspective taken	2005
	Market size (per year)	1.7 million
	Service cost impact*	£0.83 [saving if £2 per antibiotic course: First line treatment of a patient presenting with LRTI] £4.16 [saving if £10 per antibiotic course] £8.32 [saving if £20 per antibiotic course] £20.80 [saving if £50 per antibiotic course] £41.60 [saving if £100 per antibiotic course] £62.40 [saving if £150 per antibiotic course: Approximate cost of a course of antibiotics for hospitalised pneumonia patients]
	QoL Impact	-
	<b>Headroom (per patient)</b>	<b>£0.83 - £62.40</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>• A reduction in antibiotics resistance is an important world-wide goal, for which more appropriate prescribing is key.</li> <li>• One very important question is: Why is the original Kryptor assay not used in routine clinical practice? Is it anything to do with issues that the new model would address / change (supposedly cheaper, smaller, and easier to maintain)?</li> <li>• Does the Kryptor compact represent a simple product evolution that should happen regardless, in order to keep products up-to-date?</li> <li>• What other clinical areas would a PCT test be useful for?</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	11 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom is likely to have indicated a favourable development decision, but with the knowledge that the market is likely to be limited to serious LRTI patients in a hospital setting, and not as part of routine clinical practice for all LRTI patients.
	Is the device used in the UK or the rest of the world?	Yes (though I am unsure about the extent to which it is available on the NHS for LRTI).

\*Average per person treated

### *Headroom analysis*

Antibiotics prescription in LRTI patients can be reduced by 40% when guided by PCT levels, and its cost cut by 52% (from shorter treatment duration resulting from better targeting) (Christ-Crain et al. 2004). Table 7.14 presents the headroom according to various antibiotics prices (as these vary greatly across settings), and ranges from £0.83 to £62.40.

### *Follow-up*

The reimbursement opportunity varied greatly according to treatment setting, fetching a higher price in settings with higher antibiotics costs (e.g. the hospital). The actual Kryptor cost (per tested patient) is £30. This indicates that headroom would only have appeared favourable for patients prescribed antibiotics costing £70 or above. This would be feasible in a secondary care setting, but not in primary care. NICE (which has not reviewed this device) now recommends limiting antibiotic prescriptions for LRTIs in primary care (NICE 2008a). Results of clinical and cost-effectiveness studies confirm the headroom results: blood tests are viable only when the infection is severe. The Brahms product range is vast, and the Kryptor compact is directed at many different clinical areas. Brahms holds licensing agreements with other companies, to provide the PCT assay compatible with various systems.

### *Main lessons learnt*

The 'baseline' for reimbursement value was 'no test', but for the development decision the baseline was a previous model, implying lower development costs and lower risks. Such an evolution may in any case be natural. Additionally, for a diagnostic test whose applications are wide, basing headroom on just one seems spurious in the context of a development decision. Furthermore, the headroom method cannot value the worth of additional features such as ease of use or size, other than to propose that these may encourage uptake.

## 7.4.11 Aquadex FlexFlow — CHF Solutions

### *Description*

A sufferer of congestive heart failure may readily decompensate, a state in which the heart fails to maintain adequate blood circulation. Acute decompensated heart failure (ADHF) is a common cause of respiratory distress, and can cause excess fluid accumulation in the blood. Fluid overload in ADHF is principally managed with diuretics, but there are limited options for diuretic-resistant patients. Ultrafiltration with Aquadex FlexFlow is suggested for refractory patients with severe fluid overload. It is a portable trolley-based device which removes excess water and salt from a patient's circulation, can be performed in a hospital ward or outpatient department, and uses lower blood flow rates than conventional ultrafiltration (which must be performed in intensive care units). Conventional ultrafiltration has existed for many years, but is not an established component of clinical practice.

**Table 7.15 Summary of headroom analysis and follow-up for Aquadex FlexFlow**

Key characteristics:	Clinical area	Acute decompensated heart failure
	Technology type	Device (Equipment). Class IIb
	Relationship with current practice/ comparator	Incremental Development / Addition
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	2004
	Market size (per year)	60,000
	Service cost impact*	£1,786 per patient [saving] (plus) £2,930 per readmission avoided [saving]
	QoL Impact*	0.0022 QALYs per readmission avoided
	<b>Headroom</b> (per patient)	<b>A selection or combination of the estimates provided above. For patients who would currently experience (one) readmission, headroom could be as much as £3,284 if Aquadex can reduce these by half.</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>The suggested barriers to adoption of conventional ultrafiltration have been:               <ol style="list-style-type: none"> <li>1) It must be delivered in an ICU (expensive);</li> <li>2) Cardiologists are accustomed to considering pharmacological rather than mechanical means of treatment for their patients.</li> </ol>               Whilst Aquadex could overcome the first barrier, it is difficult to know whether it would overcome the second.             </li> <li>How many refractory patients are there? Some reviews do not indicate that an alternative to</li> </ul>

		<p>currently available drug therapy is required.</p> <ul style="list-style-type: none"> <li>As (conventional) ultrafiltration has been around for many years, and is similar to other filtration systems (e.g. haemodialysis technology), cheaper alternatives may pose a threat to the Aquadex.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	14.5 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	The headroom figures may have indicated a favourable development decision, but should have been considered alongside the ‘development and research questions’, which highlighted potential barriers to uptake.
	Is the device used in the UK or the rest of the world?	Ultrafiltration still does not seem to be part of mainstay clinical practice for ADHF patients, but its use (and the use of Aquadex specifically) is rising. There is evidence of a UK user base.

\*Average per person treated

### *Headroom analysis*

The appropriate comparator is difficult to ascertain (pharmacological therapy to which the patient does not respond, or conventional ultrafiltration), but the literature suggests that a reduction in ICU stay of two days—to be spent in the coronary ward instead—may be appropriate for both comparators (cost saving: £1,786). There would be a saving of £2,930 per readmission avoided. The QALY impact of one hospital admission is estimated to be 0.0022 (derived from a combination and manipulation of various literature sources). Readmission rates are unclear so presented separately. The cost of provision must be considered within the headroom presented.

### *Follow-up*

The Aquadex FlexFlow system costs £12,000; consumables cost £600 per session. As the distribution factors are unknown, the system cost cannot be amortised per patient. However, even if one system is used for twelve patients and lasts just one year, the estimated headroom for treating refractory patients outweighs the transpiring cost of the system (ignoring readmission savings, and before considering staff time), indicating a favourable development

decision from the headroom analysis. The main clinical trial for Aquadex reports a reduced LOS and reduced rehospitalisation (18% vs. 32%) (Costanzo et al. 2007). Some cost-effectiveness analyses indicate that HRQoL benefit may have been underestimated in the headroom analysis. Aquadex FlexFlow is available in many countries (including the UK), and is indicated for fluid overload associated with ADHF, kidneys, lungs, burns and trauma. Ultrafiltration is still not mentioned within UK clinical guidelines for ADHF, but is supported by US, Canadian, and European guidelines.

### *Main lessons learnt*

Due to so many unknowns, the analysis was speculative and difficult to interpret, though it did identify cost and QALY estimations which could have been manipulated according to the expectations of the developer. The threats identified in the research questions have transpired to be pertinent, especially in relation to the cheaper alternatives to Aquadex, which are very cost-effective. This analysis was time-intensive due to the scarcity of relevant information in the literature.

## 7.4.12 E-medICS — QinetiQ

### *Description*

The Electronic Medical Integrated Care System (e-medICS) would provide online decision support for paramedics at the scene of emergencies. A touch-screen panel PC with voice-enabled commands provides diagnostic aids and treatment protocols across the spectrum of acute medical emergencies. It could also act as an electronic report form (ePRF), in which a patient's vital signs and digital images can be recorded and relayed to the A&E department



before arrival. This would be the first system to combine: decision support for paramedics, better and more advanced warning for A&E, and also supporting the national movement toward electronic patient records.

**Table 7.16 Summary of headroom analysis and follow-up for E-medICS**

Key characteristics:	Clinical area	Pre-hospital care
	Technology type	Device. Class I
	Relationship with current practice/ comparator	Addition
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1999
	Market size (per year)	2,900 ambulances 1 million patients per year
	Service cost impact*	[P <sub>1</sub> ≈ £2,230 per patient (current average cost of pre-hospital care). Service cost of implementing e-medICS must be considered in <i>addition</i> to this.]
	QoL Impact	-
	<b>Headroom/MRP</b>	-
	Important extra considerations	<ul style="list-style-type: none"> <li>• Extra time at the scene incidents may adversely affect outcomes. One study compares the outcome of patients attended by emergency medical technicians or (more qualified) paramedics, finding that for those attended by paramedics, the mortality rate was higher. This was thought to relate to the increased length of time at the scene in the paramedics group, and may be indicative of the impact that e-medICS would have.</li> <li>• This product belongs to the highly dynamic and fast-moving technology sector, where competition is high and development will need to be continual.</li> <li>• The success of e-medICS will rely most crucially on its acceptance by ambulance staff, and whether they consider it a help or a hindrance. This must be explored as soon as possible.</li> <li>• E-medICS would also require the backing of the hospitals' A&amp;E departments, which may require some reorganisation to be receptive to incoming information and images from the ambulance service.</li> <li>• The up-front cost of installing e-medICS across the system would be large.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	10 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Unclear- many barriers identified.
	Is the device used in the UK or the rest of the world?	No evidence of the product's existence found for the past ten years.

\*Average per person treated

### *Headroom analysis*

The value proposition of e-medICS is the provision of more appropriate initial management for emergency patients. To quantify its effect, it is necessary to understand the deficiencies of current practice. Studies that consider the health outcome effects of staff training for ambulance staff (specifically for cardio-pulmonary arrest and trauma patients) find either moderately beneficial or insignificant results, but results vary according to the study, and cannot be generalised. Whilst no headroom value is delivered, the bulk of the analysis is conveyed in sections six and seven of the pro forma (summarised briefly in Table 7.16), which raises many clinical, economic and practical questions that should be considered.

### *Follow-up*

Significant culture and change management issues were reported after a brief trial by the Surrey ambulance service of E-medICS. Post-dating the early 2000s I identified no mention of e-medICS, which is no longer on QinetiQ's website. Whilst the main barrier for e-medICS is (as anticipated) a culture one, an unpredictable context factor has been the dismantling of the NHS IT programme.

### *Main lessons learnt*

Quantification of headroom was inhibited by the huge scope of incidents attended by ambulances. Instead, relevant developments in the clinical landscape were identified. Where users are highly and intrinsically involved in device effectiveness, these users must back the concept for it to be feasible practically. Although many questions raised by the analysis transpired to be fundamental for its case, whether it would have added anything unique to QinetiQ's development considerations is difficult to know.

### 7.4.13 HeartSmart — HeartSmart Ltd.

#### *Description*

Due to the strain placed on a patient’s heart when undergoing major surgery or in intensive care, cardiac output (volume of blood pumped by the heart in one minute) must be monitored. HeartSmart is a piece of software encoded with algorithms defining the relationships between all key blood flow variables (which can be measured by pre-existing hospital equipment), the results of which could help optimise blood flow and fluid management. Currently, the reference standard for cardiac monitoring is pulmonary artery catheter thermodilution (PACTD). The literature for PACTD paints a mixed picture, at best indicating significantly reduced morbidity, and at worst demonstrating increased mortality, morbidity, and LOS. The headroom analysis considers HeartSmart to be of equal effectiveness as PACTD in its capacity to monitor cardiac output, and presents two scenarios: (1) Patient outcome and hospitalisation costs are equivalent, so only the procedural cost of PACTD is saved, and (2) the negative impact of PACTD on patient outcome (mortality) and hospitalisation costs (LOS) may be avoided by using HeartSmart.

**Table 7.17 Summary of headroom analysis and follow-up for HeartSmart**

Key characteristics:	Clinical area	Cardiac monitoring
	Technology type	Diagnostic Device. [Class IIa]
	Relationship with current practice/ comparator	Replacement
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	2004
	Market size (per year)	200,000
	Service cost impact*	Scenario 1 & CVC <sup>40</sup> used with PACTD: £145 [saving] Scenario 1& additional expenditure on CVC required: £118 [saving] Scenario 2 & CVC used with PACTD: £12,256 [saving] Scenario 2&additional expenditure on CVC required: £12,229 [saving]

<sup>40</sup> A central venous catheter (CVC) is required to provide an input measurement for the HeartSmart. It was not clear from the literature whether PACTD already involves a CVC, and so whether this was included in its cost. Therefore, headroom is presented for both contingencies.

	QoL Impact*	Scenario 1: 0 Scenario 2: 0.11 QALYs
	<b>Headroom</b> (per patient)/MRP <sup>41</sup>	<b>Least Optimistic (scenario 1, added CVC required):£118</b> <b>Most optimistic (scenario 2, CVC already used alongside PACTD): £14,456 - £15,556 **</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>• HeartSmart would require no investment in capital costs, consumables, and no maintenance requirements.</li> <li>• There are a great number of options for cardiac monitoring, and more on the horizon. HeartSmart would be competing against all of these options rather than PACTD alone. A change in baseline comparator would have a dramatic effect on the perceived headroom, especially non-invasive options.</li> <li>• Are the risks associated with CVCs prohibitive to their future use?</li> <li>• How does the output of HeartSmart relate to the use of CVC alone?</li> </ul>
	Allowable development costs calculated?	The maximum development costs indicated by the headroom analysis seem large for the HeartSmart software (£3 million to 23 million if the maximum price were charged per patient usage)
	Time taken for headroom	13.5 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom indicative of a favourable development decision.
	Is the device used in the UK or the rest of the world?	HeartSmart is available in the UK, and used by some centres.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

### *Headroom analysis*

For scenario two, the saved cost of PACTD (£145) is added to by the (evaded) LOS costs attributable to PACTD. One study finds PACTD to be associated with a two-fold increase in mortality. The average age of the relevant HeartSmart population is around 60, the life expectancy of whom (22 years) I halve to reflect underlying illness, and weight according to the average HRQoL of this age group (0.78). This is then discounted and multiplied by the potential reduced mortality rate. Headroom ranged from £118 to £15,556 per patient.

<sup>41</sup> It is unclear how this product would be priced, and whether this would be on a per patient or per package basis. For the purposes of later analysis, I call this 'headroom'.

### *Follow-up*

The wide range of headroom estimates reflects the divergent literature base. Set-up and installation of HeartSmart costs £400, and £10-£15 per HeartSmart measurement (three to four measurements are required per patient); headroom would have indicated plenty of room for development. Current literature indicates that scenario one is the more appropriate. PACTD is still the reference standard, though alternative methods are increasingly employed. HeartSmart is available in the UK, and used by various isolated centres. The reasons for only partial uptake may be the availability of effective alternatives, and the required insertion of a CVC, both of which were identified during the analysis.

### *Main lessons learnt*

Where evidence from the literature is so inconsistent, it is not possible to produce a definitive estimate of the monetary opportunity. Although the headroom was clearly large, this example was time-intensive, mainly reflecting my desire to quantify the analysis. This quantification may not have been essential for the development decision.

## 7.4.14 CT Angiography — [various developers]

### *Description*

Angiography describes a medical imaging technique used to diagnose coronary artery disease (CAD) and guide treatment. The reference standard is invasive coronary angiography (ICA), which involves coronary catheterisation. Multi-detector CT angiography (MDCTA) could offer a non-invasive and lower risk alternative to ICA, and represents the newest potential development in CT scanners. The headroom analysis investigates whether the potential

reimbursement opportunity would be sufficient to cover the investment required to make a CT scanner good enough to replace ICA for first-line investigation of CAD. Where severe occlusion (requiring revascularisation) is indicated—in about half of patients—MDCTA would need to be followed by ICA to guide treatment. Therefore, I assume that half of all ICAs may be avoided.

**Table 7.18 Summary of headroom analysis and follow-up for CT Angiography**

Key characteristics:	Clinical area	Coronary Artery Disease
	Technology type	Diagnostic (Equipment)
	Relationship with current practice/ comparator	Replacement
	Relationship with current company portfolio	Incremental development
Analysis:	Time perspective taken	2003
	Market size (per year)	-
	Service cost impact*	£710 [saving]
	QoL Impact	-
	<b>Headroom</b> (per patient)	<b>£710</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>• MDCTA involves high-dose radiation.</li> <li>• Omitted from the analysis is the benefit (QoL and reduced risk) associated with avoiding half of all ICAs, which are invasive by nature.</li> <li>• Where angiography indicates that revascularisation is required, this can be performed in the same sitting in cases where disease staging was performed by ICA, thus reducing overall costs. This may indicate an overestimation of potential savings.</li> <li>• There are many non-invasive angiography techniques in development.</li> <li>• Sensitivity and specificity has been ignored.</li> <li>• More modest costs of ICA exist in the literature, which would reduce headroom dramatically.</li> </ul>
	Allowable development costs calculated?	-
Time taken for headroom	9 hours	
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom analysis indicative of a favourable development decision.
	Is the device used in the UK or the rest of the world?	Yes, but the models have already been updated to ‘new generation’ CT scanners.

\*Average per person treated

### *Headroom analysis*

The impact on service costs of avoiding half of all ICA procedures (cost: £1,419) would be £710 per patient. Consideration of an MRP per unit (rather than patient) would require a patient throughput estimation, as well as the service cost of provision (e.g. hospitalisation, labour costs, etc).

### *Follow-up*

An MDCTA scanner costs around £600,000 to £1.2 million. If a scanner lasted five years, this would require an expected patient throughput of 170 to 340 patients per year for headroom to look attractive, just to cover equipment costs. One systematic review (Mowatt et al. 2008) indicates a cost per MDCTA session of £206, falling well short of estimated headroom (£710), possibly indicating favourable development prospects. Most clinical studies find MDCTA to be an effective ‘rule-out’ strategy, and estimates of avoided ICAs range from none to 86%. NICE recommends MDCTA as an option for patients with a low risk of CAD. The scanners considered are already out of date; ‘new generation’ CT scanners (quicker, more accurate, and with less radiation) are updates of the previous MDCTA models, and now provide first-line imaging for a subset of CAD patients (and are also used outside of CAD).

### *Main lessons learnt*

This analysis considered the reimbursement opportunity for further developing an existing technology. Encouragingly, a large UK-based HTA for MDCTA utilised the same evidence sources as those used in this quick, date-restricted headroom analysis. Most of the issues or uncertainties expressed in the research questions transpired to be important, and when considered alongside headroom, offered a good assessment of market opportunity. This case exemplified the fast-moving nature of the medical device industry.

## 7.4.15 Stapled Haemorrhoidectomy — Ethicon Endosurgery (J&J)

### Description

Haemorrhoids are swollen blood vessels in or around the anus which can cause itching, mucus discharge, pain and bleeding. Third and fourth degree haemorrhoids involve prolapse, and may be indicated for surgical removal; the Milligan-Morgan technique is the most commonly employed method of surgical haemorrhoidectomy. Stapled haemorrhoidectomy is a less painful and less invasive alternative, during which an intraluminal circular stapling device is introduced into the anal canal, the staples applied, and the redundant tissue removed.

**Table 7.19 Summary of headroom analysis and follow-up for Stapled Haemorrhoidectomy**

Key characteristics:	Clinical area	Haemorrhoids
	Technology type	Device. Class IIb
	Relationship with current practice/ comparator	Replacement
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1995
	Market size (per year)	10,300
	Service cost impact*	Scenario one (baseline estimate): £540 [saving] Scenario two (testing the effect of improvement in current practice): £300 [saving]
	QoL Impact*	0.00912 QALYs
	MRP	<b>Base-case estimate: £772 - £814 **</b> <b>[Improvement in current practice]: £482 - £574 **</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>Is it feasible for all stapled haemorrhoidectomy procedures to be undertaken as day cases?</li> <li>Might stapled haemorrhoidectomy be associated with a greater recurrence rate than surgery?</li> <li>Cost of pain management in primary care may be reduced following stapled haemorrhoidectomy compared with conventional surgical removal. This cost-saving potential is overlooked here.</li> </ul>
	Allowable development costs calculated?	For a variable cost of stapled haemorrhoidectomy of £0 to £100, maximum development costs range from around £7.4 million to £8.4 million (MRP: £814), or from £4 million to £5 million for an MRP of £482 (which assumes further improvements in current practice)
Follow-up:	Time taken for headroom	7.5 hours
	Would the headroom analysis have indicated a favourable development decision?	MRP appears sufficient to have inspired a favourable development decision.
	Is the device used in the UK or the rest of the world?	Stapled haemorrhoidectomy has been recommended by NICE, and is available across the world (but has not replaced conventional haemorrhoidectomy entirely).

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY



### *Headroom analysis*

Conventional haemorrhoidectomy usually involves three days in hospital; by reducing pain and shortening recovery time, stapled haemorrhoidectomy could be carried out as a day-case procedure. Two scenarios are presented. Scenario one reflects today's (1995) state of affairs: 10% of conventional haemorrhoidectomies are undertaken as day cases (i.e. stapled haemorrhoidectomy would reduce LOS by two days in 90% of cases, at a cost saving of £300 per day). Scenario two incorporates the possibility of future improvements in current practice, for which 50% of conventional haemorrhoidectomies are day cases. QALY impact is estimated to be the value of two fewer weeks in a health state involving 'some problems performing usual activities' and 'moderate pain or discomfort': 0.00912 QALYs per person. Assuming variable costs of production are £100 or less, the maximum allowable development costs would be £7.4 million in the base-case (assuming full market coverage).

### *Follow-up*

The price per procedure of stapled haemorrhoidectomy is £256 according to the NHSC, or £420 according to a NICE technology appraisal; the headroom analysis would have indicated ample room for development. NICE now recommends stapled haemorrhoidectomy using Ethicon's stapling device, considering it to be both clinically and cost-effective (NICE 2003;NICE 2007). Trial results indicate that early assumptions were correct—stapled haemorrhoidectomy involves less pain and shorter hospital stay—though the risk of prolapse is greater. The model submitted to NICE by manufacturers estimates an additional 0.009 QALYs from stapled haemorrhoidectomy (elicited directly from patients), incredibly close to that estimated in the headroom analysis; NICE deemed this estimate to be plausible. The two factors that hinder cost-effectiveness were both raised as potential issues in sections six and

seven of the pro forma (not all are carried out as day cases, and subsequent prolapse and re-intervention is increased).

### *Main lessons learnt*

This example demonstrated that early estimates can offer useful predictions. Where HRQoL information is not supplied by the literature, a simple manipulation of the EQ-5D value sets can usefully estimate health impact, in this case leading to an exact match (though the influencing factors differed, so this could be considered a fluke). The follow-up also revealed the flexibility of NICE's decision-making approach. Although NICE's base-case economic evaluation found stapled haemorrhoidectomy to be dominated, consideration of other factors (such as patient/clinician preference and potential for primary care savings) influenced their decision.

## 7.4.16 Transpupillary Thermotherapy — Iridex

### *Description*

Age-related macular degeneration (AMD) is a significant cause of blindness, and can be of dry or wet-form. Wet-form AMD, also called choroidal neovascularisation (CNV), is where new blood vessels grow beneath the retina which can leak and bleed, eventually forming a scar which causes a blind spot in a person's central vision. CNV can be classic (well defined stalk of vessels and localised leak) or occult. Conventional photocoagulation is standard practice for CNV, which uses an intense light beam to burn the blood vessels and seal the leak, but is not indicated for patients with occult CNV (who currently have no treatment options and who represent around 88% of all CNV patients). Transpupillary thermotherapy

(TTT) uses a low intensity infrared laser beam with a large spot slit lamp adaptor to heat the problematic blood vessels, and aims to preserve central vision. It would offer a treatment option for all CNV patients (classic or occult).

**Table 7.20 Summary of headroom analysis and follow-up for TTT**

Key characteristics:	Clinical area	Age-related macular degeneration
	Technology type	Device (Equipment). Class IIb
	Relationship with current practice/ comparator	New Indication
	Relationship with current company portfolio	Incremental Development
Analysis:	Time perspective taken	2000
	Market size (per year)	217,000
	Service cost impact*	£207 [additional cost incurred]
	QoL Impact*	0.186 QALYs
	<b>Headroom</b> (per patient)	<b>£3,513 - £5,373 **</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>• A treatment option for the previously un-treatable would be well sought after by the health service, which may be willing to pay a premium for this.</li> <li>• The equipment indicated for TTT is the same as that developed by this company (and others) for conventional photocoagulation, with a small adaption. This means that there are likely to be many competitors if it is found to be useful for occult CNV patients, and would probably be cheap to produce.</li> <li>• Would more than one treatment session be indicated per patient? Headroom is per patient rather than per procedure.</li> </ul>
	Allowable development costs calculated?	-
Time taken for headroom	6.5 hours	
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom analysis would probably have indicated a favourable development decision.
	Is the device used in the UK or the rest of the world?	NICE has not recommended TTT for wet AMD, based on deficient clinical efficacy and safety evidence. The procedure is used elsewhere in the world.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

### *Headroom analysis*

The headroom analysis considers the impact of TTT on patients suffering from occult CNV.

The principal assumption is that TTT will be as useful for occult CNV as conventional photocoagulation is for classic CNV. Given the procedural similarities, resource utilisation

outside of the treatment session itself (consultation, angiography, follow-up appointments, etc.) are assumed to be similar: £207. As TTT would be indicated for those with no current treatment options, these resource costs would represent *additional* costs to the NHS. Data for QALY gain is elicited directly from a study on the impact of conventional photocoagulation (versus the natural course of CNV). Headroom is presented per patient: £3,513 to £5,373.

### *Follow-up*

The cost for the TTT laser and delivery device is £25,000. Although no cost per patient or treatment was identified, headroom is likely to have indicated a favourable development decision, given: the cost per patient of photodynamic therapy (which is likely to be more expensive), its Medicare reimbursement per procedure (U.S.), and noting the relatively few patients that need to be treated to make back equipment costs (as well as the fact it represents an incremental development to the company's own product). NICE has not recommended TTT, on the basis of safety and efficacy evidence. TTT is reimbursed for wet AMD in some parts of the U.S., and for other specific indications elsewhere. Treatment options have grown, and a drug ranibizumab (injected into the eye) is now recommended for most CNV patients.

### *Main lessons learnt*

Unlike replacement or 'another option' devices, this represented an example of treating the previously untreatable, meaning service costs would be incurred rather than saved/redirected, thus detracting from its cost-effectiveness. Although this is counter-balanced by the effect size (large additional QALYs), it does show that only considering the 'cost-savers'—as MTAC does—favours new treatment options for those patients that are already addressed by current means of management. The headroom analysis felt somewhat artificial, as the main component of the device was already used for other ophthalmic applications. Given the

(presumably) small costs of adapting the laser equipment to TTT, this development would probably have been worth pursuing if it had even the remotest chance of working.

#### 7.4.17 Citrasate Dialysate — Advanced Renal Technologies

##### *Description*

People with chronic or acute renal failure require the assistance of a dialysis machine to remove waste products and water from their blood. A dialysis solution is used within the extracorporeal circuit and often contains heparin, an anticoagulant that prevents clotting of the circuit, but which is contraindicated in some patients (around 100 patients in the UK). Citrasate dialysate is a citric acid concentrate which could be used as part of standard bicarbonate dialysis solutions. It could improve the efficiency of dialysis, and also work as an anticoagulant for patients who cannot tolerate heparin. Where heparin is contraindicated currently, measures include periodic line flushes, regional citrate anticoagulation, and danaparoid (probably the most relevant comparator).

**Table 7.21 Summary of headroom analysis and follow-up for Citrasate Dialysate**

Key characteristics:	Clinical area	Chronic or acute renal failure
	Technology type	Device. Class IIB <sup>42</sup>
	Relationship with current practice/ comparator	Incremental Development
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1999
	Market size (per year)	Scenario 1: 4,500 Scenario 2: 100
	Service cost impact*	Scenario 1(a): £3.00 Scenario 1(b): £3.50 Scenario 2: ? (cost of danaparoid)
	QoL Impact*	-

<sup>42</sup> There is some confusion in the literature regarding the categorisation of dialysis fluids. However, within the rules set out for the classification of medical devices by the European Commission (European Commission 2010), ‘haemodialysis concentrates’ are included under Rule 3: Non-invasive devices that modify biological or chemical composition of blood, body liquids, other liquids intended for infusion. These belong to Class IIB.

	MRP (per patient per session)	Scenario 1: £3.00 - £3.50 Scenario 2: ? (cost of danaparoid)
	Important extra considerations	<ul style="list-style-type: none"> <li>Other alternatives to heparin are being investigated, including low molecular weight heparins which may perform better than current anticoagulants, and not be contraindicated in patients who currently do not tolerate unfractionated heparin.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	6 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Prices were difficult to obtain, but overall, headroom is likely to have indicated a favourable development decision (especially if scenario two was deemed feasible).
	Is the device used in the UK or the rest of the world?	Citrasate dialysate is available globally. It is not used systematically across the NHS, but does seem to be a viable treatment option (currently procured by 6 NHS hospitals).

\*Average per person treated

### *Headroom analysis*

Two approaches are described. Scenario one considers Citrasate simply to substitute current acid additives for bicarbonate dialysate fluids (for use in all patients), and is split into two approaches: (a) considers Citrasate to be worth the price of current acid additions to bicarbonate solutions—£3, and (b) adds to this the value of a potential improvement in dialysis efficiency, around £0.50 per session.<sup>43</sup> Scenario two considers its use exclusively in those patients for whom heparin is contraindicated, for which the headroom would be the price per session of danaparoid (whose precise cost could not be identified, but is indicated to be large). Citrasate dialysate is unlikely to pose any significant / measurable impact on QoL.

### *Follow-up*

Given the very specific nature of this analysis, follow-up was difficult; prices were not readily available and the quantity required per session was unclear. One source indicates a price for Citrasate higher than the MRP in scenario 1, whereas the company's own website implies a

<sup>43</sup> This is based on an HTA which compares two dialysate fluids (bicarbonate and acetic), one of which (bicarbonate solutions) is more efficient and associated with smaller complications costs (MacLeod et al. 1998).

much lower price. Citrasate is almost certainly cheaper than danaparoid. Citrasate is available widely in the U.S. and across the world (though received EU clearing seven years after it was available in the U.S.). The (limited) literature indicates positive results for Citrasate in terms of efficiency of dialysis and anticoagulation.

#### *Main lessons learnt*

The diffusion of this product demonstrates how slow uptake can be. It offered an example of a product with a very specific application, for which prices were difficult to identify. This may have posed less of a problem for the developer.

#### 7.4.18 Tension free vaginal tape (TVT) — Ethicon

##### *Description*

Stress incontinence is the involuntary loss of urine upon physical exertion. After conservative treatments in women have failed, the bladder neck is repositioned in a surgical procedure called Burch colposuspension. Tension free vaginal tape (TVT) would be a less invasive and quicker alternative to colposuspension, involving a mesh tape being attached under the urethra via the vaginal wall like a sling. This minimally invasive technique, which will be assumed to achieve the same long-term outcomes as surgery, is likely to lower the threshold for intervention. Therefore the headroom analysis considers two groups: those for whom TVT directly replaces colposuspension ('group 1'-around 4,000 per year in England), and a wider group that includes patients who are currently treated conservatively ('group 2'-potentially up to 100,000).

Table 7.22 Summary of headroom analysis and follow-up for TVT

Key characteristics:	Clinical area	Stress incontinence in women
	Technology type	Device. Class IIb
	Relationship with current practice/ comparator	Replacement
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	1996
	Market size (per year)	Group 1:4,000 Group 2: 100,000 (96,000 when considering only those that currently do not undergo surgery)
	Service cost impact*	Group 1: £2,700 [saving] Group 2: £66 [saving]
	QoL Impact*	Group 1: - Group 2: 0.1 to 0.2 QALYs
	<b>Headroom</b> (per procedure)	<b>Group 1: £2,700</b> <b>Group 2: £4,066 - £6,066 ** or £2,066 - £3,066**</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>• QoL impact of TVT versus colposuspension was ignored, but may be important for patients and their clinicians.</li> <li>• Less invasive methods of colposuspension are beginning to emerge, which could change the relevant comparator for TVT.</li> <li>• Success rate for TVT in those previously managed conservatively has been implicitly assumed to be 100%. This may not be appropriate.</li> <li>• Full recovery of HRQoL may not be an appropriate baseline for health outcome estimations.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	10 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Favourable development decision
	Is the device used in the UK or the rest of the world?	TVT is now widely considered to be the gold standard in surgical management of stress incontinence.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

### *Headroom analysis*

The main cost-saving potential of TVT versus colposuspension is in hospital costs (shorter operation time and reduced LOS—six hours as opposed to three days). Due to the limited data predating 1996 on hospital service costs (to estimate the procedural cost of TVT and thereby net this from headroom), service cost impact is simply presented as the cost of colposuspension for group one (£2,700) and the average cost of conservative treatment for



group 2 (£66). There is assumed to be no HRQoL impact for group 1, and a HRQoL gain of between 0.1 and 0.2 QALYs for group 2 (who used to receive conservative management). This was estimated by manipulation of the relevant EQ-5D health state parameters—a one year timeframe is taken. Headroom (which must include the procedural and hospital costs of TVT) is £2,700 for group one, and between £2,066 and £6,066 for group two, depending on the developer's beliefs of potential effectiveness.

### *Follow-up*

Total TVT procedure costs fall below headroom estimates, indicating that these may have appeared viable for development. TVT is used widely within the NHS and has been recommended by NICE; it now replaces colposuspension as the gold standard surgical intervention for stress urinary incontinence. The procedure has been found to be cost-effective, and has increased the number of patients undergoing surgical intervention (but not to the extent proposed in the headroom analysis). Ethicon have expanded their portfolio of products, now selling five variations of TVT.

### *Main lessons learnt*

When considering the potential impact of TVT versus colposuspension on hospital stay, then this alone presents a clear case for TVT development (without spending 10 hours identifying numbers). QALY implications were overestimated using the EQ-5D parameter manipulation approach. Although the estimated HRQoL for incontinent women of 0.8 was identical to that identified in a later study used by NICE (Cody et al. 2003), the return to a baseline of full health was misjudged. The case study demonstrates that companies are always developing new versions of their own products, in order to stay dominant in the market.

#### 7.4.19 Penile cuff test, CT3000 — MediPlus Ltd.

##### *Description*

Lower Urinary Tract Symptoms (LUTS) in men include problems with both storing and voiding urine; the decision to intervene surgically (by means of a prostatectomy) is dependent on symptom severity and responsiveness to conservative treatment. The CT3000 penile cuff test offers a non-invasive pressure flow analysis, which could indicate the appropriateness of prostatectomy. The current ‘gold standard’ diagnostic test is an invasive urodynamic study, which is costly and requires urinary catheterisation and a rectal manometer. The best non-invasive method is peak urinary flow rates, but these cannot distinguish between obstruction (which would indicate prostatectomy) and bladder muscle weakness. Misclassification is a common reason for prostatectomy failure; around a third of men who currently undergo prostatectomy do not benefit from the procedure. I assume that the provision of this extra diagnostic test for urologists (to be used as an option/as well as/instead of current bladder function tests) would increase the overall success rate of prostatectomy from 70% to 90% by improved targeting.

**Table 7.23 Summary of headroom analysis and follow-up for Penile cuff test, CT3000**

Key characteristics:	Clinical area	Lower Urinary Tract Symptoms (LUTS)
	Technology type	Diagnostic device (Equipment)
	Relationship with current practice/ comparator	Another Option
	Relationship with current company portfolio	-
Analysis:	Time perspective taken	2002
	Market size (per year)	550 [number of units required to cover all relevant patients]
	Service cost impact	£10,000,500 [saving: total per year] £18,183 [saving: per unit per year]
	QoL Impact	-
	<b>Headroom</b> (per unit per year)	<b>£18,183</b>
	Important extra considerations	<ul style="list-style-type: none"> <li>In order to keep the analysis simple, I have not considered the costs that could be saved from a potential reduction in other urodynamic investigations (average cost: £114), or quantified the extra costs required to provide the CT3000 test (15</li> </ul>

		<p>minutes preparation/operation time by a junior technician, and 5 minutes per day from a senior technician for calibration).</p> <ul style="list-style-type: none"> <li>Although the avoidance of undergoing invasive surgery would be important for patients, the value of this has not been incorporated into headroom.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	5 hours
Follow-up:	Would the headroom analysis have indicated a favourable development decision?	Headroom is larger than actual prices, indicating that the analysis would probably have presented a sufficient reimbursement opportunity at the early stages.
	Is the device used in the UK or the rest of the world?	The device is used within various NHS trusts and across the globe.

### *Headroom analysis*

6,667 prostatectomy procedures could be avoided per year in England and Wales by better targeting of the procedure. This would generate a saving of £10,000,500 in total; if 550 units are required to test all relevant patients, each unit would be associated with £18,183 of cost savings per year. Whilst not impacting long term outcomes, short term QoL benefits are likely to arise from avoiding the disutility associated with (unnecessary) invasive prostatectomy; this is not quantified in this analysis.

### *Follow-up*

Given the actual equipment (£11,000) and consumables (£5.50 per test) costs associated with the CT3000, the headroom surpasses these (in the first year alone), indicating that the development opportunity is likely to have appeared favourable based on this analysis. The CT3000 is used in various NHS trusts (at least six across England), and also in Spain, Switzerland and the U.S. The centre for evidence-based purchasing (CEP) provide a favourable report on the CT3000 (CEP 2007). The assumptions made in the headroom analysis appear viable; a clinical study (Harding et al. 2007) has shown a prostatectomy

success rate of 87% following targeting with the CT3000, and the company confirm that it is to be used as an adjunct rather than a replacement of current methods of diagnosis.

### *Main lessons learnt*

Despite being a piece of equipment, a headroom per device was achievable as an estimate of the number needed to service all relevant patients was provided in the NHSC documentation. Although longevity was unknown, this offered a better idea of value *per device* for this piece of equipment. It also offered another example of sufficient headroom being identified in its cost-saving potential, limiting the need to quantify HRQoL impact.

## 7.4.20 PFO Closure — NMT Medical / St.Jude Medical

### *Description*

Patients who suffer from migraine with aura experience painful migraine episodes that are accompanied by visual and other neurological disturbances (light flashes, clouded vision, pins and needles, hearing, vertigo, etc).

In the womb, babies have a small opening between the right and left atria of the heart, allowing blood to bypass the lungs; this hole usually closes soon after birth. A person has a patent foramen ovale (PFO) when this hole remains patent throughout life, which is reasonably common and usually causes no problems, but is a well-established risk factor for ischaemic stroke. PFO closure (which has already been used for stroke patients), may also be useful for people who suffer from refractory migraine with aura. An umbrella-like closure device is placed to seal the PFO, which may reduce the frequency and impact of migraine attacks.

Table 7.24 Summary of headroom analysis and follow-up for PFO Closure

Key characteristics:	Clinical area	Migraine
	Technology type	Device. Class III
	Relationship with current practice/ comparator	New indication
	Relationship with current company portfolio	Device already developed, for other indications. The headroom method is being applied to explore its value in this market, in order to inform the decision of whether to invest in the research required to prove its clinical merit for migraine.
Analysis:	Time perspective taken	2005
	Market size (per year)	-
	Service cost impact*	Time horizon- 1 year: £843 [cost incurred] Time horizon- 5 years: £391 [cost incurred] Time horizon- 10 years: £93 [saving] Time horizon- 20 years: £843 [saving]
	QoL Impact*	Time horizon- 1 year: 0.021 QALYs Time horizon- 5 years: 0.0981 QALYs Time horizon- 10 years: 0.1808 QALYs Time horizon- 20 years: 0.3089 QALYs
	<b>MRP</b>	Time horizon- 1 year: -£423 to -£213 ** Time horizon- 5 years: £1,571 to £2,552 ** Time horizon- 10 years: £3,709 to £5,517 ** Time horizon- 20 years: £7,021 to £10,110 **
	Important extra considerations	<ul style="list-style-type: none"> <li>An association between PFO and migraine has been identified, but whether there is a <i>causal</i> link remains to be proven. This will be critical.</li> <li>PFO closure devices have been found to be efficacious at sealing PFO for stroke patients. However, there has been no conclusive evidence to show that this has reduced the risk of stroke (and therefore is not recommended in a NICE IPG).</li> <li>The effect of migraine on productivity is large, which has a big knock-on effect for the whole economy. These indirect costs are between ten and fifty times those incurred directly by the health service.</li> <li>The process and cost that would be associated with PFO <i>investigation</i> has gone unmentioned. As it is likely that only around half migraine with aura patients may have PFO, investigative screening and its associated cost should be considered.</li> </ul>
	Allowable development costs calculated?	-
	Time taken for headroom	8.5 hours
	Follow-up:	Would the headroom analysis have indicated a favourable development decision?
Is the device used in the UK or the rest of the world?		PFO closure in migraine patients has not been integrated into clinical practice, on the grounds of clinical ineffectiveness.

\*Average per person treated

\*\*Depending on a WTP by the health service of £20,000-£30,000 per QALY

### *Headroom analysis*

In this case, headroom is calculated not for a development decision per se, but to ascertain the potential value of PFO closure devices in a new clinical area, to observe whether this could accommodate the devices' price (additionally, targeting this market would require costly research to prove effectiveness). I assume that the relevant migraine with aura patients cost the NHS £245 per year, and that this could be halved after PFO closure. The procedure may have similar resource implications as angiography (£1,221), but involve just one hospital bed day rather than two (average cost for an excess bed day in this area: £255). The resultant service cost for providing PFO closure would be around £966 (one-off cost). As a proxy for QALY impact, the result of an HTA on acupuncture therapy for migraine is used, which generates 0.021 QALYs over a year. Whilst procedural costs are one-off and incurred today, savings in treatment costs and impact on HRQoL would accumulate over a patient's lifetime. MRP is presented for one, five, ten, and twenty year time perspectives, and range from -£423 (NHS would need to be *given* money to consider the procedure) to £10,110.

### *Follow-up*

In the headroom analysis, the initial investment required to undertake the PFO procedure more than outweighed the combined value of health benefit and saved medication costs seen in the first year, even before the device price is incorporated. Given an actual price of around £4,000 per PFO closure device, the NHS would need to take at least a ten year time horizon before the procedure has a net health economic gain, given the assumptions made in the headroom analysis. The result of headroom in terms of decision to pursue this market is uncertain, but it should be noted that the health economic case for the product hinged crucially on its proposed health impact (the net cost of the procedure is high), and even with

optimistic efficacy assumptions, the decision to pursue this market was unclear. Important caveats were the potential cost of screening, investment required for research, and the uncertainty surrounding the relationship between PFO and migraine. PFO closure seems no longer to be indicated for migraine patients, and NICE does not recommend the procedure due to insufficient evidence. NMT Medical undertook the only RCT for PFO in patients with migraine, which did not produce favourable results (and was shrouded in controversy and expensive libel suits, see Appendix 6 for details); the company has since gone bust. St. Jude Medical began an RCT which has subsequently been abandoned. As this company has a larger product portfolio than NMT medical, this is likely to have been less critical for them.

### *Main lessons learnt*

Although PFO closure turned out not to be viable clinically, the case study brought up some interesting considerations: (a) the method can be used to investigate the potential of an existing product within a new market; (b) the timeframe willing to be considered by the reimbursers can be critical; (c) interventions for clinical areas in which most costs are born by the patient are less likely to appear cost-effective; (d) strategic issues such as the free-riding of research might be important; (e) RCTs that involve sham surgery can be difficult and; (f) targeting new markets can be risky (but less so for larger companies). Specific costs and prescription guidelines were difficult to identify during the analysis, but this may have been easier for the manufacturer. Although clinical efficacy cannot be predicted with certainty, information that is currently available should influence an early judgement. The interesting follow-up for this case study showed that companies are predisposed to bias, and this can even extend to misinterpretation and misrepresentation of results in RCTs (whose very design should eliminate biases). Given the subjective nature of a headroom analysis, might companies always find a favourable case for development?

## 7.5 Headroom Results

This section presents the principal lessons drawn from the application of the headroom method to these 20 case studies. Firstly, overall characteristics of the technologies and headroom results are outlined, and potential relationships between these are explored. This is followed by a list of the main headroom lesson themes, and the strength of support for these themes from the data.

The explanation of potential decision outcome was given for each case study in the summary section. In most cases the decision outcome was not absolutely clear cut, but an inclination was presented and explained. For illustrative purposes, I generally err on the side of certainty in this presentation of results (except in two cases where this would have been too speculative), describing the headroom decision outcome as favourable, unfavourable, or intuitively favourable/unfavourable in cases where no headroom number was generated. Evidence of uptake of the technologies is used as a proxy for commercial success. Three levels of uptake are considered: (a) evidence of any uptake within the NHS for the specified indication, (b) evidence of *widespread* uptake within the NHS for the specified indication, and (c) evidence of any uptake (globally or for other clinical indications). It is important to reiterate that the favourability or otherwise of the development decision informed by the headroom analysis (as summarised in the third column of Table 7.27) is based only on the numerical assessment that was generated by the headroom analysis (with the exception of the four cases that were made intuitively). It therefore does not encompass the suggestions or warnings provided by sections six and seven of the pro forma.



Table 7.25 Summary of NHSC case studies: Characteristics

Characteristics							
	Type*	Regulatory class	Equipment**	Relationship with		Clinical area	NICE guidance?*****
				Comparator***	Company portfolio		
1. FibroTest	IVD	-	-	R	-	Liver disease	-
2. MARS	Device	IIb	Equipment	NI	-	Liver failure	IPG
3. SpeechEasy	Device	IIa	-	ID	-	Stammer	-
4. SLF bypass graft	Device	IIb	-	ID	-	PAD	-
5. Meniett	Device	IIa	-	AO	-	Ménière's disease	IPG
6. AmpliChip	IVD	-	-	NI	-	Breast cancer	-
7. Agento I.C.	Device	IIa	-	ID	-	VAP	-
8. Cool-Cap	Device	IIa	Equipment	NI	-	Perinatal asphyxia	IPG
9. ChondroCelect	Other: ATMP	-	-	ID	-	Cartilage defect	-
10. Kryptor compact	IVD	-	Equipment	NI	ID	LRTI	-
11. Aquadex FlexFlow	Device	IIb	Equipment	NI/A	-	ADHF	-
12. E-medICS	Diagnostic device	I	Equipment	A	-	Pre-hospital care	-
13. HeartSmart	Diagnostic device	[IIa]	Equipment	R	-	Cardiac monitoring	-
14. CT angiography	Diagnostic device	[IIa]	Equipment	R	ID	CAD	CG
15. Stapled haemorrhoidectomy	Device	IIb	-	R	-	Haemorrhoids	IPG & TA
16. Transpupillary thermotherapy	Device	IIb	Equipment	NI	ID	AMD	IPG
17. Citrasate dialysate	Device	IIb	-	ID	-	Renal failure	-
18. TVT	Device	IIb	-	R	-	Urinary incontinence	CG
19. Penile cuff test	Diagnostic device	[I]	Equipment	AO	-	LUTS	-
20. PFO closure device	Device	III	-	NI	Already developed	Migraine	IPG

\*In the selection strategy section presented at the beginning of the chapter, medical technologies were either defined as 'device' (labelled 'Device' in this column) or 'diagnostic' (which includes 'IVD' [in-vitro diagnostic] or 'diagnostic device' in this column). Whilst diagnostic devices technically belong to the devices category from a regulatory perspective, they have been set apart here due to their use for diagnostic purposes, which makes the health economics approach distinct. ATMP is an advanced therapy medicinal product.

\*\*Describes whether the product is a piece of equipment (used for multiple patients)

\*\*\*Replacement (R); New indication (NI); Incremental development (ID); Another option (AO); Addition (A).

\*\*\*\*This describes whether (and what type of) NICE guidance was available for follow-up: Interventional Procedures Guidance (IPG); Clinical Guideline (CG); Technology appraisal (TA).

Table 7.26 Summary of NHSC case studies: Analysis

Analysis						
		Estimate provided?				
	Date perspective	Market size	Δ Service costs *	ΔQALYs **	Development cost analysis	Time taken (hours)
1. FibroTest	2001	Yes	Yes (incomplete)	Yes (lit)	Yes	6
2. MARS	1997	Yes	No	Yes (lit)	No	12
3. SpeechEasy	2005	No	No (unnecessary)	No (unnecessary)	No	6
4. SLF bypass graft	2006	No	No	No (unnecessary)	No	8.5
5. Meniett	1999	Yes	Yes	No	Yes	9
6. AmpliChip	2004	Yes	No	No	No	8.5
7. Agento I.C.	2005	Yes	Yes	Yes (lit)	Yes	10
8. Cool-Cap	1997	Yes	No (unnecessary)	No (unnecessary)	No	7.5
9. ChondroCelect	2006	Yes	No (unnecessary)	No (unnecessary)	No	8
10. Kryptor compact	2005	Yes	Yes (incomplete)	No (unnecessary)	No	11
11. Aquadex FlexFlow	2004	Yes	Yes (incomplete)	Yes (lit)	No	14.5
12. E-medICS	1999	Yes	No	No	No	10
13. HeartSmart	2004	Yes	Yes	Yes (lit)	Yes	13.5
14. CT angiography	2003	No	Yes (incomplete)	No	No	9
15. Stapled haemorrhoidectomy	1995	Yes	Yes	Yes (EQ-5D)	Yes	7.5
16. Transpupillary thermotherapy	2000	Yes	Yes (incomplete)	Yes (lit)	No	6.5
17. Citrasate dialysate	1999	Yes	Yes (incomplete)	No	No	6
18. TVT	1996	Yes	Yes (incomplete)	Yes (EQ-5D)	No	10
19. Penile cuff test	2002	Yes	Yes (incomplete)	No (unnecessary)	No	5
20. PFO closure device	2005	No	Yes	Yes (lit)	No	8.5

\*Service cost estimates were either provided in full—‘Yes’; provided but incomplete—‘Yes (incomplete)’; not provided as it was unnecessary or inappropriate to do so—‘No (unnecessary)’; or not provided, usually due to the complex nature of potential impact—‘No’.

\*\*Impact on QALYs was either not provided because of the difficulty in doing so—‘No’; not provided as it was unnecessary or inappropriate to do so—‘No (unnecessary)’; estimated by manipulating the EQ-5D health parameters—‘Yes (EQ-5D)’; or estimated using data derived from the literature—‘Yes (lit)’.

Table 7.27 Summary of NHSC case studies: Results

Results					
			Evidence of uptake		
	Output	Headroom development decision?*	Evidence of any uptake within the NHS for the specified indication?	If 'Yes' to previous, is there evidence of <i>widespread</i> NHS uptake?***	Evidence of any uptake? (Globally or for other clinical indications?)
1. FibroTest	Headroom	Favourable	Yes	No	Yes
2. MARS	Headroom	Favourable	Yes	No	Yes
3. SpeechEasy	<i>Headroom method not fit for consumer products</i>				
4. SLF bypass graft	-	Intuitively favourable	Yes	No	Yes
5. Meniett	MRP	Unfavourable	No	-	Yes
6. AmpliChip	-	Intuitively unfavourable	No	-	Yes
7. Agento I.C.	MRP	Favourable	No	-	Yes
8. Cool-Cap	-	Intuitively favourable	Yes	No	Yes
9. ChondroCelect	-	Intuitively unfavourable	Yes	No	Yes
10. Kryptor compact	Headroom	Favourable	Yes	No	Yes
11. Aquadex FlexFlow	Headroom	Favourable	Yes	No	Yes
12. E-medICS	-	Uncertain	No	-	No
13. HeartSmart	Headroom	Favourable	Yes	No	Yes
14. CT angiography	Headroom	Favourable	Yes	No	Yes
15. Stapled haemorrhoidectomy	MRP	Favourable	Yes	Yes	Yes
16. Transpupillary thermotherapy	Headroom	Favourable	No	-	Yes
17. Citrasate dialysate	MRP	Favourable	Yes	No	Yes
18. TVT	Headroom	Favourable	Yes	Yes	Yes
19. Penile cuff test	Headroom	Favourable	Yes	No	Yes
20. PFO closure device	MRP	Uncertain	No	-	No

\***Note:** This development decision indication is taken from the numerical part of the headroom analysis only (apart from the intuitive decisions). As explained in the description of each case study, the research questions were always pertinent. See below for discussion of this.

\*\*Evidence of 'widespread' uptake is determined by the relevant clinical literature (indicating that it has become the 'gold standard') as well as NICE guidance.

### 7.5.1 General observations and trends

Table 7.25 outlines the main characteristic of the study sample. Of the 20 medical technologies analysed, twelve were devices, four were diagnostic devices, three were in vitro diagnostics and one was an ATMP. Their regulatory classes, which generally reflect risk, ranged from I to III, but were mainly IIa or IIb. The paucity of class I devices (only two) reflects the NHSC's remit. Whilst this is not representative of the industry as a whole, it may be representative of those devices for which headroom would be most useful. Nine case studies were pieces of equipment. There was a variety in change proposition: five replacements, six new indications, five incremental developments, two 'another option's, one addition and one mixed. There were four case studies for which the company's own baseline was not 'nothing' (i.e. they represented incremental developments or ready-established products), and eight had NICE guidance for follow-up (only one was a technology appraisal).

Table 7.26, which describes the analysis inputs and outputs, shows that UK market size could not be identified in four cases. Service cost impact was not estimated in seven cases, but three of these were because this was unnecessary or inappropriate. Incomplete service cost estimations were usually a result of not understanding the suggested implementation of the new device; this was mainly due to lack of clarity or detail in the briefing. Estimates may have been more complete had they been elicited from the developer. QALY impact was estimated for nine cases, and just over half of the missing QALY estimates were due to their inclusion being unnecessary. Only five case studies were accompanied by development cost analysis. The mean time taken per headroom analysis (pre follow-up) was 8.85 hours (median: 8.5; range: 5 to 14.5). Although the case studies with the date perspective further back in time felt more difficult, this was not reflected in time taken, which was actually a

mean of 8 hours for the earlier half (those dated pre-2002—the average year), and 9.3 hours for the later ones.

The results table (Table 7.27) shows the categorical outcomes of each case study: the principal output (MRP, headroom or nothing), the likely decision to have been made from this, and the degree of its subsequent uptake. Five case studies generated an MRP, nine a headroom estimate, and six produced no numbers. However, only one of the case studies that produced no headline monetary estimate resulted in an ‘uncertain’ development decision; the rest resulted in intuitively favourable/unfavourable headroom decisions, based on an exploration of the relevant numbers and other factors. Headroom analysis led to what was considered to be a favourable development decision in fourteen cases, unfavourable in three cases, and uncertain in two cases (SpeechEasy is the missing case here).

The anomaly within the sample was SpeechEasy, which was a consumer purchase. Although this was an exclusion criterion, this only became apparent after some investigation. The case study was left in as it was deemed to be a pertinent example, both highlighting the difficulty in evaluating technologies whose demand will be consumer (patient)-led, and being an example of a typical offering of innovation in the device sector: a small change to an existing technology. That the headroom method would encounter difficulties in evaluating a device whose customer is not the health service is no surprise—such a device is not likely to ever undergo an economic evaluation, at least not by NICE. ChondroCelect was another outlier as this was neither a device nor a diagnostic.

#### *7.5.1 (i) Are there any characteristics of a good headroom candidate?*

The characteristics of the medical technologies for which headroom/MRP/no estimate were calculated may indicate the type of medical technology to which the headroom approach is

best suited. Overall, the analyses that resulted in an MRP took a mean of 8.2 hours (median: 8.5), those that provided a headroom estimate took 9.7 hours (median: 10), and those for which no monetary estimate was calculated took a mean of 8.1 hours (median: 8.25).

Categorising all technology disease areas according to whether headroom/MRP/no estimate was generated reveals no obvious patterns; all three categories contain examples of chronic and transient medical problems. 60% of case studies for which an MRP was generated had NICE guidance for follow-up, versus 45% for those with headroom and 17% for those with no monetary estimate. This reflects the greater ease of analysis for those technologies that are relevant for national economic evaluation. There was no clear pattern in how the change proposition (relationship with current practice) related to outcome type, apart from the fact that all 'replacement' technologies generated either headroom or MRP. Unsurprisingly, none of the 'equipment' technologies resulted in an MRP, as the briefing notes lacked detail regarding the distribution and patient throughput parameters of these. In terms of regulatory classification, 60% of MRPs were for devices of class IIb or above, compared with 57% for headrooms and 25% for those with no monetary estimates. The time perspective taken for the analyses had no impact on output type. All five case studies that were able to generate an MRP were devices.

The above analysis indicates that whilst some factors seem to be significant in the ability to estimate value, no individual characteristic appears overwhelmingly prohibitive. The biggest factor seems to be technology type: no MRPs were generated for the diagnostic technologies (though most were able to produce a headroom estimate). This may relate to the greater difficulty in understanding the potential health and cost impact for diagnostics.

### 7.5.1 (ii) *Relating headroom to subsequent market uptake*

The potential implications of using the NHSC database as the source of case studies were described early in the chapter, and are confirmed by the ‘evidence of uptake’ results. Whilst the primary aim of follow-up was to determine the NHS uptake of a product for the clinical application investigated by the headroom analysis, evidence of *any* uptake (globally) provides a better indication of general product viability. For all but two of the products, some evidence of uptake was identified. This is unsurprising, since the NHSC database provided a close-to-market sample of case studies. This should be taken into account when interpreting the result statistics presented below, along with the fact that the postulated decision to develop is in relation to quantified headroom only. Additionally, though informed by the literature, the implications of the headroom analyses in terms of the suggested decision outcomes (which were generally informed by their follow-up) were speculative. Whilst these three factors may make the statistics generated somewhat artificial, by exploring what they convey we can explore the possible implications of using a numerical headroom assessment (as the headroom method has traditionally been described) to explore the feasibility of uptake.

Figure 7.1 summarises graphically the uptake results in relation to whether headroom was perceived to be favourable, unfavourable, or uncertain. As headroom considers the potential for a product’s reimbursement within the NHS context specifically (and for the clinical indication originally specified), the medium-grey lines show the total number of products which achieved NHS uptake; the dashed box indicates the proportion of these that achieved widespread uptake (becoming the gold standard for the clinical scenario considered)<sup>44</sup>. The number of products which did not achieve NHS uptake is shown underneath this in white.

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<sup>44</sup> Widespread uptake was determined in both cases by favourable NICE recommendations, as well as the current clinical literature (which implies that these are the new reference standard) and indications from wider patient-facing information sites and manufacturers’ websites.

Presented alongside these is the number of products which turned out to be viable, which is shown by the light-grey lines and represents the total number of products for which there has been evidence of some uptake (including international uptake and use of the product outside of the original clinical specification).

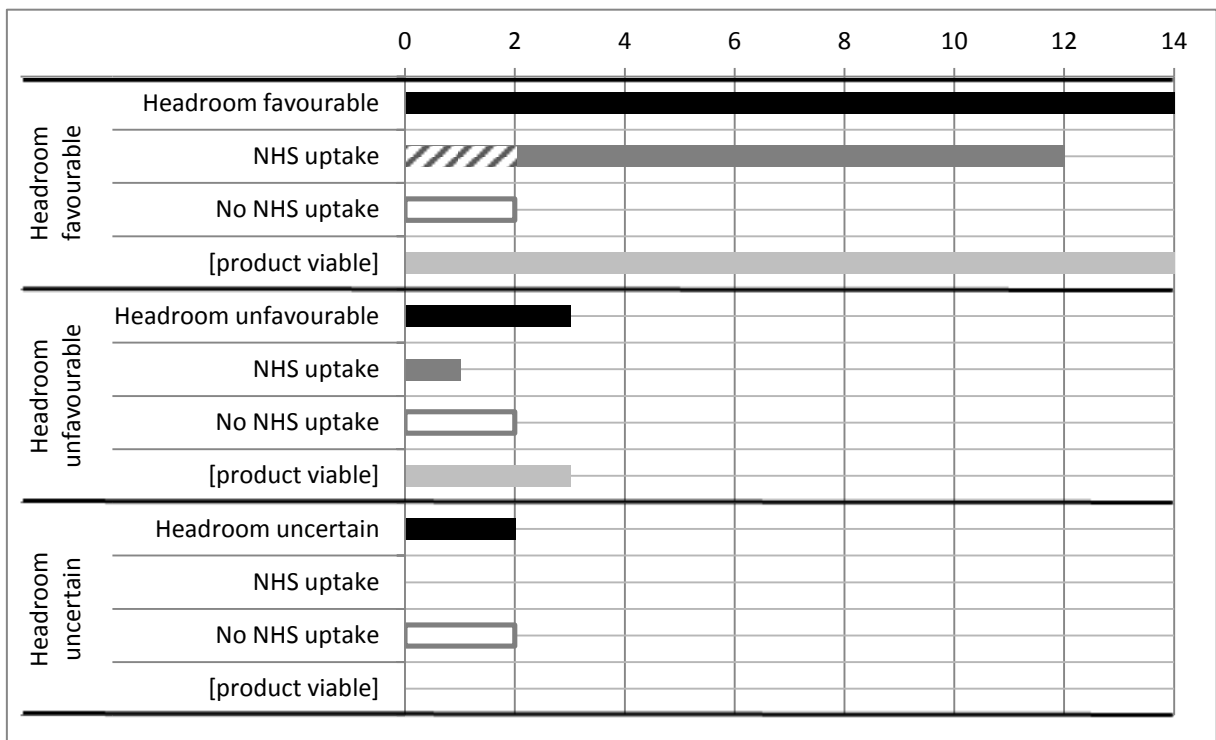


Figure 7.1 Summary of headroom decisions and subsequent uptake

If product success was defined by becoming the gold standard in clinical practice, then Figure 7.1 demonstrates that this was only achieved for two products (headroom was considered to be favourable for both: stapled haemorrhoidectomy and TVT). However, the market landscape described in chapter 3 demonstrated that this is rarely achieved for medical technology, due to strong product competition and the important role of user preferences. Therefore, it may be more appropriate to judge the relevance of headroom against evidence of



any NHS uptake (in relation to the clinical application considered by the headroom analysis); this is the definition of NHS uptake utilised for the performance statistics outlined below.

Figure 7.1 shows that 12 of the 14 products for which headroom appeared to be favourable achieved some level of NHS uptake. The two that did not were due to clinical ineffectiveness (TTT) or what appears to be a change in clinical practice (Agento IC: follow-up indicated that this device may indeed be cost-effective, but has not achieved NHS uptake due possibly to the implementation of other guidelines of best practice; these were highlighted descriptively in the headroom analysis). The headroom decision outcome was described as uncertain in two cases: E-medICS (for which no number was generated) and PFO closure (for which an MRP was generated). These represent the two products in the study sample which appear not to be viable products. The headroom analyses for these two products offered strong caution around the case for development, but as I cannot be sure how these would have been interpreted, it may be unwise to infer that they would have engendered an unfavourable decision. The effect on the summary statistics of having interpreted these uncertain decisions as unfavourable ones will be discussed briefly below.

At the outset of the project, it was thought that a headroom analysis that was indicative of a favourable development decision would hopefully lead to subsequent uptake, but this may not always be the case, e.g. where early expectations of clinical effectiveness transpire to be too optimistic. This led to the perhaps more appropriate definition: that the headroom method should be used to ‘rule-out’ technologies that will never be cost-effective. Headroom was considered unfavourable in three cases, two of which have not achieved NHS uptake (and thus were successfully ‘ruled-out’). However, by this logic, any headroom analysis that would have indicated an unfavourable development decision but that actually *has* achieved NHS uptake, may disprove the method. This was the case in one headroom analysis:

ChondroCelect. Although no monetary headroom was presented, the case for development was intuitively unfavourable, given the necessary requirements of clinical effectiveness or cost for ChondroCelect, based on NICE’s evaluation of the technology that ChondroCelect was incrementally developing. These did not seem feasible, and indeed the product has not proven to offer such large benefits. However, ChondroCelect (an ATMP rather than a device or diagnostic) *is* offered by some specialists, due to alternative methods of reimbursement (e.g. pass-through payments by the NHS for some new technologies).

The Contingency Table 7.28 describes the relationship between the headroom result and NHS uptake (the reference). The ‘uncertain’ headroom decisions are omitted (as well as SpeechEasy), making the denominator 17.

**Table 7.28 Headroom and NHS Uptake contingency table**

		REFERENCE		
		NHS Uptake	No NHS Uptake	
HEADROOM	Favourable	12	2	14
	Unfavourable	1	2	3
		13	4	17

Based on the data presented, Table 7.29 provides the common measures of test performance for the headroom method.

**Table 7.29 Summary headroom performance statistics and their interpretation**

Sensitivity	0.92	Of those that achieved NHS uptake, the proportion for which headroom was favourable
Specificity	0.50	Of those that did not achieve NHS uptake, the proportion for which headroom was unfavourable
Positive predictive value	0.86	Of those for which headroom was favourable, the proportion that went on to achieve NHS uptake
Negative predictive value	0.67	Of those for which headroom was unfavourable, the proportion that were unsuccessful in achieving NHS uptake
Accuracy	0.82	‘Getting it right’: the proportion of case studies whose subsequent NHS uptake was correctly predicted

The low specificity of the headroom method (50%) reaffirms the fact that a favourable headroom result does not guarantee future uptake, meaning that false positives are not uncommon (two out of the four that did not achieve NHS uptake had been considered favourable, and thus represent false positives). The use of optimistic early assumptions (which may reasonably transpire to be too optimistic) intends to rule-out the perusal of device ideas that could *never* be cost-effective, and therefore it is no surprise that specificity is low. More importantly therefore, the headroom method should not rule-out technologies that have some chance of future uptake. It is for this reason that sensitivity is the more important measure here. Sensitivity was found to be not 100% but 92%, due to the one case described above for which alternative means of reimbursement has led to the uptake of a technology which, by NICE standards, cannot (currently) be considered cost-effective: ChondroCelect.

The positive predictive value of 0.86 indicates that 86% of those products for which a favourable headroom case was provided later achieved NHS uptake. More interesting, however, is the negative predictive value which shows how predictive the headroom method is as a rule-out tool; this illustrates that just 67% of those for which headroom appeared unfavourable did not achieve NHS uptake (two out of three). This, again, is driven by the ChondroCelect case only. Due to the very small number of ‘unfavourable’ headroom outcomes in the study sample, these figures should be interpreted with caution. Overall, the headroom method and its suggested decision outcome correlated with subsequent NHS uptake in 82% of cases (representing the ‘accuracy’ of the headroom method for these retrospective case studies).

Table 7.30 and Table 7.31, show the same analysis as above, except the uncertain headroom decision outcomes are now re-categorised as unfavourable.

**Table 7.30 Headroom and NHS Uptake contingency table: re-classifying 'uncertain' headroom as 'unfavourable'**

		REFERENCE		
		NHS Uptake	No NHS Uptake	
HEADROOM	Favourable	12	2	14
	Unfavourable	1	4	5
		13	6	19

**Table 7.31 Summary headroom performance statistics and their interpretation: re-classifying 'uncertain' headroom as 'unfavourable'**

Sensitivity	0.92	Of those that achieved NHS uptake, the proportion for which headroom was favourable
Specificity	0.67	Of those that did not achieve NHS uptake, the proportion for which headroom was unfavourable
Positive predictive value	0.86	Of those for which headroom was favourable, the proportion that went on to achieve NHS uptake
Negative predictive value	0.80	Of those for which headroom was unfavourable, the proportion that were unsuccessful in achieving NHS uptake
Accuracy	0.84	'Getting it right': the proportion of case studies whose subsequent NHS uptake was correctly predicted

By assuming that the cautionary headroom analyses described for E-medICS and PFO closure would have been interpreted by the developer as unfavourable, the summary statistics become slightly more favourable for the headroom method (as it successfully ruled out two further technologies). In particular, the negative predictive value rises to 80%, and the method becomes more specific.

As discussed previously, the two most important caveats to the interpretation of the result statistics outlined above are: (a) the close-to-market nature of the sample, meaning that unsuccessful products are underrepresented, and (b) that the headline 'result' in terms of headroom favourability (to which subsequent uptake was compared) relates only to the numbers that were generated in the analyses, rather than the exercise as a whole. The case study documentation demonstrates that, even at a very early stage of development, by

considering and researching the parameter inputs required to calculate headroom, the relevant threats to uptake can be brought to light, as well as the additional opportunities for a product that have not been characterised by the numerical headroom assessment. By considering these factors alongside the monetary headroom assessments, subsequent market uptake was generally well predicted.

It has been shown that the viability of product development is not captured by simply considering uptake within the NHS; even the two medical technologies that were successfully ‘ruled-out’ by the headroom method in terms of NHS uptake turned out to be viable products (one transpiring to be a patient purchase and another used within a different clinical context). Therefore, the numerical headroom calculations described should not be used directly to consider the viability of product development, and to rule-out development based on this. However, I have demonstrated that the exercise as a whole does get much closer to an assessment of development viability.

The reason for headroom analyses and results not being entirely straightforward are largely explained by the factors presented below, which outline some of the important lessons learnt regarding the headroom method and its application.

### 7.5.2 Main headroom lessons

As an exercise undertaken to evaluate the headroom method, some of the most useful findings of this investigation are insights into the headroom method itself. Table 7.32 outlines the important lessons learnt, in an attempt to understand better how useful the headroom method might be in practice. The particular case studies to which they relate are noted in brackets.

Table 7.32 Summary of Headroom Lessons learnt

<b>1. APPROPRIATENESS OF SCOPE</b>	
<b>A global market</b> (general observation)	The focus of these case studies was the UK market: a) using the NICE perspective on health gain ‘value’ and b) exploring the context of the UK market specifically (e.g. market size, NHS costs, etc). Of course, the device market is a global one, and the results may not translate directly to other settings. Often, uptake by the NHS was non-existent or limited, but the product was still viable given its use in other countries. This is clearly a crucial factor in a decision to develop a product.
<b>Expansion into different clinical areas</b> (1,2,6,10,11,14,16,20)	Where the application of the medical technology turned out to be relevant for a wider spectrum of clinical areas, the headroom analysis underestimated the potential value of the product and the market opportunity.
<b>Market coverage</b> (general observation)	A product can be perfectly profitable in the absence of its widespread use across the NHS. This is rarely achieved by medical devices.
<b>Alternative avenues of reimbursement</b> (9)	By adopting the NICE decision-making framework, the headroom method considers a product’s cost-effectiveness to dictate its reimbursement prospects. The ChondroCelect case study demonstrates that a product can be viable even where NICE regards the intervention unfavourably. The procurement landscape is infinitely more complicated than the simple approach taken by the headroom method, and schemes such as pass-through payments and reimbursement by private insurance companies can widen the purchasing landscape.
<b>2. INTRINSIC LIMITATIONS</b>	
<b>Unpredictable external factors</b> (12)	Changes in the clinical context can be unpredictable, for example the dismantling of the NHS IT programme for e-medICS. Additionally, current practice (the comparator) can change rapidly, which alters the headroom of a new product (though I have actually found that in most cases these changes can be predicted).
<b>Headroom for equipment</b> (2,8,10,11,12,13, 14,16,19)	A common difficulty in estimating the MRP for devices that are not used on a per-patient basis was a lack of practical understanding around their likely distribution. This sets devices apart from pharmaceuticals, and requires an understanding of patient throughput.
<b>Non-health related preferences</b> (5,8,10,11,12,15)	The ‘value’ identified by the headroom method does not incorporate non-health related <i>preferences</i> . This is a limitation of much health economic analysis, as currently practiced, and can be an important issue for medical devices and their uptake (more so than many other medical products).
<b>Irrationality of decision-makers</b> (6,8,9,11,12,15)	The fundamental notion that all decision-makers are rational is mistaken. There are many other factors that go into these buying decisions, which cannot necessarily be modelled or predicted.
<b>Difficulties in proving health benefit</b> (general observation)	Providing evidence can be particularly difficult for new medical devices. This was clear from the follow-up of case studies, where often the provision of RCT data was limited. The RCTs that were conducted often demonstrated the intrinsic difficulties of generating this evidence, e.g. the use of sham surgery for the control arm for PFO closure.

<p><b>Literature base</b> (4,5,6,11,12,13,16,17,18,20)</p> <p>[15,19]</p>	<p>The headroom method is only as informed as the information that informs it. Where the literature base is thin or contradictory, the ability of the method to offer a useful insight into the market opportunity is compromised. Obtaining relevant information for the headroom of <i>new indications</i> was particularly difficult.</p> <p>[In some cases, the lack of information in the literature did not pose too much of a problem in getting a good idea of headroom.]</p>
<p><b>No single ‘gold standard’</b> (13,14,17)</p>	<p>Often there is not one single reference standard, but many options at the disposal of medical professionals in the treatment of their patients. This makes the relative impact of a new technology difficult to predict.</p>
<p><b>Over-simplification?</b> (most)</p>	<p>For assumptions to be made in a headroom analysis, a simplification of the clinical scenario is usually required. In some cases this can be useful, for example where a development decision can be based on a partial headroom (e.g. from the cost-saving effect alone). In other cases, this simplification may omit important value-affecting factors, simply because these are too difficult to quantify.</p>
<p><b>3. IMPORTANT EXTRA CONSIDERATIONS</b></p>	
<p><b>User input</b> (12)</p>	<p>Where users are intrinsically involved in the effectiveness of a device, those users must support the intervention for it to be feasible practically.</p>
<p><b>Importance of time-frame</b> (20)</p>	<p>The time horizon willing to be considered by purchasers is crucial for headroom results in some cases. Whilst this should be the number of years for which benefit and cost impact are applicable, some procurement decisions might have a shorter timeframe in mind. This should be explored pre-development.</p>
<p><b>Strategic factors</b> (most)</p>	<p>Strategic considerations are not dealt with by the headroom method. These might relate to how the product is priced (especially for equipment), willingness to accept reduced market share, licensing agreements, and strategic competition considerations.</p>
<p><b>First to market?</b> (8,20)</p>	<p>In the cool-cap example, the headroom turned out to be a ‘no-brainer’, as it was the first intervention proposed for this clinical area; headroom was huge. However, if the relevant comparators that exist now were available at the time of analysis, headroom would have been unfavourable (cool-cap is less cost-effective). The co-existence of many cooling options demonstrates not only that user preferences matter, but that being the first to market may be an advantage. On the other hand, companies can free-ride on the research of the market leaders.</p>
<p><b>4. WHERE THE HEADROOM METHOD MAY BE LESS APPROPRIATE</b></p>	
<p><b>Model updates</b> (10,11,14,16)</p>	<p>Where new products are simply incremental developments of a company’s previous model, then health economic matters may not be of unique relevance in the decision to develop. For example, the update may represent a natural evolution in product design, and be necessary for the company to keep its product portfolio up-to-date and competitive (especially relevant for the constantly evolving high-tech sector). The development cost of these modifications may be small, making the case for development an obvious one.</p>
<p><b>Multiple applications</b> (6,10,12,14,16)</p>	<p>Where products are applicable for many clinical indications, valuing it from the perspective of just one is not a reasonable platform for a development decision.</p>

<p><b>Applicability to the ‘NICE’ evaluation framework</b> (3,12)</p>	<p>The headroom method is simply the application of the NICE technology appraisal framework, applied early on to inform development rather than procurement decisions. Therefore, those technologies that are not ‘NICE’-able, are not easily evaluated with the headroom method either.</p>
<p><b>5. METHOD APPLICATION AND INTERPRETATION</b></p>	
<p><b>Potential for bias</b> (2,7,11,13,14,17,18,20)</p>	<p>Many of the analyses felt very speculative, or required some creativity in finding / manipulating the relevant information. Where there were big discrepancies in literature estimates, personal judgement and bias could creep in, which will have a large impact on the perceived headroom. Companies may be predisposed to overestimate the potential impact of their innovations. Two of the follow-ups demonstrated this explicitly (Agento I.C and PFO closure).</p>
<p><b>Where MRP cannot be calculated</b> (4,6,8,9,10,11,12,14,16,18,19)</p>	<p>The headroom method is an approach rather than a strict set of rules. In many of the case studies, an MRP could not be calculated (usually due to too many unknowns), but it was still possible to get a feel for whether the prospects for the product were favourable or not.</p>
<p><b>Reasonable pricing</b> (general observation)</p>	<p>Although MRP is estimated exclusively by estimating its health-economic value, this might not represent a feasible or sensible reimbursement price (for example where this MRP is an awful lot larger than the treatment it replaces). It may be that the MRP of a new device should be scaled in some way to the baseline treatment price.</p>
<p><b>Versatile method</b> (20)  (ALL)</p>	<p>Although this investigation intended to apply the headroom method to development decisions, it has also demonstrated its direct applicability to other investment decisions, such as new market entry (for which investment in clinical trials and marketing would be required).</p> <p>The analyses also demonstrated that where impact was uncertain, the headroom method can be used to explore a range of possible implications.</p>
<p><b>Widening the perspective</b> (ALL)</p>	<p>A critical finding has been that the reimbursement perspective <i>alone</i> is too narrow to inform a development decision, but set within the context of other factors, can offer a useful insight into the reimbursement opportunity.</p>
<p><b>Clinical and market context are critical</b> (ALL)</p>	<p>Nearly all of the caveats, limitations, and observations outlined in this table can be (and <i>were</i>) picked up in the individual headroom analyses, in the ‘developments’ identified and ‘research questions’ posed. These sections (six and seven of the pro forma), which outlined the relevant external or unquantifiable factors, turned out to be pertinent in all examples, and must be considered alongside the headroom value when considering the investment opportunity of product development. In some instances, this meant that a seemingly unfavourable headroom value would actually have implied a favourable development decision. However, these extra considerations mainly proposed why the reimbursement opportunity might not be as favourable as calculated (i.e. presenting the suggestions from the literature of why the ‘best case’ assumptions might not be met). When combining the economic case made in the headroom analysis with the factors described in sections six and seven of the pro forma, an accurate description of market opportunity was generally presented.</p>



The lessons outlined in Table 7.32, which are divided into five themes, should contribute to our appreciation of the place for the headroom method in business decision-making, and its potential limitations. A consideration of the appropriateness of scope reveals that the headroom method can both over and underestimate the market size and value, and that this may invalidate the findings of any development cost decision analysis (though this was only presented in five cases). It is because of the global nature of the device industry that many technologies that are unsuccessful in the UK are actually viable products, due to their uptake elsewhere across the world. The intrinsic limitations described are largely problems associated with health economic evaluation more generally, and specifically the difficulty of its application to medical devices; these findings corroborate the distinguishing features of devices outlined in chapter 3. The ‘important extra considerations’ relate to critical elements in the success of a medical technology that are out of the scope of a headroom analysis, as they relate to unquantifiable factors or strategic concerns. The fourth theme offers three examples of where the headroom method may not be appropriate or feasible: model updates, multiple applications, and those technologies unsuitable for national evaluation by NICE. Finally, specific factors relating to the method’s application and interpretation are outlined, especially important being the incorporation of the clinical and market context factors (identified during the analysis) into development decisions. Consideration of these factors or threats that cannot be quantified would have been useful in all cases, and should be considered alongside the monetary case.

#### *7.5.2 (i) Headroom lessons: Costs and QALYs*

Using the resources and approaches outlined in the headroom template (see Appendix 2), these case studies have shown that, even prior to development, the literature can often supply some useful estimates that help to quantify the potential impact of a new technology, both in

relation to costs and QALYs. By outlining the relevant sources of information available and describing the appropriate strategies of approach, it is hoped that the application of the headroom method may be amenable to developers themselves (this is considered more formally in chapter 9). There is a wealth of cost data available in the literature (especially nowadays) though estimating service cost impact does sometimes require some creativity (and therefore may be subject to bias).

The estimation of HRQoL in these case studies raised some interesting issues, and demonstrated that much can be gleaned from manipulating information that is already available. The ‘QALY ladder’ developed by McAteer (2011) was not utilised, as it contained up-to-date estimates of HRQoL that went beyond the relevant timeframe of most of these case studies. In most cases, either: (a) there was no need for an estimate of HRQoL as the benefit was clearly large enough, or there was sufficient headroom in costs alone; (b) there were relevant HRQoL studies in the literature, or (c) I manipulated the relevant health parameters from the EQ-5D questionnaire, and used the work by Williams (1995) to quantify these. The EQ-5D manipulation approach was applied formally in two cases, to stapled haemorrhoidectomy and TVT. For stapled haemorrhoidectomy the estimated HRQoL impact turned out to be surprisingly accurate upon follow-up. Whilst the impact estimate provided for TVT overestimated its potential, the HRQoL associated with people suffering from urinary incontinence was well predicted; the presumption that symptoms would be alleviated completely was incorrect. Although just two examples are not sufficient to provide a well-balanced impression of efficacy, this has shown that this approach can offer at least some insight into the potential value of a new product.

### 7.5.3 Potential confounding factors

This investigation was designed to mimic as far as possible what might be achievable by industry in applying the headroom method, including a template to follow, a pro forma to fill in, and a reasonable time limit for the analysis. However, it is of course impossible to completely ‘remove the researcher from the research’. Whilst completing the 20 case studies, a log was kept regarding the aspects of the investigation itself that might have offered me, the researcher, an artificial advantage or disadvantage in eliciting headroom.

There were many aspects of the (necessary) design and context of this investigation that may have made the headroom method more readily applied compared with its use by developers. One obvious factor is my research background, both from previous academic endeavours and practice in applying the method to a number of case studies. This may mean that the relevant information was more easily or quickly obtained due to previous experience in applying the tool (though time taken per analysis showed no downward trend through the 20 case studies). Industry members with no background in health economics may, even with the provision of the necessary resources, find the problem difficult to approach (I was forced to seek advice in one instance, regarding a statistical challenge presented by the MARS case study). Interpretation of the literature would be more difficult for someone not experienced in reading information in such a format, and access to this literature may be problematic outside of an academic institution. I found that a non-research background may have posed a barrier to headroom elicitation particularly for case studies 7, 11, 13 and 20. Given the large discrepancies in parameter estimates in the literature (especially the case for 7, 11, 13, 14, 17 and 20), conducting the analysis from the viewpoint of third party independent researcher (such as myself) may have reduced the potential for bias in these instances. This may have a big impact on the size of the investment opportunity identified.

As well as advantages, there were also many artificial disadvantages relating to the application of headroom within this study. These mainly related to the provision of information on which to base appropriate assumptions for potential impact, as the NHSC briefings were sometimes unclear or offered limited detail on the aspirations of the developer (which is why a range of headroom was presented in many cases). Direct elicitation of impact expectations from the developer would have been much more straightforward. The other critical disadvantage was my knowledge base within the specific clinical and treatment areas. Having no medical/clinical background, all understanding was informed only by the literature and background searches. The developer is much more likely to have a deeper appreciation of the relevant issues. I felt that my own (lack of) clinical knowledge hindered the potential for more useful estimates in some cases in particular (2,11,16,17 and 20) or made the process much slower (13 and 20). Patient throughput for equipment (uncertainty of which often made an MRP difficult ascertain) may have been better understood by the developer. Given the date restrictions for searches, the earliest being 1995, relevant information was sometimes limited, especially relating to cost data (though according to the analysis above this does not seem to have had an impact on ability to estimate headroom). Information available today is much richer and wider in scope, so applying the headroom method from today's perspective may well be more straightforward or meaningful.

Interpreting headroom values was difficult where the available information for follow-up was limited (attempts to contact the manufacturers were largely unsuccessful). In some cases, estimates of potential impact were offered not out of necessity (it would not have changed the decision outcome), but simply to show that it was possible. In these instances, the ability of headroom to inform a development decision is likely to have been much simpler and quicker had it been undertaken by the developer, who would have a more pragmatic approach.

## 7.6 Summary and discussion

The results of this investigation go some way to determining the headroom method's use as an early gauge of market opportunity. As far as possible, the application of the headroom method aimed to reflect what might be achievable by a device developer, and differs in this respect from the (headroom method related) investigations of others. It also offered the possibility of follow-up, which for the first time has given an insight into the possible implications of basing a development decision on the outcome of a headroom analysis. The results have shown that a lot can be learnt about the market opportunity for a device early on, and in a reasonably short space of time. The importance of having a large sample of case studies was confirmed by the fact that each offered a new and unique insight into the method (but also implies that there may be more to learn).

The biggest impact on the generalisability of these findings is the source for the case studies evaluated: the NHSC. Crucially, this limited the potential for evaluating medical technologies whose development was abandoned pre-launch. The sample was also biased towards the bigger-impact technologies. Another potential restriction on generalisability is the time perspective adopted in the case studies; the real aim of the thesis as a whole is to investigate how useful the headroom method might be to developers in the future. This investigation considers the usefulness of the headroom method in the past, and may underestimate its potential given the ever-increasing information base at the disposal of the investigator, which may make headroom analyses easier or more accurate.

There was a lot to be learnt about the method by studying the characteristics of those technologies excluded from the study or for which difficulties arose in estimating headroom. These showed that a clear understanding of the application and potential consequences of a

new medical technology is necessary, though where this clarity does not exist, some exploratory elicitation of headroom according to various scenarios can be useful. Diagnostic technologies are often more problematic than others, though collaboration with the developer in the COPD case study (chapter 6) showed that estimates can still be made. Headroom analyses that painted an unfavourable investment opportunity have in some cases turned out to be viable, investable products (even where headroom accurately ‘ruled-out’ those that have not been bought by the NHS). All of the limitations and caveats outlined above offer potential explanations for this, and mainly reflect the narrow perspective taken. Whilst the headroom method considers the viability of national reimbursement, it is clear that the market for medical technology is a global one, and not restricted to national purchasing agencies.

It is within the nature of early evaluations that uncertainties around potential impact or changes in the clinical and procurement landscape are inevitable. However, the case studies evaluated here have demonstrated that these factors can often be predicted from a very early stage. In this respect, the headroom approach has been furthered, and should no longer be considered a ‘back of the envelope calculation’, as described previously (McAteer 2011). The present study has shown that important factors can be missed if this approach is taken (either missing potential investment opportunities, or investing in the un-profitable). It should not be forgotten that the headroom method of early economic evaluation is, just as the name suggests, a method of *evaluation* rather than a prognostic tool per se. The method has demonstrated its ability to generate a good idea of reimbursement opportunity, and this study has highlighted some important considerations in its use.

The word ‘useful’ has been intentionally omitted from any declaration of value of the headroom method, the reason being that such a tool can only be considered useful if its output is valued by its intended user: the developer. Chapter 9 considers this question explicitly.

# **CHAPTER 8 HEADROOM ANALYSIS FOR A LEG ULCER PROTECTIVE STOCKING**

## **8.1 Introduction**

This chapter describes the second of two prospective case studies which, like the first, involved interaction with its innovator at an early stage of development. The approach to the headroom analysis, however, is more akin to that of the retrospective case studies, where the time is limited and the analysis follows a pre-determined approach (using the pro forma). By keeping to this format for a prospective study I demonstrate the use of this approach in real time. An understanding of the innovation was developed through just one meeting and a few confirmatory emails. Subsequent work was independent. The product is kept generic for commercial reasons and is referred to as the Ulcer Protector throughout this chapter, which is divided into three parts: the first (section 8.2) explains the headroom analysis; section 8.3 offers a brief interpretation of the results; and a summary is provided in section 8.4.

## **8.2 Headroom Analysis**

The headroom analysis is presented in the format that it was conducted, using the pro forma.

### **8.2.1 Description**

A leg ulcer is a chronic (non-healing) wound, which develops on the leg or foot and takes longer than six weeks to heal (NHS Choices 2010). There are various types of leg ulcer, which are outlined in Table 8.1.

**Table 8.1 Types of leg ulcer**

<b>Leg ulcer type</b>	<b>Description</b>
<i>Venous leg ulcer</i>	A venous leg ulcer is the most common type, accounting for 80-85% of all cases. This is where increased blood pressure in the veins of the lower leg causes damage to the skin. This problem mainly affects older people, especially women.
<i>Arterial leg ulcer</i>	An arterial leg ulcer is caused by poor circulation (which also prevents them from healing).
<i>Diabetic foot/ leg ulcer</i>	Diabetic foot/ leg ulcers are caused by high blood sugar.
<i>Vasculitic leg ulcer</i>	These are related to inflammatory disorders such as rheumatoid arthritis and lupus.
<i>Malignant leg ulcer</i>	Malignant leg ulcers are caused by skin tumours.

Source: (NHS Choices 2010)

Venous leg ulcers alone are thought to affect 1 in every 500 people in the UK, but 1 in 50 over the age of 80 (NHS Choices 2010). The biggest risk factors are immobility, obesity and varicose veins.

Treatment for leg ulcers can involve various methods. Where an ulcer does not have circulatory causes (such as peripheral arterial disease), a compression bandage/sock is often used. Ulcers are initially washed before a dressing is applied to promote healing, which is initially changed at least weekly by a nurse (The British Association of Dermatologists 2010). The cleansing and dressing of ulcers is principally to avoid cross-infection with sources of contamination rather than the removal of bacteria from the site (Royal College of Nursing 2006). Antibiotics are prescribed if the ulcer becomes infected.

Patients are advised to keep ulcer dressings dry. Failure to do so impedes wound recovery; if the dressing gets wet and is left to dry of its own accord, infection can occur. This makes washing very difficult, and showering/bathing impossible.

The Ulcer Protector is a completely waterproof protective stocking that allows a patient with a leg ulcer to bathe or shower whilst keeping the ulcer site completely dry. Given the impact this could have to a patient's QoL, and also the NHS resources that could be saved



from the reduced redressing of ulcers, it is thought that the product could and should eventually be made available on the NHS.

## 8.2.2 Comparator

There is much research and innovation in the area of wound dressing and ulcer treatment. The Ulcer Protector is not intended as a treatment for leg ulcers, nor does it *replace* anything in the current treatment pathway. Rather, it acts as an aid for patients who must live with a leg ulcer, by providing the means to wash properly. This would promote general hygiene, reduce ulcer infection and redressing, and—crucially—boost QoL.

To the knowledge of the developers, there had been no other product developed specifically to help protect ulcers and their dressings and allow for contact with water. This would imply that the appropriate comparator for the Ulcer Protector is ‘nothing’. My own searches identified some potentially relevant comparators, outlined in Table 8.2, though none seem to be embedded into the current clinical management of leg ulcer patients in the UK.

**Table 8.2 Comparator products for the Ulcer Protector**

<b>Comparator product</b>	<b>Description</b>
Seal-Tight	This seems to be the most relevant comparator for the Ulcer Protector, given its proposed benefits to patients and the NHS. The developer of seal-tight, Autonomed, is a company based in West Yorkshire that has developed a number of products to help patients with practical solutions to common medical problems. Seal-tight is marketed as a cast and bandage protector, but has also been targeted specifically at diabetic foot patients and their clinicians as a ‘waterproof woundcare protector’ (Autonomed Ltd 2009). The product is available on NHS prescription, but it is difficult to know the extent to which this has been picked up—some sources indicate that it may only be available to NHS Lancashire patients (Stang 2010).
Cast protectors	There are various makes and models of waterproof ‘cast protectors’ available, that are principally targeted to help patients keep their casts dry after having injured or broken a limb. Various medical supplies websites provide links to the various offerings on the market (Betterlifehealthcare Ltd. 2012;CastCoversNow 2012).

The developers believe (having been made aware of Seal-Tight) that, compared to all other products available, the Ulcer Protector offers a much newer and more compatible material and design. Practically, this means a safer, more flexible and easy to use product. It would also be marketed more specifically toward leg ulcers, as compared to the majority of products available whose proposed application is very wide (and mainly targeted toward people with casts and bandages).

Two approaches are therefore considered:

- 1) To consider Seal-Tight as the appropriate comparator, being the most closely matched competitor and already having achieved reimbursement from the NHS.
- 2) Taking the stance that most leg ulcer patients today have no appropriate means of protecting their ulcer dressing, making washing or being around water very difficult.

### 8.2.3 Market size

In 1983, Dale and colleagues estimated (for the Scottish population) that around 1% of adults suffer from a chronic leg ulcer (Dale et al. 1983). Callam et al. (1985) estimated that active leg ulceration (i.e. those being treated) represents 1.5/1,000 of the population at any one time. This estimate is upheld by Royal College of Nursing statistics, which estimate a UK prevalence of active leg ulcers of 1.5 to 3 per 1,000 of the population (Cheater et al. 2001). Considering a UK population of about 60 million (and England: 50 million), this equates to around 90,000 to 180,000 for the UK (and 75,000 to 150,000 for England). Other estimates identified in the literature tend to fall within this range. I will conservatively assume the lower bound of these estimates.

<b>Market size per year (UK)</b>	90,000
<b>Market size per year (England)</b>	75,000

## 8.2.4 Health service

In 2004 the annual treatment cost of leg ulcers in the UK was £300-£600 million, with nursing time being the main cost driver of leg ulcer care (Soares et al. 2009). It was estimated that in 1988 the cost of caring for leg ulcer patients was around £1,200 per patient per year (Budgen 2004) (this is equivalent to about £3,260 in today's prices<sup>45</sup>). Another source estimates that each unhealed leg ulcer costs the NHS £1,067 per year, the largest element of which is district nurse time (Skene et al. 1992) (£2,161 in today's prices<sup>46</sup>). Some other estimates are more modest, with one more recent one being £1,500 to £1,800 per patient per year (Chuang et al. 2011).

From an NHS perspective, the main cost saving that could reasonably be associated with the Ulcer Protector is in nursing time, which is the main cost driver for leg ulcer care (Anderson 2010; Callam, Ruckley, Harper, & Dale 1985; Iglesias, Nelson, Cullum, & Torgerson 2004). The Ulcer Protector could reduce the utilisation of nursing services by a) improving the general hygiene of a patient by allowing them to bathe or shower properly, and b) decreasing the number of re-dressings by reducing the incidence of accidental wetting of the dressing (which, according to the developer, would always prompt a re-dressing).

By taking the perspective of approach one, the headroom (and MRP) would simply be equal to the price of Seal-Tight, if we assume equivalent performance. Approach two requires an estimation of the potential cost saving from a reduction in nursing visits.

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<sup>45</sup> The Hospital & Community Health Services (HCHS) Pay & Prices Index (PSSRU 2010) is used to inflate:  
Inflation rate: P&P Index (present year) ÷ P&P Index (year of cost data)  
= 271.5/100  
= 2.715  
£1,200 \* 2.715 = **£3,258**

<sup>46</sup> As above:  
= 271.5/134.06  
= 2.03  
£1,067 \* 2.03 = **£2,161**

An economic evaluation was undertaken alongside a UK clinical trial, which considered the impact of a new type of bandage for leg ulcers (Iglesias, Nelson, Cullum, & Torgerson 2004). The number of nursing visits per patient per month was recorded; for one type of bandage the mean number of nurse visits was 6.03 per month (median of 5) and for the other 5.14 visits (median of 4). Across all centres, most of these were home visits. It may be reasonable to presume that the Ulcer Protector may (like the better style of bandage) allow for one fewer nursing visit per month, from around five to four. This is consistent with the recommended care advice, that re-dressing *should* occur weekly. This monthly perspective also matches the expected lifetime of the product, which is likely to last around one month.

NHS reference costs for 2009/10 (Department of Health 2011b) provide the average cost of community nursing services, in its various forms. The national average unit cost for district nursing services (face to face) is £39, £42 for ‘health visiting services: all other services’, and £41 for ‘health visiting services: core services’. I use £40 as the approximate value of a community nursing visit. By assuming that one nursing visit is saved per month, the Ulcer Protector may save £40 per month in healthcare costs.

### **Approach 1- Comparator: Seal-Tight**

By taking Seal-Tight as the comparator, I assume no impact on service costs. Autonomed promote Seal-Tight for £19.99, and stipulate that it should last for 6 to 8 weeks. About £10 therefore represents its monthly price.

<b>(Total) ΔSC</b>	£0
<b>(Av. per person) ΔSC</b>	£0
<b>P<sub>1</sub></b>	£10

## Approach 2- Comparator: Nothing

By assuming there is no relevant comparator, there may be a cost saving of £40 per person:

<b>(Total) ΔSC</b>	£3,600,000*
<b>(Av. per person) ΔSC</b>	£40
<b>P<sub>1</sub></b>	£0

\*£40 multiplied by 90,000, the estimated number of patients being treated for leg ulcers in the UK

### 8.2.5 Patients

There is a strong need for QoL assessment in wound care (Teare & Barrett 2002). A ‘Technical Guide’ published in the online journal *Wound Essentials* emphasises the impact of not being able to bathe / shower properly on QoL and general hygiene (Lindsay 2007). The importance of understanding the HRQoL implications of leg ulcers, and incorporating these issues into patient care, has been underlined in the literature (Budgen 2004), and in 2011 González-Consuegra and Verdú (2011) presented a review of the relevant studies. Three of those twenty-one studies reviewed use the EuroQoL EQ-5D questionnaire to elicit the HRQoL of people with leg ulcers, and find this to be 0.6 to 0.7 (Iglesias, Nelson, Cullum, & Torgerson 2004;Michaels et al. 2009). However, I am interested in the *difference* that the Ulcer Protector could make on a patient’s HRQoL rather than the average HRQoL of leg ulcer sufferers.

Autonomed present research of their own on the impact of Seal-Tight on HRQoL for diabetic foot ulcer patients (Autonomed Ltd 2009). Using a disease-specific measure, the Cardiff Wound Impact Schedule (CWIS), they find that physical functioning is improved by 27%, well-being by 44%, and overall QoL was improved by nearly 20%.

In order to consider this from a reimbursement perspective, I consider the five health dimensions of the EQ-5D questionnaire, and use the results of a large UK study to estimate potential QoL benefit (Dolan 1997;Williams 1995). It seems reasonable to assume that the main health state of relevance to the Ulcer Protector is self-care. Presuming that having a leg ulcer would cause ‘some problems with washing or dressing’, and that using the Ulcer Protector could turn this into ‘no problems with self-care’, then the impact of this on a patient’s QoL weighting<sup>47</sup> would be 0.104. As the product will last one month, each Ulcer Protector would provide (0.104/12): 0.0087 QALYs.

#### **Approach 1- Comparator: Seal-Tight**

<b>ΔQALY*</b>	0
<b>(Av. per person) ΔQALY</b>	0

\*This assumes equivalent effectiveness between the Ulcer Protector and Seal-Tight.

#### **Approach 2- Comparator: Nothing**

<b>ΔQALY</b>	783
<b>(Av. per person) ΔQALY</b>	0.0087

### 8.2.6 Developments (clinical and healthcare context)

Table 8.3 lists some of the relevant developments in the clinical and healthcare context, alongside ‘Red’ if it poses a significant threat to the opportunity identified in the market, ‘Amber’ if it represents a potential threat, and ‘Green’ if it further supports the case for the new technology.

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<sup>47</sup> I will not add to this the intercept estimation, which is a constant that should be added for any deviation from ‘full health’, as I presume that, given the likely age of the relevant patient population, their baseline would probably not be a HRQoL of 1 (perfect health). [See headroom method chapter 4 for a more detailed explanation of this approach].

Table 8.3 Developments in the clinical and healthcare context that may affect the headroom for the Ulcer Protector

[Green]	Patient-facing websites such as NHS Choices offer no guidance or information on looking after ulcer dressings, and how to adapt normal everyday routines to accommodate for them (NHS Choices 2010). This (along with accounts from people working in the field) demonstrates that these problems go largely unaddressed; the Ulcer Protector offers a simple way to overcome an everyday problem.
[Amber]	Competitors: As well as Seal-Tight, it is clear from the many websites that offer waterproof cast protectors, that similar types of product are available (Betterlifehealthcare Ltd. 2012;CastCoversNow 2012).
[Green]	An article in the Nursing Times highlights the costly nature of leg ulcer care when patients are not managed properly (Anderson 2010). It emphasises that costs can be reduced if nurses are provided with appropriate training. This demonstrates that there is room for improvement in the care provided for leg ulcer patients, and the Ulcer Protector could provide a cheap way to make care more effective, involving no extra investment in training or staff time. Clinical practice need not be altered.
[Red]	The fact that Seal-Tight is already available on prescription may represent a barrier to adoption for another similar product. Some sources indicate that Seal-Tight is available across the UK (Autonomed Ltd 2009). The significance of this barrier should be investigated. If the product is widely available, then ‘approach 1’ taken above is likely to be the more appropriate, with the price of Seal-Tight providing a cap on the Ulcer Protector’s MRP. One source indicates that Seal-Tight is available on prescription to all patients who wear bandages or plaster casts (Lindsay 2005). The product received the Nursing Times product gold award in Product Awards 2010 in the ‘Dignity and Daily Living’ category (Nursing Times 2010).
[Green]	On the other hand, the fact that a product of a similar nature has been successful in achieving reimbursement indicates that the NHS is willing to reimburse this sort of product. Research undertaken for Seal-Tight has also shown the large potential impact on QoL of protective ulcer stockings.
[Amber]	One source finds that just 4% of dressing changes arise from accidental wetting (Stang 2010). In the analysis presented above, I have assumed this rate to be 20% by estimating that one nursing visit could be saved each month (from five to four). It could be argued, however, that the general improvement in hygiene of patients who would now be able to wash, may further contribute to the reduced demands on nurses and healthcare resources.
[Green]	The Ulcer Protector will have applications outside of those indicated in this analysis, and the innovators already have ideas around these. Leg ulcers have been chosen as professional opinion indicated that there was a real gap in the market here. However, future models could be developed and targeted to different areas, and may add to the business case for this product.

### 8.2.7 Research Questions

- To what extent has Seal-Tight been picked up by clinicians? Would the NHS be prepared to offer both Seal-Tight *and* the Ulcer Protector on prescription?

- If Seal-Tight is offered at a discounted rate to the NHS, then this should be identified and used as the base-case.
- The introduction of other similar products on the market should be monitored.
- Is it reasonable to assume that the Ulcer Protector could save one nursing visit per month, or is this an over/under estimation?

## 8.2.8 Headroom

Table 8.4 and Table 8.5 illustrate the MRP for the Ulcer Protector under approaches 1 and 2.

**Table 8.4 MRP for Approach One**

<i>Comparator: Seal-Tight</i>			<i>NHS willing to pay £20,000 per QALY</i>
Impact on Health (QALY <sub>2</sub> -QALY <sub>1</sub> )	Impact on Service Costs (SC <sub>1</sub> -SC <sub>2</sub> )	Price of displaced device: P <sub>1</sub>	<b>MRP:</b> [(QALY <sub>1</sub> -QALY <sub>2</sub> )*£20,000]-(SC <sub>2</sub> -SC <sub>1</sub> )+P <sub>1</sub>
0	£0	£10	<b>£10</b>

**Table 8.5 MRP for Approach Two**

<i>Comparator: Nothing</i>			<i>NHS willing to pay £20,000 per QALY</i>
Impact on Health (QALY <sub>2</sub> -QALY <sub>1</sub> )	Impact on Service Costs (SC <sub>1</sub> -SC <sub>2</sub> )	Price of displaced device: P <sub>1</sub>	<b>MRP:</b> [(QALY <sub>1</sub> -QALY <sub>2</sub> )*£20,000]-(SC <sub>2</sub> -SC <sub>1</sub> )+P <sub>1</sub>
0.0087	- £40 [saving]	£0	<b>£214</b>

The high value of improved self-care is represented by the high reimbursable price in approach two (which would reach £310 for a WTP of £30,000). However, if the closely matched competitor is deemed to be the more appropriate baseline, then this MRP is reduced to £10. Using the graphical representation presented in the headroom chapter, Figure 8.1 and Figure 8.2 illustrate the MRP within this framework.



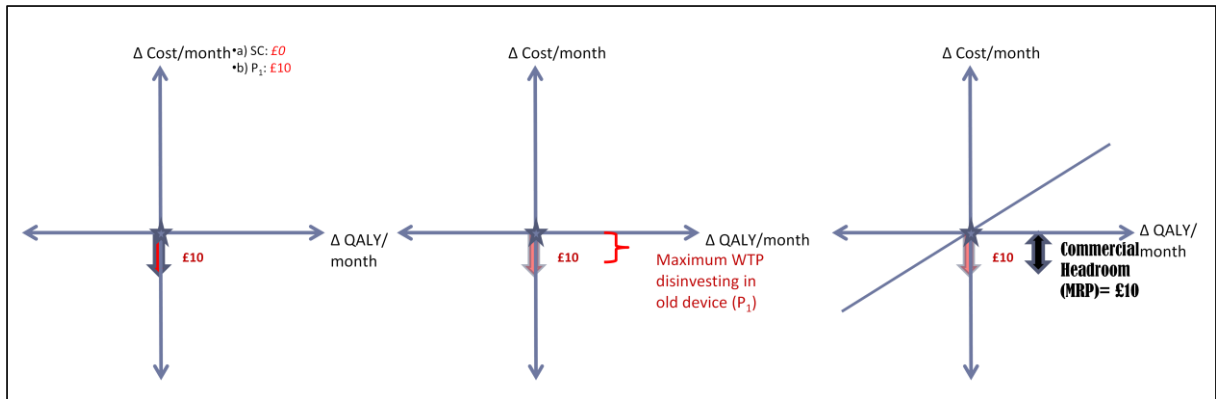


Figure 8.1 Ulcer Protector: Graphical MRP for approach one

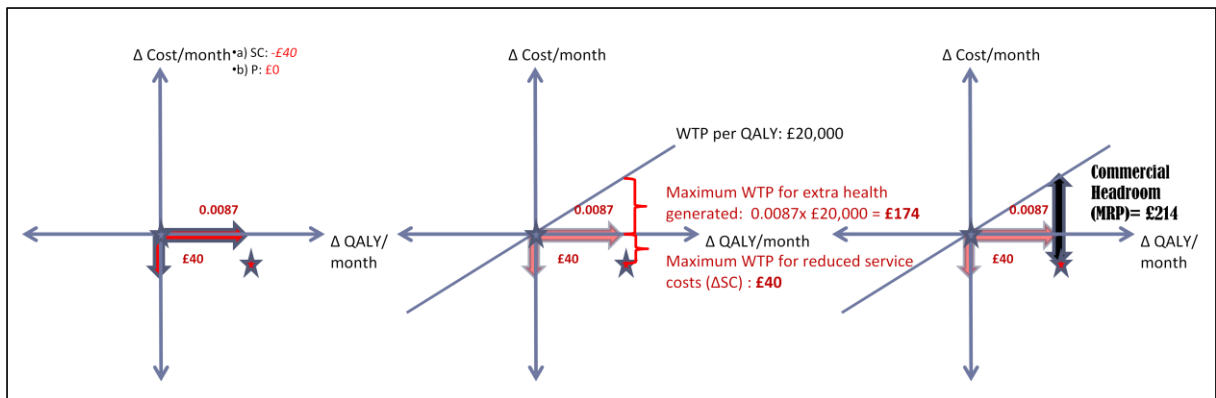


Figure 8.2 Ulcer Protector: Graphical MRP for approach two

### 8.3 Interpretation

The headroom exercise is meant to allow the developer to observe the reimbursement potential for a new device idea, in order to then decide whether this makes it worth developing. This does not mean that the MRP should directly inform pricing decisions in the future (even if early expectations are confirmed). In this case, the higher of the two MRP estimates (£214) would represent an unreasonably high price for this type of product. Not only is there a comparable and much cheaper device on the market (which probably represents the more reasonable price cap), but also the costs of production would be relatively

low. Indeed, the developers indicate that the headroom analysis provides plenty of room for development and that price is likely to be set on the basis of cost plus reasonable profit, which would be below the competitors' prices.

The headroom analysis considered the NHS to be the target customer, and therefore used NICE's WTP threshold to value health impact in the second approach. In reality, such a product (very simple and with low costs) would never be evaluated by NICE, and so conducting such a valuation may seem artificial. However, although the price in the future will be set independently of this, it could act as a good marketing tool, demonstrating that the value obtained from its use far outweighs any investment required for its purchase.

Although the headroom analysis considered the potential value of the product from a health service perspective (as the main aim is for product to be available on prescription), the Ulcer Protector may be targeted directly to patients. In this case the headroom analysis would not be applicable and, like other consumer products, value would be determined by the buyers. Competing products would be particularly important in this case.

## **8.4 Summary**

This headroom analysis, which utilised the resources developed for the retrospective case studies, illustrates the use of this approach in a real-life prospective example. The analysis and write-up took a total of 10.5 hours, thus adhering (loosely) to the notion of 'headroom in a day'. Analysis of development costs, which makes use of the total market size estimate to explore the likely room to re-coup costs of development assuming full market coverage, was not pursued for this example given the nature of the company and its likely capacity (a very

small start-up), and also the unrealistic notion in this case of the MRP being the actual price charged in the future.

The value of the method for the innovators is explored in the next chapter, where potential stakeholders (including the developers of the two prospective case studies) are asked to consider the value and practicality of the approach. However, what this chapter has demonstrated is that, in a reasonably short space of time, understanding of impact can be communicated (through just a two hour meeting) which, when combined with literature work, was able to produce realistic assumptions and to quantify these into monetary values. The process also brought to light some direct competitors, an important finding at an early stage. The work also showed that the headroom method is less relevant to consumer products, although the interviews chapter explores this and other questions in more detail by consulting the method's potential future users.

# **CHAPTER 9 QUALITATIVE INVESTIGATION INTO THE VALUE AND USABILITY OF THE HEADROOM METHOD FOR ITS POTENTIAL USERS**

## **9.1 Introduction**

As an evaluation of the headroom method, this thesis aims to assess if and in what ways the method provides medical device developers with a useful indication of product viability. Having applied the method prospectively to two case studies and retrospectively to twenty, issues relating to its application have been exposed, and its predictive value explored. However, the method—a tool to facilitate decision-making by medical device developers—has so far been assessed outside the context of its intended users. Whilst elements of the study design, particularly for the retrospective case studies, attempted to replicate the potential constraints of device developers and to provide resources for its implementation, without capturing the views of the intended user, any results would lack a grounding in / translation into the real world. Through thematic analysis of semi-structured interviews with 12 stakeholders, this chapter explores the potential value of the headroom method, and thereby provides a deeper understanding of its merits and limitations as a method of early economic evaluation for device developers.

## **9.2 Contribution of this investigation to the mixed methods**

### **research design**

As described in the methodology chapter, the research methods employed for this project were based on their capacity to address the prominent research questions. The inclusion of this qualitative study was grounded in the desire both to validate the assumptions made and the conclusions drawn by other methods (in the case studies), as well as to further the evaluation by exploring factors that cannot be assessed by the techniques used so far.

The hypothesis underlying the set-up and design of this research is that by integrating the headroom method into early development decisions, innovators could improve the efficiency of development expenditure by only pursuing those ideas with feasible reimbursement prospects. To evaluate the headroom method, the implied assumptions of this hypothesis must be tested. The first implicit assumption is that economic evaluation of this nature does not currently feature in early decision-making by developers; determining the novelty of the approach was therefore one important objective of the interview process. Whilst the potential efficacy of the method was addressed by the retrospective studies, the conditions which facilitated its application may not be representative; the usability and practicality of the method in the eyes of potential users are therefore also explored. Additionally, consideration of the usefulness of the method's output is investigated, as well as any important omissions.

An outline of the various motivations for a mixed-methods evaluation design is given by Greene and colleagues (1989), all of which relate in different ways to my motivation to incorporate this qualitative investigation into the study. A summary of these is provided in Table 9.1. 'Expansion' relates to the underlying reason for taking a mixed methods approach,

whilst ‘Development’ relates to how this was done. ‘Complementarity’, ‘Triangulation’ and ‘Initiation’ describe what the mixing of methods contributes to the overall research findings.

**Table 9.1 Rationale for including interviews: Purposes of mixed-method evaluation design**

<b>Purpose</b>	<b>Rationale for inclusion of interviews</b>
EXPANSION. To extend the breadth and range of inquiry, by using different methods for different components of the inquiry.	In the methodology chapter, two distinct components of the headroom method’s evaluation were outlined, which related to its efficacy and usability. The interviews permit an investigation of elements of usability that cannot be tested through the case studies, as well offering the chance to examine other components of its proposed ‘value’ that remain unaddressed by other methods. <i>E.g.: Does the method add / is it different to what developers already think about?; Can costs (which must be considered alongside headroom) be projected at such an early stage?</i>
DEVELOPMENT. Uses the results from one method to inform the other, to increase the validity of constructs and results by capitalising on inherent method strengths.	Both the process of and results from the prospective and retrospective case studies shaped the interview inquiry and the types of questions asked, as well as the material provided and the participant sample. <i>E.g.: Interviews with developers of the prospective case studies; Is nine hours a useful / feasible time to allocate to this sort of analysis?; Does the simplification process render the analysis ineffectual?</i>
COMPLEMENTARITY. Seeks to elaborate, enhance, illustrate and clarify the results from one method with the results from the other, thus increasing the interpretability and meaningfulness of results.	The context chapter outlined the diverse nature of innovation and innovators in the medical device market. The anecdotes provided by the varied sample of potential users, relating to their thoughts on the method in relation to their own roles and experiences, can complement the case study findings as well as placing these findings into a real-life setting, thereby increasing their meaningfulness. <i>E.g.: Is the method intelligible (and by who)? What would the real barriers be to its implementation?</i>
TRIANGULATION. Seeks convergence, corroboration and correspondence of results from the different methods, thereby increasing the validity of constructs.	The discovery of convergent results between interviews and case studies, relating to headroom method implementation issues and the extra factors considered, substantiates and provides validity for the conclusions drawn. <i>E.g.: Exploring the factors that are omitted by the method in the eyes of the user and cross-checking these with the findings of the case studies.</i>
INITIATION. Aims to discover contradiction or new perspectives.	By exploring the interpretation of the method by different people with varying perspectives, new potential usages and roles for the method emerge, and patterns can be drawn from these findings. <i>E.g.: The discovery of disagreement in responses, and provisional theorising of what works for whom and in what way.</i>

Adapted from Greene and colleagues (1989, p. 259)

## 9.3 Methods

Approval for this interview study was granted by the University of Birmingham’s Science, Technology, Engineering and Mathematics Ethical Review committee on the 31<sup>st</sup> of January 2012 (ERN\_10-0531, see appendix 7). Details on the methods employed for both the collection and analysis of data are provided below.

### 9.3.1 Sampling

A maximum-variation purposive sampling technique was employed to select interview participants, for which the intention was to capture the perspectives and opinions of stakeholders with a broad range of insights, backgrounds, and roles in the innovation process. Two sets of interviewees were the developers of the prospective case studies described in chapters 6 and 8. The remaining participants were contacts established either through their past or present contact with MATCH, through contacts established through the course of the project, or through the connections of colleagues. Participants were approached and provided with a participant information sheet and consent form (see Appendix 8). In exchange for their participation, interviewees were provided with a presentation of the headroom method, as well as the materials developed for the method’s application (pro forma and resource guide). Generic names are used to refer to the interviewees, which are summarised in Table 9.2.

**Table 9.2 Characteristics of interviewees**

	<b>Label</b>	<b>Description</b>
<b>Interview 1</b>	Clinician	Clinician and Professor, specialising in respiratory medicine.
	Technology consultant [COPD case study]	Director of a (small) medical device technology consultancy company, and an academic medical device researcher.
<b>Interview 2</b>	Start-up (1) Start-up (2) [Ulcer protector case study]	The two staff members of a start-up micro business set up to develop and pioneer a product to help leg ulcer sufferers.
<b>Interview 3</b>	SME	Senior director of a medium sized company (around 100 employees) with a global reach. This medical device company specialises in regenerative medicine.

	Business consultant	Chief executive of company that provides business support to the health technology sector, including strategic marketing, and business development.
<b>Interview 4</b>	NHS Innovation manager	Innovation manager for an NHS trust, providing support and advice to both NHS trust staff with new ideas and also small companies.
	Research project facilitator	Research management role within an NHS trust, facilitating collaborative projects and the development of new medical devices for urinary incontinence.
<b>Interview 5</b>	Design consultant	Director of a (small) company that provides consultancy in the design and development of medical (and other industrial) products, including prototyping.
<b>Interview 6</b>	Large MNC (1) Large MNC (2)	Head of scientific development (1) and global business development director (2), at a global company with a large multinational health technology division, which operates in 50 countries, employs 3-4,000 people and has a turnover of around €1.5 billion per year.
<b>Interview 7</b>	Academic	Teaching fellow at a UK university, interested in translating their research into a product for use in teaching and for clinicians in the NHS (has recently applied for a first round of i4i funding).

The intention was to interview a heterogeneous sample of potential users of the method, in order to gain an insight into the various perspectives they might offer. Although probability sampling (involving a random sampling method) would be required to maximise the generalisability of results, this was neither feasible nor necessarily desirable. Statistical representation is not the objective of this study, which instead aims to understand the headroom method's potential use within a range of settings. This non-probabilistic sampling technique is widely acknowledged in the literature to allow the researcher to identify and include a wide range of key informants who enable an exploration of specific issues related to the research (Mays & Pope 1995). As indicated, the participants were identified through connections made either through previous collaboration, or through the wider network of contacts provided by my academic setting or MATCH. It must therefore be noted that the sample may be biased toward those with a more favourable appreciation of this sort of method, especially given their agreement to participate. Two participants (business consultant



and design consultant) have had previous exposure to the headroom method (having attended MATCH courses) and claim to incorporate its principles into their thinking; whilst these participants can offer valuable insights, their willingness to engage with this interview process may reflect their (positive) attitude to the method.

### 9.3.2 Interview design

The seven interviews with twelve participants took place between February and June 2012. The semi-structured interview script (see Appendix 9) was designed to elicit pertinent factors relating to the current way development decisions are made or conceptualised by the participant, thoughts on the headroom method itself and its application, and the usefulness of its output. The logic of these question topics was checked with the project supervisors, who agreed them to be appropriate and inclusive.

All interview sessions followed a similar format, and were conducted at a location amenable to the participant. The headroom method was presented to participants through a (20 minute) power point presentation followed by a discussion (see Appendix 10 for presentation slides). After talking through the material provided and discussing any questions or uncertainties, consent forms were signed and the interviews were undertaken. The interviews lasted around 20 minutes (minimum 13 maximum 35), and were tape recorded. All tape recordings were transcribed and these were checked for accuracy against the recordings at a later date.

In an effort to ensure reliability of data and consistency of findings, the interviews were all conducted in a similar format, and the same presentation and materials were provided for each participant. Furthermore, an attempt was made to ask non-leading questions, and the interviewees were informed that all comments (both positive and negative) were useful and

welcome. All presentations and interviews were conducted by me. Whilst this provides consistency, responses may have been affected by previous interactions (both within and outside the meeting). I also transcribed all interviews, and although no external inspection of the transcriptions was carried out, these were double-checked for accuracy.

### 9.3.3 Thematic Data Analysis

The method chosen to organise and analyse interview data should suit the purpose of the qualitative investigation. For this study, the intention was not to develop deep theories of underlying experiences and a constructivist account of behaviours and motivation, for which methods such as Interpretative Phenomenological Analysis (IPA) or Grounded Theory may have been appropriate. Such methods are bounded by theory, and do not match the objectives of this research project. Although thematic analysis has in the past been criticised as representing a very general notion of qualitative analysis, the method is increasingly discussed and used as a concrete method in its own right (Braun & Clarke 2006). Thematic analysis is not bound to any particular theoretical framework, and so suits the stance of this research project, which for the purpose of these interviews seeks to report the meanings, experiences, and reality of the interviewees. It is a method by which patterns (themes) within the data can be identified, analysed and reported, allowing the researcher to both organise data and interpret the research topic (Braun & Clarke 2006).

Themes (and sub-themes) relate to patterns identified in the data which provide a significant insight. Whilst the questions asked in the interviews were driven by my interest in the topic and what I wanted to find out (as described in section 9.2), the initial coding and organising of data extracts were simple and non-creative. Coding and theme identification was based exclusively on what was said in the interviews, rather than being structured by the questions asked; this process should increase the reliability and validity of the subsequent

analysis, by not guiding the results or missing important information (Kvale 1996). Data was interpreted on a semantic (explicit) level, where the surface meanings of the data were taken.

### 9.3.3 (i) *Thematic analysis: the process*

After the audiotapes were transcribed and checked, the scripts were re-read to gain further familiarity with the text. Coding—the process whereby all data (individual sentences and/or chunks of text) are assigned a descriptive label—was then carried out by hand for all interview scripts. Coding is referred to as ‘...*the transitional process between data collection and more extensive data analysis*’ (Saldaña 2009, p. 4), and at this stage helped to organise the data into meaningful groups. The data extracts corresponding to each code (some data was given multiple codes), were then copy/pasted into a tabulated word document. After all the data were coded and collated, the analysis was re-focused at a broader level and organised into four wider themes which captured the groups of codes and reflected the data within them. A table of the codes (grouped into themes) can be found in Appendix 11. The findings section that follows describes the story that each of these themes tells, and how their messages relate both across themes and more broadly to the overall research questions.

## 9.4 Findings

Four themes emerged from the analysis: (1) the participant’s guiding principles and motivation, (2) the practicalities of the headroom method, (3) its scope, and (4) its impact. The analysis that follows will demonstrate the individual importance of each theme, showing the first three to be intrinsically linked and which, together, shape the fourth.

#### 9.4.1 THEME 1: Involvement in innovation: guiding principles and motivation

The codes and data within this theme encapsulated the background or guiding principles of interviewees, reflecting their underlying motivations or involvement in the innovation process (which will be shown later to influence their interaction with the headroom method). Across all interviews, participants brought in their own perspectives and personal experiences, expressing or relating comments or ideas to their own roles. This was an encouraging signal, demonstrating a genuine engagement with the questions. A slight exception was the interview with the business consultant and SME, who less frequently related the questions asked entirely to themselves (they therefore feature minimally in this theme).

##### 9.4.1 (i) Motivation

The participants fell into two main groups: those looking to develop their own innovations (group 1: clinician, start-up and academic) and those who deal with the ideas of others (group 2: consultants, MNC and NHS trust). For the first group, discussion of underlying motivations centred mainly on improving patient care or services, and the desire to improve QoL or to reduce the cost of patient care. The clinician in particular emphasised the scale of disease burden. The motivation to develop a medical device appeared personal for this group of interviewees, with the academic describing the decision as such. Although acknowledgement of the need for a project to be viable and to make business sense was made by the start-up and clinician, a much greater emphasis was placed on the innovators' belief in their products. In response to their motivation to develop, the start-up noted:

*'It was an ethical decision in a sense. In as far as, we felt there was a need for this product, and it was a great shame people who suffer from leg ulcers actually couldn't bathe properly, which must have affected their quality of life terrifically'. [Start-up]*

This captures the strong passion the innovators feel for their products. All noted their qualms around quantifying their products' proposed benefits, talking of their *'fear of numbers'* and their having *'no idea where to start'*.

The motivations of group 2—linked by their advising capacity or working with the ideas of others—appeared less personal, with a focus on a product's viability as a business proposition. Rather than stressing numbers as the difficulty, this group highlighted their sometimes limited ability to influence decision-making (either that of their clients or, for the MNC, within their company):

*'...sometimes a company wants to do what they want to do. You know, and it's their risk and it's their cost, and we're just an advisory base.'* [NHS trust project facilitator]

Likewise, the head of scientific development at the MNC noted that *'...you can't choose the team'*, and suggested internal difficulties and a divergent set of opinions and perspectives within the decision-making team.

#### 9.4.1 (ii) Current feasibility checks

Information relating to any current (economic) feasibility considerations was also collected. Group 1 indicated no concrete decision-making processes for the consideration of development opportunities. Worthy of note, however, is the network of expertise available to the academic (which helped her to compose the cost-side of her i4i funding application). This support and knowledge base is not likely to be replicated within an industry setting, especially for small companies.

On the other hand, group 2 provided details of some fairly structured approaches to early opportunity assessment. For the NHS trust employees this mainly revolved around their own feasibility to deliver a project, but the importance of market size was also stressed. The large MNC gave a particularly informative account of their current screening process for new

innovations, which involves an initial rule-out process for which considerations include clinical feasibility, intellectual property (IP), regulatory situation, business fit, time to market, scale of development costs, and possibility (rather than size) of reimbursement; for those that pass this stage, a presentation is compiled for an innovation board who consider these factors in greater detail:

*‘The board will review each of those elements and make a decision which ultimately and usually is gut feel... I know they wouldn’t like to agree to that, but that’s the reality of it’.*  
[MNC]

Both the MNC and the NHS trust employees noted the lack of formal incorporation of health economics at the early stage. As indicated previously, both the design and business consultants incorporate the headroom approach into their current consideration of new products.

#### 9.4.2 THEME 2: Headroom Practicalities

Exploring the practicality of the headroom method was an important motivation for conducting the interviews. The method’s accessibility, ease of use, usefulness of output, and feasibility of application are considered here, an appreciation of which necessarily precedes any understanding of the method’s real potential.

##### 9.4.2 (i) *Understanding*

All participants indicated a positive understanding of the method, considering it to be clear and often alluding to its presentation within the meeting: *‘...it looked very attractive as well because it was so neat’*. Whilst this type of commentary may allude to the possibility of participants relating to me/the presentation, rather than the method alone (denoting potential partiality in responses), the topic seemed accessible to all interviewees.

*‘...I’m not an economist, I’m not even a scientist, so if it’s reasonably clear to me I would think it’s reasonably clear to most people.’ [SME]*

This quotation mirrors the sentiment of many responses, with participants asserting their own disparate backgrounds in relation to this understanding. However, based on their experience or setting, the participants identified with the method in different ways. The SME, for example, made reference to QALYs being the most obscure element, whilst the clinician indicated the method to become much more tangible when framed in this way.

#### **9.4.2 (ii) Barriers to calculating the ‘headroom’**

Making appropriate assumptions for a product’s potential impact was highlighted by many as a potential difficulty, though the possibility of making these assumptions iterative (as with the COPD case study), and testing ranges, were suggested. The design consultant indicated (from experience) that innovators will ‘...*always have rose-coloured spectacles on*’, potentially making realistic assumptions problematic. The two prospective case study innovators (clinician and start-up) indicated that the assumptions made for the headroom analyses, although potentially underestimating benefit, were pragmatic and justified. However, this does not mean they would have made the same assumptions themselves.

*‘All models are basically the same in that they function on garbage in garbage out. If you don’t have the right stuff to put in it doesn’t matter how good your model is.’ [SME]*

The template / resource pack and pro forma were compiled to aid the making of appropriate assumptions as well as to identify the data to furnish them. Accessing the data was highlighted as a potential concern by all except the clinician, academic, and NHS trust, perhaps reflecting their background in research, signifying the potential importance of this.

#### **9.4.2 (iii) Can costs be conceptualised at an early stage?**

The premise of the headroom method’s value is allowing developers to compare potential future value with their own costs of development, manufacture, and sales. However, the

ability to predict these costs varied according to respondent type. The businesses and consultants believed themselves to have a good grasp of future costs even at a very early stage (except, according to the MNC, where a product is truly novel), though according to the design consultant the small businesses he deals with overwhelmingly underestimate costs. Conversely, those in research roles (within the NHS and universities) expressed much greater uncertainty around costs.

#### *9.4.2 (iv) The feasibility of applying the method yourself*

Notwithstanding the existence of practical calculation difficulties for headroom (or lack thereof), the feasibility of the method being used by the developers themselves was explored. Two main issues were raised: expertise and time. Whilst all interviewees understood the method, some consultants considered an impracticality to be the expertise of the innovator. Indeed, the academic indicated that she would probably not approach the analysis by herself, and the technology consultant (from the COPD case study) noted that it was useful having an ‘expert’ making you think about the right questions. However, the business consultant stressed the virtue of the template / pro forma in this respect:

*‘The important thing which I thought was good about that is asking the right questions. Usually they know the answers but nobody’s asking the right questions of them’.*  
[Business consultant]

The MNC employees were able to articulate quite clearly what the barrier would be within their own company: time. They therefore suggested that, as with their market research, they would look to outsource a headroom analysis as a service. This highlights the fact that, however useful a tool, it must fit within a (ready-established) way of doing things, and even ‘headroom in a day’ may be too much to ask of a person’s job role and task list which is already stretched. Similarly, the start-up indicated that ‘...we’re trying to run a business as well, so there’s only so much time you can allocate to that’, although they indicated their



surprise that the headroom analysis for their product had taken just 10.5 hours, suggesting it to be a very good use of time. Others noted the importance of investing time in a method that considers future reimbursement prospects:

*'If you spend a day assessing whether your product has legs, will run, then it's got to be worth doing.'* [Design consultant];

*'...of course it's worth investing in doing it no matter how long it takes.'* [Academic]

### 9.4.3 THEME 3: Headroom Scope

All interviewees noted the importance of health economics, although their agreement to participate denotes their intrinsic interest in the subject. Some important findings emerged around the method's scope: in what way the method is appropriate / reflective of the actual situation, how complete the message it presents is, and what the major omissions are.

#### 9.4.3 (i) *The simplification process*

The case studies demonstrated that to make assumptions for potential technology impact, the clinical scenario must be (often greatly) simplified. Despite the passion for their products described previously, the prospective case study innovators suggested that this did not render the analysis uninformative: *'It was an informed, pragmatic approach for a clinically complex need'* [clinician]. Similarly, the start-up proposed that, whilst they were always interested in *'...that little bit more'*, those to whom they would want to describe the product's value would only want that (straightforward) information. From his experience working with innovators, the design consultant noted their temptation to go into minute detail, which can be counter-productive at that early stage. Other interviewees believed the simplification process to be necessary and useful, so long as the potential weaknesses were understood.

#### 9.4.3 (ii) Actual reimbursement

As well as simplifying the clinical story, the headroom method sets the development decision within a world where future product value is determined by a rational buyer, who utilises economic evaluation within an NHS system-wide decision-maker's framework (like that used by NICE). The comments of those who have worked directly with the reimbursement process (in particular: business consultant, SME and NHS trust), cast doubt over this view. The basis of this criticism lies in the reality that decision-makers' incentives are distorted by the organisation of the system; the main issues are neatly summarised by the SME director:

*'...with the proviso that I'm not sure you could ever address these with a model, the two major things are 1) fixed reimbursement tariffs... If that's set then the willingness to pay is already determined and it's not a flexible scale at all, it's flat. And the other one is... silo budgeting, which is to say... I don't care how good it is for everyone, if it's not good for me it's not happening.'* [SME]

Concerning reimbursement tariffs, the business consultant indicated that, to be attractive to commissioners, a new product (even if more effective) must match or better the monetary value of current practice which, in cases where cost to the NHS come under the tariff, provide a revenue stream for a hospital. Together with silo budget problems, it is clear that individual decision-makers are not given the right incentive structure to allow for the optimisation of their own decisions to align with the optimal outcome for the NHS as a whole.

Additionally, according to the NHS trust there is a great deal of variation within the NHS, which even for them presents a complex, confusing and fast-changing landscape.

#### 9.4.3 (iii) Completeness of scope

Omissions of the method (in its direct computational sense) were noted to be: that the market is a global one, trends in care or health service targets, the market context, alternative buyers (e.g. private or end-user), and market size. Overwhelmingly, however, interviewees

considered that broadening the scope of the headroom calculation would make the method too complicated, and those with screening processes in place indicated that these other factors would already be taken into account: *'I think it's incredibly useful... It shouldn't be an answer in its own right. That doesn't discount its value'* [MNC]. This corroborates the findings of the retrospective case studies (for which there is much cross-over), and re-emphasises the result that consideration of sections six and seven of the pro forma, which consider the un-quantified / un-quantifiable, are essential.

The method's simplicity was widely acknowledged to be a strong asset of the approach, making it (necessarily) quick and simple. The MNC illustrated this with an account of an internally developed project appraisal process, which was too detailed and complex to be useful in practice: *'...they spent an enormous amount of time, money, and effort to put it together. Looked fantastic, but nobody utilised it'*. This resonates with a comment made by the NHS innovations manager, who had previously attended a MATCH course on the HE tool (an excel-based decision tree health economic analysis). Having understood the tool on the day, and being keen to utilise it and share it with colleagues, she came up to a difficulty, *'fell off'* and has not returned to it since.

#### *9.4.3 (iv) Product versus application*

The headroom method requires a concrete vision of for what and whom a device will be used. A product and its application are considered to be one and the same, a result of taking a demand-side approach for which the product's *application* is of paramount concern. However, this notion is at odds with the perspective articulated by the SME, who indicated that (at least for biotechnology) innovation tends to be an *'idea in search of an application'*. This standpoint is complemented by the retrospective case studies, where a product transpired to have multiple applications and headroom was valued in relation to only one of these. This

highlights the potential incongruity in applying a demand-side approach to a business decision for product development.

However, this product–application relationship differed according to the type of developer. For example, where an idea has stemmed from an association or involvement with its end use, the direction appears to be opposite, with the application preceding (and informing) the product. In the experience of the NHS research project facilitator: ‘... *sometimes it’s a concept and you’re kind of designing a device for a problem.*’ This mimics the conception of the near-patient monitor for COPD, which was born from the desire of a clinician to improve the process of care for her patients.

#### 9.4.3 (v) *Extra Scope*

Ideas around extra scope for the method or its interpretation, outside of its proposed remit (to inform go / no-go development decisions) arose from the interviews. The first relates to the aforementioned product-application consideration:

*‘...if you know that maximum price, you ought to be designing your device to fit that to some degree.’* [Research project facilitator].

This suggests that, particularly where application ideas precede concrete notions of the product, design choices may be guided by the headroom value, e.g. the intended regulatory class of the device, materials used, whether it is durable or disposable, etc. This was also suggested by the design and technology consultants.

The impracticality of estimating headroom where thoughts on the product precede application ideas, or where multiple applications are indicated, was noted above. However, just as a method benefit was considered by the clinician to be its ability to value different scenarios / distribution strategies *within* a specific application, exploring value *between*

applications was also noted by the SME as a potential strength rather than necessarily a limitation of the method:

*‘...in actual fact it [the product] is potentially going to be used in a wide range of different applications. So it’s actually not too late to apply that [the headroom method] to other indications, that one might or might not move into’. [SME]*

This highlights the method’s flexibility, illustrating its potential use in considering or comparing value across different markets.

The headroom method was presented and discussed as a rule-out method for early development decisions, and all interviewees believed it to be useful in this respect. However, consideration of the later stages of development arose in some interviews (particularly with the medium and large businesses). The theoretical MRP was related to how pricing decisions are actually made: generally, according to the SME, on a ‘*cost-plus*’ basis. Indeed, the very high theoretical value of the ulcer protector discussed in chapter 8 would be an unreasonably high price to charge. This demonstrates that although the method (within the remit of this project) is not proposed to set future price, it may be misguided to consider that the NHS would be willing to pay up to its maximum theoretical value.

This brings to the fore a new potential role of the method: to communicate value in the later stages of development. For example, where the headroom method indicates a clearly positive development decision (such as that of the ulcer protector), and the actual product price would be set well below MRP, this could be used to present an attractive case for buying it; the larger this difference, the bigger this willingness-to-buy factor should be.

On top of its early and later applications, the research project facilitator considered its potential integration into the management process throughout a project: to review the case and update expectations. Other comments alluding to the method’s wider potential scope included

indications of its global relevance (clinician and technology consultant), and the MNC and design consultant considering the method, in its most simple conceptual form, to be applicable to all industry. Improvements were suggested in the form of wider guidance on the reimbursement process, but were more directed to MATCH rather than this specific method.

#### 9.4.4 THEME 4: Headroom Impact

This theme captures the pertinent messages from all three themes discussed, and brings the observations and patterns identified forward to consider the method's (potential or realised) impact. They cover the method's novelty, the motivation of the interviewees for carrying out a headroom analysis, for whom the method might be most useful, pertinent roles established, and evidence of actual or intended action.

##### 9.4.4 (i) Novelty

To determine the novelty of an approach is to assess the extent to which it adds to or differs from current practice. For many participants, the method provided a learning opportunity. This learning experience was, for some (clinician, start-up and academic), based on an insight into health economics in general:

*'Well I certainly learnt a lot. And I think any other clinician would learn a lot... You will have read a lot about what clinicians think of NICE. We don't usually see them as our friends, because we wonder why we can't use such and such a drug... But I now understand the workings behind that, you know, and the importance of that. For me, it's given me a very healthy perspective of health economics and the work that NICE does on behalf of the NHS. It was very useful.'* [Clinician];

*'It's been a huge insight into how it all works.'* [Start-up].

For the academic and those working with innovation in the NHS trust, learning about NICE's cost-effectiveness threshold was deemed particularly useful. Whilst this does not convey much insight into the headroom method itself, it does highlight the gap in health economic

knowledge of many innovators, and also shows that this insight can be delivered in a short space of time using this framework.

Interviewees already familiar with health economics, such as the SME, indicated that while they did not learn anything new, they may have learnt a '*better way of looking at it*', at that early stage. All participants (apart from the business and design consultants who are already familiar with the approach) acknowledged that the method offered a novel contribution to current decision-making protocol (where there was one), and by expressing the value they saw in it, believed it to be useful despite the limitations or omissions described in the scope theme.

I believe that the basis of this 'novelty' in fact derives from the method's provision of a way to better articulate the things that developers already think about; to transform notions into numbers: to back up assertions and quantify them. This may be what makes the method accessible: '*I think conceptually it's very similar [to what she was already considering], which is I think why I found it attractive because I thought 'ooh', I recognise what to try and do.*'[Academic].

#### *9.4.4 (ii) Motivation for employing the headroom method*

##### **a) To '*open the purse*': a practical motivation**

For the innovators—the 'group 1' described in the first theme—the underlying motivation for engagement with me and with the method seemed practical. Rather than to inform their decision to develop, they seemed driven by wanting to learn about health economics and the way in which value is perceived in the health sector, either because they were looking to promote their product to the NHS (start-up), or were applying for NIHR research / product development funding (clinician & technology consultant and academic):

*'I think the days of blue sky funding are gone... It has to be relevant economically.'*  
[Academic]

Additionally, the graphic presentation of the method was noted to potentially add some impact to this application process, being: *'...sharper. Instead of wordy text, it's just there, and it leaps out at you, and I think that sort of impact is hugely important.'* [Academic]

#### **b) To assess viability at an early stage**

*'The main reason for using a headroom method is to try and decide whether an idea is viable. To avoid me spending time working on a product which isn't going to go ahead.'*  
[Design consultant]

Comments of this nature, expressed by the business and design consultants (who already use the method), SME, and MNC align more closely with the method's traditional remit: to get an idea of the *'prepared to pay'* number, so that by comparing this to manufacturing costs, the viability of development can be explored. By way of illustrating this, the MNC offered an example of an instance in the past where the company had invested significant time and resources into a product which was a no-goer from the start:

*'...it was dire. It had SWOT analysis, PEST analysis, god knows what, and it was garbage. Whereas something like this [the headroom method] ...might well have said, actually, that's what you're going to get.'* [MNC]

The head of scientific development noted that by incorporating the headroom method into their current system, this expense may have been avoided.

#### **c) Injecting some 'objectivity'**

For those in advisory roles or dealing with the ideas of others—group 2 in the first theme—a real motivation was adding *'objectivity'* into early development decisions / interactions, with words such as *'rigour'*, *'something definitive'*, *'formalised process'*, and *'structure'* being used extensively. The reason for this becomes apparent when considering the earlier



exposition of guiding principles and current feasibility checks. For example, to tackle the problems associated with a diverse innovation board and the subjective ‘*gut feel*’ nature of decisions, the MNC suggests:

*‘... you can use this tool to get an objective point of view into a very open discussion’;*  
*‘...you need some financial objectivity... this would give an element of that, that they [the innovation board] would find very very acceptable.’* [MNC]

It therefore seems that, even for those with set processes, there is a call for increased objectivity and structure to these early decisions, and early indication that the headroom method could fulfil this role.

#### **d) Further roles**

In considering the method’s scope, some new roles for the headroom method were explored, outside of its original remit as a ‘rule-out’ tool. Most notably, these included informing product design, assessing new market entry opportunities, and its use for later marketing purposes.

##### *9.4.4 (iii) For whom might the method be most useful?*

In the opinion of most participants, the method would be most useful for small or young companies: as a reality check, to force them to consider the ‘*unpleasant truth*’ about the potential value of their products. The premise of this response is that (a) small companies have limited resource to apply to early decisions, but a lot to lose if the wrong decision is made, and (b) that ‘*small companies tend to be driven by optimistic people because optimistic people found companies.*’ [SME]. This is consistent with the description of the innovators’ guiding principles and motivation, which is grounded in a belief in their products and a passion to improve practice. This optimism represents both a strong rationale for integrating

the method into early development decisions, as well as a potential barrier to doing so with detached objectivity.

The above theory matches my own hypothesis going into these interviews, believing that large companies are likely to already consider the potential health economic value of their product early on (but that small companies dominate the sector). This belief was reiterated by the SME and design consultant, who confirmed that very large medical companies have teams of in-house health economists and a good grasp of market opportunity early on. However, these companies are few, and the interview exchange with the MNC (whose healthcare division has a global outreach and is worth €1.5 billion per year, employing 3-4,000) indicated an absence of health economic expertise within their own company. When asked who would benefit most from the method: *'I would say... anyone and everyone. I think you'd be surprised at large companies how badly some of them do this'*. The method's use by manufacturers selling their ideas to large medical companies (whose product development often stem from acquisitions) was also suggested to hold promise.

Despite the participants' focus on (usually small) companies being the most likely to benefit from the method, all interviewees discussed how they themselves could benefit from its application. In particular, it appears to have a strong function for those dealing with the ideas of others. Indeed, the two participants who already employ the method are both consultants. The often limited influence on decision-making of people in consulting or advisory roles was noted in theme one. However, rather than this hindering the method's potential, it was expressed that in fact the method could aid those interactions, making them more productive and successful. This function relates to the method's suggested association with objectivity and its provision of a formalised approach, which was mainly discussed in relation to restraining enthusiasm. For those dealing with innovation from within the NHS, it

was suggested that the method could help defend the position of the advisors when interacting with the subject experts, and by taking them through a formalised process, to put off those whose commitment is superficial.

#### *9.4.4 (iv) A tool for communication*

The headroom method's role in sharing information and communicating value with relevant interested parties and stakeholders was highlighted by all interviewees. For the academic and clinician, this meant selling their ideas to funders.

*'...which allows me to bridge the gap in the language that can be used not only to further my collaboration with the commercial partner, because after all the commercial partner needs to see whether this is going to be viable, but also... in talking with commissioning groups, the purchasers. ... Because you don't want your product to end up on the shelf.'*  
[Clinician]

This demonstrates quite explicitly that the method is seen as something not only for justifying the case for development early on, but in carrying through to later conversations with buyers as well (which was also emphasised by the business consultant, in describing the use of 'headroom' to sell a new product based on the revenue stream it could provide for an NHS trust). This communicative role is also reflected in the method's use to facilitate consultants' interactions with their clients, and in facilitating internal discussions around potential new projects within companies.

#### *9.4.4 (v) Action points*

Finally, impact (realised and potential) is considered in relation to actual action points. Evidence of the method's use is provided by the business and design consultants, who indicate its worth in considering the commercial viability of their clients' ideas; this offers a promising signal of the method's utility in this function. Indeed, the NHS trust employees described their interest in utilising the method to appraise product ideas they are approached

with, both aiding the selection process—*‘I want to see it as part of the tools that I use to make decisions. To either proceed or not proceed’*—as well as facilitating more productive interactions with their clients (NHS staff or small businesses).

For the clinician and technology consultant (from the COPD case study) and the academic, their own decision to develop is dependent on their ability to successfully access funding opportunities. Whilst the academic expressed her interest in using the approach in the future, the method’s application to the COPD case study has had a practical output, in helping to secure a second round of i4i funding for the product by presenting its economic case:

*‘I think as well from the funding point of view it added a lot of credibility, and also a lot more confidence knowing that we had that on board from an early stage.’* [Technology consultant]

Both the SME and start-up expressed a desire to use the headroom method in the future, with the former looking to consider new market entry opportunities: *‘...it’s not too late to use the tool, and I shall be passing it on to my colleagues.’*

The MNC saw value in the method’s potential integration into their current screening process. However, the form of this in their eyes would most feasibly be outsourced consultancy work, an option which NHS innovations also mentioned to be of consideration. Whilst this may reflect the previous contact with MATCH of these two sets of participants, it is also indicative of the limited time they have to allocate to the method. Another shared characteristic is that both deal with the ideas of others, probably implying a lower level of intrinsic interest in the products themselves (and this interest is not financially incentivised in the same way it is for consultants).

The potential impact of the headroom method is clear. The form of this impact, however, has been shown to be diverse, and to vary according to the user.

## 9.5 Summary and discussion

The purpose of this qualitative investigation was to elicit, from those involved in the development of medical devices, the potential limitations of and opportunities provided by the headroom method. As described in the literature review, there has been limited research into the use early economic evaluation within the device industry, although two studies conducted by researchers within MATCH investigate the practices of their industry partner base (Craven, Morgan, Crowe, & Lu 2009; Johal & Williams 2005) (see literature review for description). More recently, MATCH academics have performed a survey of 19 academic staff involved in healthcare innovation, and find that participants had little or no knowledge of health economics (Lu, Martin, Craven, & Morgan 2012). The current study set out to investigate this issue, intending not only to describe the potential gap for the headroom method, but also to explore its potential to fill that gap.

The themes presented in this chapter were based on interviews with 12 participants, recruited to suit the goals of a maximum variation sampling frame. New perspectives and insights were gained from each interview; although many of the themes and ideas were supported within the sample, it is unlikely that data saturation has been attained. It would therefore be unwise to suggest that these results are generalisable. Limitations of the study may include the pairing of some of the interviewees (see Table 9.2), which might have limited the diversity of potential responses. Additionally it is possible that, through either previous interactions or discussions within the meeting, my own thoughts were conveyed which may have consciously or subconsciously influenced the responses of the participants. Time and resources inhibited the re-assessment of transcripts and analysis by an independent qualitative researcher.

Despite its limitations, this qualitative investigation elicited the views of a wide range of informant types, who were able to impart a broad spectrum of ideas and insight. The analysis of these views, both between participants and across themes, has revealed some important practical issues as well as further opportunities, and how both of these are likely to depend on the user's background and relationship with the innovation process. Figure 9.1 summarises the themes and subthemes identified, and visually depicts the interrelationships between these.

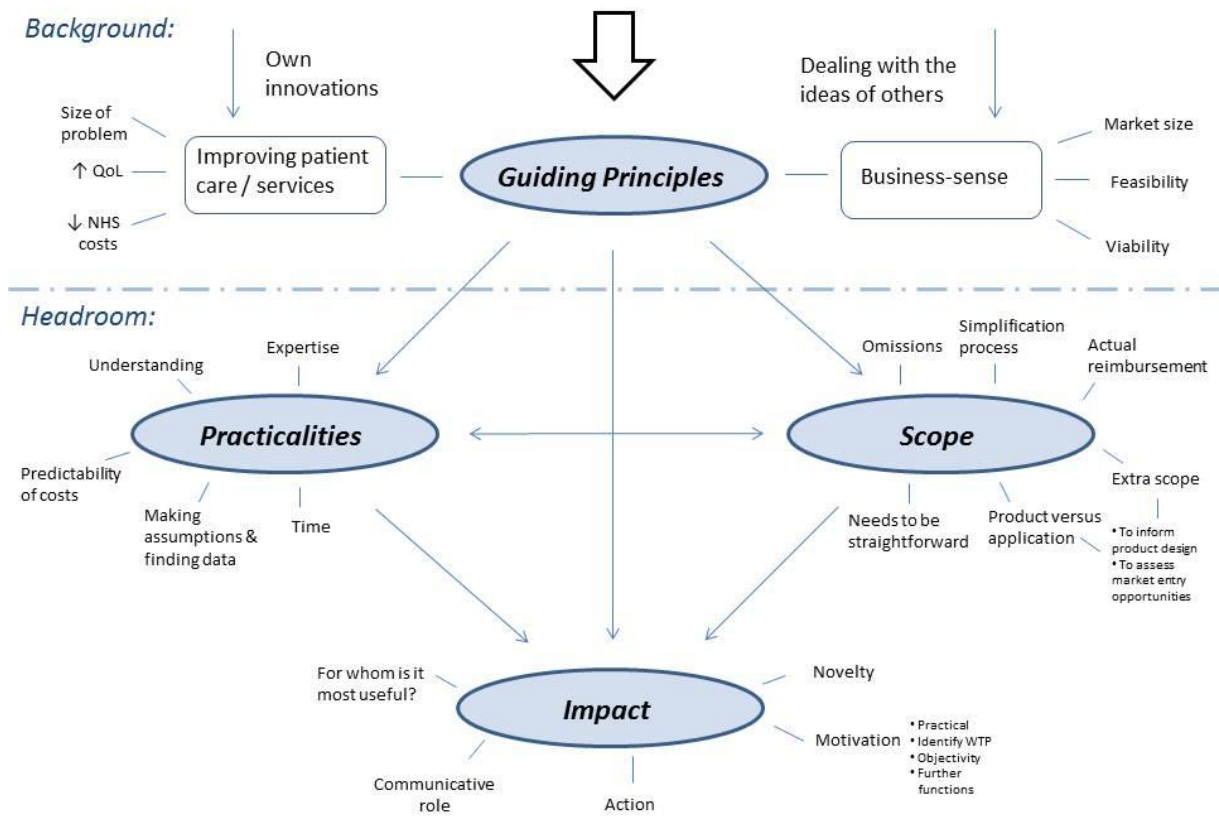


Figure 9.1 Mind map: diagrammatic summary of themes and subthemes

In relation to guiding principles, the sample was shown to be broadly dichotomised into (1) innovators, driven by a strong belief in their products and a desire to improve practice, and (2) those dealing with the ideas of others, who had a stronger commercial orientation. These positions influenced potential practical problems, which included possible difficulties for the innovators in making appropriate and realistic assumptions. Additionally, those with a research background specified fewer problems around finding data than did those in a commercial setting, whereas the costs of development (which were easily conceptualised by those in commerce), presented more difficulties for researchers. Expertise and time to allocate to the method's application may present further barriers to implementation.

The complexity of the actual reimbursement scene was noted, but overall the simplicity of the method's scope was considered to be a positive attribute. By asking the right questions, the method was regarded to usefully estimate market potential, offering a novel contribution to the decision-making process of all interviewees, including the MNC. The realised or potential impact of the headroom method differed according to the type of interviewee, and related fundamentally to their involvement in the innovation process. The impact of the method was discussed in relation to two main functions: to make decisions, and to sell ideas.

The first of these included the method's original aim—to help developers decide whether to invest in a new medical device idea, by grounding that decision in the consideration of potential value versus likely costs. Its use by consultants and advisors to help their clients make these decisions was also identified. However, in addition to this original remit, value was also seen in using the method to make further decisions: to inform product design, and to consider entry into new markets.

The second function—to sell ideas—was described in relation to the early and late stages of the development process. Early on, the method can (and has) been used to communicate value to prospective funders. This communicative role of the method was indicated to also be of value later on to make the case for a product's purchase, especially where price would be set below MRP.

The purpose for the mixed methods design of this project was introduced in the methodology chapter, and elaborated in the introductory sections of this one. The discussion chapter which follows considers the combined results of the various methods employed in this thesis, and how together they contribute to an evaluation of the headroom method.



## CHAPTER 10 DISCUSSION

### 10.1 Introduction

The mixed-method approach to this evaluation was designed to overcome inherent method weaknesses, to expand the evaluation enquiry, and to confirm and elaborate findings across methods (Clarke 1999; Greene, Caracelli, & Graham 1989; Yin 1994). So far in this thesis, interpretation of the results has been undertaken in relation to each of the evaluation's component parts as they have been presented. This discussion chapter synthesises and interprets the evaluation's findings as a whole, and in doing so provides a firmer appreciation of the headroom method's potential contribution to the decision-making processes of device developers.

Methodological triangulation, as described in the methodology chapter, allows the researcher to improve the validity of their research results by exploring any convergence in findings (Campbell & Fiske 1959; Simons 2009; Stake 1995). This chapter presents the results of this triangulation, and is organised as follows. Firstly, the evaluation and its outcomes are discussed in relation to the literature and the market context, which were described in the opening chapters. The triangulation of findings is then presented, offering a synthesis of results across the whole evaluation. Results are organised according to their capacity to address the initial research questions. Following this, the study's findings are extended so as to consider the resulting form in which the headroom method is proposed to be most effective. A careful consideration of the study's limitations is then discussed along with suggested avenues of further research, which is followed by the overall implications of the research and final conclusions.

## 10.2 Triangulation: The literature and market context

The literature review in chapter 2 demonstrated that, methodologically, the early application of HTA is still in its infancy—especially for medical devices. Most research focuses on pharmaceuticals and relates to the integration of HTA considerations throughout the development cycle (Bartelmes et al. 2009; Hartz & John 2008; Ijzerman & Steuten 2011). The academic literature relating specifically to the appraisal of medical devices pre-development is scarce, and the previous headroom literature fails to answer the calls of the field: to ‘critically appraise the relevance of early HTA for its stakeholders’ (Ijzerman & Steuten 2011, p. 342), and to ‘investigate the practicality and likely value of the approach’ (Vallejo-Torres et al. 2008, p. 463). Bartelmes and colleagues (2009), in reviewing the literature, note the lack of standardisation of any proposed method of early economic evaluation, which are mostly described vaguely and whose application rarely exceeds pilot implementation. The authors additionally note that an evaluation and validation of any method in relation to its predictive capacity does not exist (Bartelmes et al. 2009). The results presented in this thesis therefore offer a novel and important contribution to the field.

The market context within which device developers operate was described in chapter 3, setting out the landscape for innovation as well as its evaluation. The interrelated themes that emerged from this account aimed to ground the research in its real-life subtext. Subsequent findings from this study have substantiated many of the issues raised, including the methodological challenges in applying HTA to medical devices, which were frequently illustrated through the case studies. It is no surprise that the difficulties surrounding device evaluation were also found in its early application, and often meant that headroom was problematic to calculate, that an MRP could not be estimated, that a range of options were

presented, or that the headroom case was made descriptively. These methodological challenges are summarised in Table 10.1

**Table 10.1 Methodological challenges in the HTA of medical devices which were reflected in headroom case studies**

<b>Methodological challenge</b>	<b>Explanation</b>
Headroom for Equipment: patient throughput issues	Where medical devices were not for individual use, estimating the headroom associated with an individual device (MRP) was difficult, as the number of units required to service the relevant patient population was unknown. Additionally, an estimate of device longevity is required to estimate MRP. This presented difficulties for nine of the retrospective case studies. Although not prohibitive in most cases, this often meant that headroom per patient (and/or per year) was presented rather than MRP, or where relevant an intuitive case was presented.
Service delivery interventions	Where the impact of the proposed technology was potentially very wide, concrete assumptions were difficult to make. In the case of E-medICS, this resulted in no quantification of headroom, although the COPD case study demonstrated that such assumptions can be made with careful study of the literature and expert input.
Non-health related preferences	Due to the third party administration of medical devices, user preferences influence product demand. Where health outcomes are not affected (e.g. from process utilities), these preferences are not captured in the economic evaluation. This was relevant for six of the retrospective case studies, where these relevant user-related factors were described in sections six and seven of the pro forma.
Providing evidence of health benefit	The follow-up of retrospective case studies often demonstrated the evidence generation issues described in chapter 3. These were exemplified by the limited availability of RCT data for follow-up, and specific device-related difficulties were identified in some of these (e.g. the problems associated with sham surgery for trials of the PFO closure device).
No single 'gold standard', or the comparator changes quickly	As there are fewer guidelines for devices than drugs, there are often many co-existing options available to medical professionals. As a result, the reference standard (the 'baseline' for an economic evaluation) was often difficult to define. Relative impact may differ according to the chosen comparator. Annemans and colleagues (2000) describe this selection problem in early health economic models for drugs, declaring that often more than one comparator should be considered (to potentially include different competitors as well as improvements in general medical practice). I have shown in many of the case studies that this is often intuitive, and can be incorporated into a headroom range. The relevant comparator can also change quickly due to the short life-span of a medical device. The CT scanner case study, for example, had already been superseded by a newer model when it came to follow-up the case study.
Long-term impact	Often a long time frame is required to consider the real benefit of a medical device. This requires buyers to be willing to consider a long time horizon which, depending on the financial situation, may not be possible. This presented some uncertainty for the headroom analyses.

These methodological challenges, rather than presenting insurmountable barriers, introduced some methodological opportunities. In particular I found that a complete analysis may not always be necessary to support an investment decision—often a partial headroom estimation sufficed. Where the new technology would offer clear cost-savings, for example, these were often easier to quantify and justified development on their own; this also suits the landscape of tightened health service spending and the increased pressure on innovators to deliver interventions of equivalent (or improved) benefit but at reduced costs (a necessary qualification, for example, of attaining NICE’s medical technology guidance). This demonstrates the headroom method’s ability to adapt to the prevailing procurement landscape. The case studies also demonstrated the potential negative ramifications of this cost-saving landscape, in noting that devices for new indications which deliver health benefits to previously untreatable patients are likely to be disadvantaged. Additionally, follow-up of the retrospective case studies often illustrated the slow uptake of devices within the NHS described in chapter 3.

Another opportunity presented was the ability to choose the target market by using the headroom method to identify where the net gains would be highest. This was explored in depth through the COPD case study, which also demonstrated that important justification for a new innovation could be found by considering the wider clinical context, including sought-after changes in clinical practice; the retrospective case studies showed that this wider market context should be investigated for its potential to curtail the case for development as well as promote it.

The industry landscape, representing the cohort of potential headroom method users, was shown in the introductory chapters of this thesis to be diverse in nature and dominated by small companies. The varied provenance of device innovation was demonstrated by the

sample of interviewees in the qualitative investigation, who were able to reveal the method's utility in relation to their particular roles. The interviews also corroborated an underlying assumption which was articulated in chapter 3: small businesses lack time and health economic grounding, which may currently inhibit rational decision-making in the early stages. Moreover, it was demonstrated that even large businesses may not incorporate health economic considerations into development decisions, thus also standing to potentially benefit from the headroom method.

The following results synthesis section presents the findings of this evaluation with respect to the initial research questions: does the headroom method work, and is it usable by device developers?

### **10.3 Triangulation: Results synthesis**

Discussion of the study's findings in relation to the two main research questions are broken down into the subsidiary questions described in the methodology chapter (Table 5.1, page 103).

#### **10.3.1 Does it work?**

To establish the efficacy of the headroom method, the evaluation sought to determine its novelty to developers and its predictive capacity, and to identify what is left out of the suggested framework.

##### *10.3.1 (i) Is it novel?*

Determining the novelty of the method in relation to current early feasibility checks for device development was a strong motivation for the interviews; even if the headroom method were to

‘work’, it would not improve decision-making outcome if a similar method were to already be employed by developers. The method provided a learning opportunity for many of the participants. For those already familiar with health economics, its incorporation into the development decision stage was perceived to be novel. Despite the MNC noting the novelty of the approach in relation to its own decision-making practices, other very large medical technology companies are likely to already systematically and comprehensively consider reimbursement prospects pre-development; the method is likely to be of less use to such companies.

As indicated in the interview analysis, the method seemed to provide participants with a more concrete way to express and quantify the benefits of their innovations, of which they already had a general notion. In four of the retrospective case studies, the headroom development decision was indicated to be either intuitively favourable (SLF bypass graft and Cool-cap) or intuitively unfavourable (AmpliChip and ChondroCelect). In these cases headroom was not quantified, either because it was not possible or not necessary to do so. Whilst the prevailing research questions transpired to be pertinent, it is difficult to know in these cases whether the method’s output would not have contributed an insight beyond that already perceived by the developer, or whether the analysis forces such insight to be recognised.

#### *10.3.1 (ii) Is it a good predictor of market uptake?*

There appeared to be no strict qualifications for an ideal headroom candidate, although those technologies that directly replaced the baseline treatment were most likely to generate a concrete monetary estimate. Most difficulties in estimating headroom derived from the methodological challenges outlined in Table 10.1; diagnostics were the most problematic, due

to the less direct impact these technologies have on patient outcomes and future cost implications.

The method's predictive capacity was addressed by the retrospective analyses and their follow-up; for the purposes of comparing the headroom decision to later success, the latter was judged primarily on its availability in the UK. A favourable headroom decision outcome was followed by widespread NHS uptake for just two of the case studies, which became the 'gold standard' for the indications considered. This re-emphasises the fact that a product need not achieve full market coverage to be viable, and in fact this is rare for medical devices (due to the market factors described in chapter 3). Indeed, in assessing the business proposition of his clients' products the business consultant interviewed uses a 40% estimate of market coverage as a baseline. In two of the case studies, the decision outcomes of the headroom analyses were uncertain (due partially to the inability to follow the products up), but strong caution was offered in relation to their health-economic case for development; these were the only two case studies for which no evidence of uptake (anywhere) has been identified. The follow-up of all other case studies identified some evidence of uptake (either internationally, and/or for another clinical indication).

Evidence of any NHS uptake (for the clinical indication specified) was used as the main outcome to which headroom decisions were compared. Of the 17 headroom decisions that were followed-up (eliminating SpeechEasy due to it being a consumer product, and omitting the two cases for which headroom was uncertain), the headroom method 'got it right' in 14 cases—around 82%. The remaining three decisions were contradicted (ChondroCelect, TTT and Agento IC). The headroom for both TTT and Agento IC appeared to indicate a favourable development decision, but neither is used within the NHS for the proposed clinical indication, due to unsatisfactory clinical effectiveness for TTT and possibly changes in

clinical practice for Agento IC. Before conducting the analyses, this scenario was considered to be the less disparaging of inaccurate predictions by the headroom method, as early expectations of clinical effectiveness may transpire to be too optimistic. Therefore, if the method is seen primarily as an aid to ‘rule-out’ the development of devices that will never be cost-effective, then the more discrediting scenario is for an unfavourable headroom decision to be followed by future uptake. This was realised in the case of ChondroCelect. This could imply that the headroom method may direct resources away from viable products which would otherwise have been developed. In the case of ChondroCelect, this was due to the reimbursement perspective being too narrow, not acknowledging that the NHS allows pass-through payments for some innovative high-cost technologies. This one case of an unfavourable headroom decision being followed by subsequent NHS uptake led to the headroom method’s sensitivity being recorded as 92%, and its negative predictive value (its performance as a rule-out tool) as 67%. By re-categorising the uncertain headroom decisions as unfavourable, accuracy would be 84%, sensitivity would remain 92% (though the test would become more specific: 67% instead of 50%) and the negative predictive value would be 80%.

The main limitation of the quantified headroom analyses in relation to the viability of product development (which must more appropriately relate to uptake anywhere and for any purpose) was the narrow reimbursement perspective taken. However it was shown that, through the process of assessing headroom, the relevant barriers and opportunities to commercial viability can often be identified, and when considered alongside the monetary headroom analysis offer a good assessment of uptake prospects.



### *10.3.1 (iii) What is left out of the analysis?*

Economic evaluations form only part of an HTA when reimbursement is being considered. This was shown to be the case for Stapled Haemorrhoidectomy, where the result of the late-stage cost-effectiveness analysis was marginally unfavourable, but where the NICE committee nevertheless recommended the procedure based on other factors. This is crucial, and vindicates the necessary consideration of the peripheral factors which are noted but not quantified in the headroom analysis as well (such as user acceptability, likelihood of competitors, and potential changes in clinical practice). Whilst this discounts the value of the headroom method as a strict decision rule, the retrospective case studies demonstrated that the pertinent additional factors can usually be predicted at a very early stage, and that when considered alongside headroom 'value', always offered a useful prediction of market opportunity. Unlike the suggestion by Girling et al. (2010) that early valuations need necessarily be deflated (due to lower actual cost-effectiveness compared with early predictions, healthcare provider budgetary constraints, effectiveness of the marketing campaign, and competing products that may arise during development) these exogenous factors were found to inflate as well as deflate perceived value. The findings relating to omissions of (numerical) headroom are presented below, and where relevant supported by the views of the device developers interviewed.

The reimbursement perspective was found to be too narrow and somewhat idealistic. The most obvious caveat is that the device market is global. Whereas six of the retrospective case study medical technologies did not become available within the NHS, only two of the products were not available anywhere upon follow-up (either in other countries or for different clinical indications). This perspective was reiterated by the interviewees, who also mentioned alternative types of buyer such as private healthcare providers and the end-user.

Indeed, one case study was omitted from the results analysis as it turned out to be a patient purchase, and ChondroCelect has achieved funding by means of supplementary reimbursement specifically for novel products. The Ulcer Protector described in chapter 8 may in the future be made available directly for patient purchase. Therefore, whilst the headroom analysis provided guidance on potential NHS value, if the result had been unfavourable it would have been unwise to rule out its development based on this alone. The rationality of local decision-making within the NHS is regularly discussed in the literature, and has been found to differ from the perspective taken by NICE (Buxton 2006). In the interviews, the non-alignment of actual reimbursement with the framework assumed by the headroom method was also raised.

Both the case studies and interviews demonstrated the tension between a headroom analysis (intended to help investigate the commercial viability of a product) and a standard economic evaluation (intended to understand the health economics of a specific application). The difficulty of patent protection becomes important here; whereas for drugs the valuation of a therapeutic outcome is synonymous with the value of a particular drug (which in the early years is patent protected), device competition is much greater. Additionally, the multiple application possibilities of some devices, especially diagnostics, means that their value to the health provider should be some weighted average of their impact across all relevant applications (Drummond, Griffin, & Tarricone 2009). In such cases the headroom analysis felt somewhat artificial, and whilst the device's potential applicability to other markets was described within the case studies, basing the development decision on the monetary headroom figure for that market alone would have been misguided. Despite this limitation, the ability to assess value by indication was regarded by the SME to be an advantage, proposing to use the

method to consider entry into new markets. The PFO closure case study demonstrated the method's use in this capacity.

Strategic factors also require specific consideration in the decision to develop, which may be especially relevant where the innovation is an incremental development of a company's own product; these considerations are not dealt with explicitly by the headroom method. Diagnostic devices were often assumed in the headroom analyses to either be completely accurate or equivalent to the comparator. This kept analyses simple, but an extension of the method may involve incorporating sensitivity and specificity assumptions more explicitly.

The omitted factors outlined provide justification for a remark made by the MNC: *'It shouldn't be an answer in its own right. That doesn't discount its value'*.

### 10.3.2 Is it usable by device developers?

Besides efficacy, the headroom method cannot improve current decision-making if it is not usable by those for whom it could provide benefit. An understanding of its usability was attained by assessing: its use at concept stage, the possibility of its application by device developers, and the practicality of its incorporation into current decision-making practices.

#### *10.3.2 (i) Can it be utilised at 'concept' stage*

The two prospective case studies demonstrated the method's application at an early stage of development, and showed how the literature may be used alongside the developer's own thoughts to inform and furnish headroom assumptions. The 'concept' stage for the retrospective studies was modelled to be around three years pre-launch (or two years for incremental developments); whilst it is not known whether this accurately reflects the

development time for all of these technologies, it certainly restricted the potential to pick up any data relating directly to the product itself.

In applying the headroom method across manifold medical technologies, the dependence of the method on the quality, consistency, and availability of the literature became clear. Whilst both this reliance on the literature (not being an expert in the clinical area) and its sometimes limited availability (especially where there were very early date restrictions) were probably exaggerated within the investigation, this posed a problem particularly for new indication devices. The strategy used to overcome this was to present headroom under various scenarios or assumptions, a strategy in which the interview participants saw promise.

A headroom analysis assesses the potential future monetary benefit of a medical technology, but in order to appraise the viability of a project (by considering profit prospects: *net* monetary benefit) this must be considered in relation to projected costs. Of those interviewed, the businesses and consultants indicated very few problems in anticipating development and production costs, whereas those in research and clinical settings (and according to a consultant: small businesses) find these difficult to fathom, potentially underestimating their magnitude. This may limit the ability of these developers to usefully appraise commercial viability, even if the headroom's assessment of future monetary benefit was accurate.

### *10.3.2 (ii) Can the method be applied by device developers?*

The pragmatic approach taken for the retrospective studies and the ulcer protector aimed to mimic the restricted time available to device developers, and to make its application systematic and accessible by using the pro forma and template of resources. There is an early

suggestion from the interviews that these resources may be useful in helping developers to take the method forward and apply it themselves.

Two of those interviewed (business and design consultants) claim already to use the method; this indicates that the method (or some form of it) is usable, and their positive comments reveal its contribution. All interviewees claimed to understand the headroom method, and believed its simplicity to be a strong virtue. That is, despite the factors that were identified as being left out (discussed in 10.3.1 (iii)), the method should not be made more complicated. However, some pertinent patterns emerged from the interview data and case studies which suggest two primary application difficulties: making the appropriate assumptions, and finding data to furnish them.

On the assumptions side, the strong rose-tinted belief of the innovators in their products may lead to biased assumptions, whereas those acting in advising capacities may be more independent and objective (though may lack the experience in the clinical area that the innovators are likely to have). The retrospective case studies illustrated that often assumptions were necessarily very speculative. The interview analysis suggested that those users in research roles (or with a research background) may more easily identify data in the literature, whereas those in business may find this challenging. The potential for bias extends to the identification of data, which regularly required a discerning approach where the literature base was wide; indeed, in some cases selecting a different source for data would have altered the implied development decision. The follow-up of some case studies demonstrated that companies are indeed selective in the data they choose to report from the wider literature (this was particularly the case for the PFO closure device and the Agento IC), and this tendency may extend into early headroom estimates.

The above commentary should be considered in relation to the headroom method's application in this evaluation study. Being both independent and a researcher, I may have had advantages in the method's application, the results of which may not be replicable in practice. On the other hand, being removed from the innovation and the innovator's field of expertise may have represented a disadvantage.

### *10.3.2 (iii) Could it practically be incorporated into decision-making?*

The main practical barriers were identified to be expertise and time. The issue of expertise relates in some ways to the ability to make assumptions and find data described above. Although this has not been tested directly in this evaluation, different parts of the headroom analysis were found to resonate more clearly with different users. The positive understanding of the method from just a short presentation was encouraging.

The time available to developers to allocate to researching the development opportunity is another matter which is not easily tested, and the assertion that this could pose a barrier to its implementation is difficult to argue against. The retrospective case study analyses took a mean of nine hours; whilst most interview participants indicated this to be a reasonable and worthwhile use of time, others (most notably the MNC) indicated that to add this to their current job function would be unfeasible (and thus would look to outsource such analyses). The MNC also hypothesised that analyses would take longer, at least initially, for someone unaccustomed to applying it. However, the time taken for each retrospective case study in my own investigation showed no downward trend, reflecting perhaps that each case was unique. The average time taken was slightly longer for retrospective studies with a later time constraint than those with earlier ones. This may indicate that the exponential growth in the literature base—whilst helping to better inform assumptions and quantify benefits—may increase the time required to sift through it and identify the most useful sources; indeed, the

wealth of information available for the COPD case study was certainly time-consuming to manage.

By summarising the results in relation to the research questions posed at the beginning of the project, an insight has been offered into the potential use of early economic evaluation in practice, which goes beyond any such understanding conveyed in the literature. However, by exploiting the mixed-methods evaluation output, the lessons that can be drawn reach beyond the original remit. These are summarised below.

### 10.3.3 The method's form

During the closing remarks of one stakeholder interview I was asked, in jest, whether I had considered the headroom for the headroom method. Upon reflection, this eloquently describes the motivation for this study, and is what I believe to have achieved. Echoing the elicitation of headroom for individual devices, the overall evaluation has taken on an inclusive approach, and as a result has extended the analysis beyond the initial research questions. This has been achieved by guiding method choices and analysis around what Patton (1997) describes to be a utilisation-focused evaluation, informed by an overarching evaluation goal: intended use by intended users. By broadening the scope and investigating the reasons behind the method's efficacy and usability, the results attend not only to 'Does it work' but '*What works for whom in what circumstances and in what respects?*' (Pawson & Tilley 2004, p. 15): the objective of the realist evaluator. The interpretation of results in relation to this explanatory perspective is presented over the next two pages.

### *10.3.3 (i)...What works?*

A unifying theme across all case studies was the need to be flexible and adaptive in the application of the headroom method. Accordingly, the step-by-step guide offered by the pro forma and template of resources, rather than supplying the precise steps to calculate headroom, provided the right questions to work out the most appropriate approach, which will differ according to the product under evaluation. The choices made for a headroom analysis must be conscious choices, for which the user should be aware of the underlying assumptions and potential limitations of these. Additionally, other factors identified through the process, which are not quantified but which may (either positively or negatively) affect the chances or scale of reimbursement, should be recorded. Together, these inform the research questions, which should be considered pre-development or, if it is decided that development should proceed, should guide future investigations. When these were considered alongside the quantitative headroom gap, the headroom analysis provided a good assessment of future market potential, and thus may provide a useful aid to decision-making.

### *10.3.3 (ii)...For whom?*

The stakeholder interviewees reflected just some of the diverse origins of innovation in the medical device sector. Whilst previously considering small businesses to be the foremost potential beneficiaries of the headroom method, the interviews illustrated a much wider relevant user base. It was found that even large companies may profit from the method, and that its potential use extends beyond industry to anyone involved in the process of innovation. However, the way in which different users derive (or perceive to derive) benefit varies according to their role and their relationship with that innovation process.



### 10.3.3 (iii)...In what circumstances and in what respects?

For those looking to explore early indications of product viability, or to sell their ideas to funders who must make a similar judgement, the headroom method can be seen to hone in on the value proposition where previously reimbursement prospects were either not addressed or were considered in a vague or notional manner. The case studies showed that a clear understanding of potential impact was necessary, which was particularly difficult for diagnostic devices or medical equipment used for multiple patients. However, some exploratory testing of alternative scenarios can be useful where this clarity is lacking. As well as ascertaining the method's capacity to inform very early development decisions, the evaluation identified further possible roles which fall beyond this original scope, relating to the timing of the assessment and the utilisation of its output.

Whilst most case studies considered the development prospects of a new innovation (where headroom is compared with projected costs of development/production), others related to alternative decisions. For example, some retrospective studies investigated the reimbursement value of upgrading a company's own device (where headroom must be compared with upgrade costs, e.g. CT scanner case study), or considered the reimbursement value of directing a current device to a new market (where headroom is compared with research and marketing costs, e.g. PFO closure case study, and SME's intentions).

Economic models are described by Miller as the '*interface*', the '*vehicle of communication with external decision-makers*' (Miller 2005, p. 5). The headroom method provides an economic model of a new innovation's value, and its use to communicate this value with decision-makers (be they funders, buyers, or in-company) was considered by interviewees to be important in the later as well as earlier stages. For those involved in

innovation in an advisory capacity, the method was considered to be a useful tool to add rigour and structure to their interactions with clients or with those making the decisions.

Having described the results of this evaluation—outlining the limitations of and opportunities provided by the headroom method—the next section considers the limitations of this study and the opportunities these may present in terms of future research.

## **10.4 Limitations of the study and opportunities for further research**

The results and analysis of a research study are inextricably bound to the methodological choices made, either purposefully or for practical reasons. Consideration of their potential limitations is therefore necessary, in order to judge the validity of results as well as to identify possible avenues of further research. The discussion of these study design limitations and further research opportunities are presented below under four main categories: (1) study sample, (2) the headroom method's application, (3) the approach to the overall evaluation, and (4) the indirect nature of evidence.

### **10.4.1 Study sample**

There were three sample groups in this thesis: the prospective case studies, the retrospective case studies and the interviewees, and for each the selection process was distinct. Due to the research setting of this project, the identification of prospective case studies was in fact not a very selective process, and was more opportunistic. Their contribution to the evaluation results were not as significant as the retrospective studies due to their lack of follow-up, although they played a strong role in informing the evaluation study design and both offered

unique methodological insights. Although both prospective case studies provided particularly insightful interview opportunities, their contribution to the evaluation may have been greater had they been designed to address the study's research questions more directly. As efficacy could not be addressed, our understanding of usability may have been advanced had the headroom analyses been carried out by the innovators themselves. Although this was addressed indirectly through the interviews, a study of the method's direct application by developers would be the logical next step in future research.

The selection process of the retrospective case studies from the NHSC database was described in detail in chapter 7. Most notably, exclusion was on a practical basis, and was largely due to lack of clarity in the NHSC briefings. However, the tendency for those excluded to be diagnostics and to represent non-replacement technologies may indicate an inherent difficulty in ascertaining their potential impact; this finding may have been under-represented due to their exclusion. The biggest source of bias for the retrospective case studies was their source, being selected from a database whose remit is to provide early warning of medical technologies which are close to launch, and which have the potential to make a big impact on the clinical or procurement landscape. This was reflected in the fact that only two of the 20 case studies were class I devices. As discussed, this is not likely to be representative of the sector, and most crucially it biased the sample toward successful products. However, a study by Simpson et al. (2004) which assessed the accuracy of this forecasting by the NHSC (spanning across all types of briefings including those for drugs), found that of a sample of 117 technologies, 35 were initially predicted to make a big impact on the NHS but 30 of these (86%) transpired to be false positives. Of my own case studies that were followed-up, six were not available on the NHS for the indication considered.

The possible partiality of the interviewees, who were proactively sought but whose interest in taking part inherently reflects their interest in the subject, was discussed in chapter 9. Responses may therefore have been biased as a result. Although the interviewees span a wide range of potential users, it is difficult to know whether their attitude is typical of their sector. Certainly, if larger companies were better represented in the sample, then the investment appraisal techniques currently used by these could have been explored. Nevertheless, the presentation of the UK's medical device market landscape showed these larger companies not to be representative of the industry as a whole. Moreover, the interviews did not intend to provide a thorough characterisation of current decision-making practice across the medical technology sector, but to develop a better understanding of some of the barriers and opportunities around the headroom method's use. A postal survey directed at a large number of device developers may provide a way to better explore current practice, and presents a potential future avenue of research (although, as noted by Pike & Sharp (1989), this technique may be subject to response bias also, with those using more sophisticated investment techniques being more likely to respond).

#### 10.4.2 Headroom application

##### *10.4.2 (i) Uncertainty*

The application of the headroom method through this thesis has been described in some detail, and the development of materials (the pro forma and template) intended to make this application as systematic and reproducible as possible. However, the precise approach taken was noted to vary case study by case study, according to the source of the technology's proposed value and the information available in the literature. Uncertainty was not formally incorporated into the analyses, though a form of sensitivity analysis was often performed to test the effect of altering assumptions (with regards to comparators or magnitude of health /

cost impact) on the headroom outcome. This lack of formal incorporation of uncertainty may be regarded as a limitation, especially given the inherent financial risks associated with product development.

The development process for a new product comprises in reality not of a one-off investment decision made at the outset of a project which cannot be reversed, but a chain of decisions, considered to take place at a series of stage gates (Cooper 2009). Although the initial concept-screening stage decision is perhaps the most critical but most difficult point for investment, the real options approach recognises the flexibility offered by adapting or revising budget allocation decision at a future date when some uncertainties have been resolved (Johal, Oliver, & Williams 2008). The value provided by this flexibility (reflecting the ability to defer the decision to abandon development or to adapt to changing market conditions or technology performance) necessarily inflates early valuations so that, perhaps un-intuitively, *'the larger the amount of uncertainty, the greater the opportunity for value creation'* (Johal, Oliver, & Williams 2008, p. 109). Whilst much of the real options literature does not provide details on how the initial valuation should be made within the context of the healthcare sector, Girling and colleagues (2010) consider uncertainty alongside early headroom valuations, and simplify the options approach by considering there to be just two decision gates. The authors reveal mathematically how a subset of these uncertainties could be considered, providing a partial valuation and therefore placing a lower bound on expected product value (Girling, Young, Brown, & Lilford 2010). Further research into the formal incorporation of uncertainty into headroom may represent a potential future avenue of research.<sup>48</sup>

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<sup>48</sup> As described in the literature review, Vallejo-Torres et al. propose integrating health economics into the product development of a medical device at the early, mid and late stages (Vallejo-Torres et al. 2011). However, uncertainty is explored in the mid and late stages only (when some clinical evidence is available).

The decision not to formally incorporate uncertainty in this way lies in its impracticality. This options-style approach involves a complex mathematical manipulation and quantification of expectations and (stage-related) uncertainties, which may be unfeasible in practice. The use of real options by businesses has been described more readily in relation to the pharmaceutical industry (see for example Nichols (1994) and Rogers, Gupta & Maranas (2002)). One practical barrier to its use by device firms is the required numerical estimate of volatility, which in the case of larger and more established pharmaceutical firms may be more tangible: *‘Merck’s experience with R&D has given us a database of information that allows us to value the risk or the volatility of our research projects, a key piece of information in option analysis’* (Nichols 1994, p. 90). Johal and colleagues (2008) indicate that the medical device industry face similar issues to the pharmaceutical sector early on, where early valuations are subject to considerable technological, regulatory and market demand uncertainty, which must be accounted for. However, I demonstrated in the context-setting chapter 3 that, in fact, the uncertainties surrounding device development tend to be lower than for pharmaceutical innovation, due in part to their engineered design (which is often an incremental modification) rather than discovery process, lower regulatory hurdles, and shorter development time (thus limiting the uncertainty surrounding the changing market context). Indeed, the retrospective case study analyses demonstrated that the clinical and market context factors which did transpire to affect demand were largely predictable—though of course this is not always the case.

By not accounting for the positive value of uncertainty and decision-deferral, the main concern is that an NPV approach (such as that proposed in this thesis) would lead to the non-development of potentially successful products (Girling, Young, Brown, & Lilford 2010;Johal, Oliver, & Williams 2008). In my own test of headroom decision implications,

there was just one case for which the headroom analysis (though not quantified) implied an unfavourable development decision which was subsequently successful in achieving reimbursement: as discussed, ChondroCelect has achieved reimbursement via pass-through payments. This highlights the ambiguity around reimbursement routes, which does represent a limitation of the naïve perspective of the headroom method. This being said, the developer of the technology may have been better informed of alternative means of reimbursement, and could have incorporated this into his decision qualitatively.

The interview analysis highlighted that, to impact current decision-making, the headroom method must be simple. Formally incorporating uncertainty may therefore be prohibitively complex, though this could be investigated in the future.

#### *10.4.2 (ii) Expanding the analysis*

The HTA of new products by decision-makers has been shown to consider aspects of a technology's offering outside of its cost-effectiveness alone. There has therefore been a call for appraisal committees to incorporate these other factors more transparently and consistently into coverage decisions, for which multicriteria decision analysis has been suggested (Tony et al. 2011). First introduced by Saaty (1994), the analytical hierarchy process (AHP) (as presented in the literature review) is one regularly cited method of multicriteria decision analysis, which involves structuring a decision-problem into its key elements and attaching weightings to those elements based on their relative importance to the decision-maker. This technique has been applied to various decision-making settings and scenarios in the literature, and may be relevant to device developers given the multiple strategic factors that must also be considered at the concept-screening stage. Mayhew (2009), for example, describes other contributors of value to a company which would not be captured within a headroom analysis: human resources value, marketing value, reputation value and innovation value. Thus,

incorporating these into a development decision systematically (e.g. using AHP) may represent a worthwhile methodological extension to the headroom method which could be investigated in the future. As the relevant factors and their relative importance would vary according to the user, this was outside the remit of this particular evaluation, which aimed to evaluate the headroom method according to its capacity to provide a simple tool that could be applied across technologies and by any device developer.

#### *10.4.2 (iii) Approach to QoL estimations*

The recommended approach to HRQoL estimation was described in chapter 4, which described three methods in order of preference. An original methodological contribution to the headroom framework was provided by the second of these methods: manipulating the five health dimensions of the EQ-5D. This technique was applied to three case studies: stapled haemorrhoidectomy, TVT and the ulcer protector. Whilst its application to the ulcer protector cannot be validated (though the innovators indicated that the approach contributed to their understanding of HRQoL), the other two were followed-up and compared with subsequent evidence. The health impact valuation for stapled haemorrhoidectomy transpired to be fairly accurate. In the case of TVT the impact was overestimated; although the baseline health state of urinary incontinence was well predicted, the assumed resumption to full health was not. This may be improved when validated value sets become available for the updated EQ-5D-5L, where the increments will be smaller and thus sensitive to more moderate health impact (EuroQol 2012b). This greater sensitivity to smaller changes in health may also be more appropriate for valuing the improvement in self-care modelled for the Ulcer Protector. This updated instrument could be incorporated into future research.



#### 10.4.2 (iv) *Development cost analysis*

Another novel contribution of this study was to consider the allowable magnitude of development costs, in cases where MRP and market size could be estimated.<sup>49</sup> This was demonstrated in some detail for the COPD case study, was deemed inappropriate for the Ulcer Protector, and transpired only to be possible for five of the retrospective case studies. One of the main limitations in estimating these allowable development costs was the presumption of full market coverage. As discussed, this is particularly unlikely for medical devices. In order to more appropriately conform to the guideline of optimistic but *plausible* assumptions, the market size estimate should probably be revised downwards.

Due to my limited understanding of the appropriate timeframe for companies to recover development costs, this was implicitly assumed to be the amount of time it would take for the company to sell the device to the full (estimated) market size (i.e. the number of relevant patients identified, which was often presented on a per year basis). This may be somewhat artificial, as companies are likely to have their own preferred timescales, which will be capped by the time it takes for the technology to be superseded by competitors (which may be within or beyond the timeframes used in this thesis).

#### 10.4.2 (v) *The present value of costs and benefits*

NHS-relevant costs and benefits were discounted at the appropriate rate for the calculation of headroom throughout this thesis, in accordance with NICE's stated discount rate (3.5%) (NICE 2008b). However, the objective of the headroom method has been described as estimating the future benefit to be considered within a developer's own CBA. By comparing the NPV of commercial costs and benefits (benefit being the product's value, as estimated by

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<sup>49</sup> In some retrospective case studies the allowable development costs were subjectively explored where a headroom rather than MRP was available.

the headroom method), the potential for profit may be explored from a very early stage. An omission of this framework, as presented in this thesis, is therefore the failure to convert these costs and benefits into their present value (pre-development). This has been explained by noting that the internal rate of return (the discount rate) required to convert the value of costs and benefits to their present value is likely to differ substantially by developer, and even throughout the period of investment (due to varying risks associated with different parts of the development process (Johal, Oliver, & Williams 2008)). It is proposed, therefore, that this should be considered by the developers individually when they come to use the tool. As a result, however, the effect of the cost-benefit timescale has been underestimated in this thesis, and the value of benefits accrued in the future by selling the device (i.e. headroom) would receive relatively less weight than the upfront costs of development, which must be incurred earlier.

#### 10.4.3 Approach to the headroom method's evaluation

##### *10.4.3 (i) Absence of investigator triangulation*

Investigator triangulation is where data is collected and analysed by more than one researcher (Clarke 1999). The pro forma and template of resources aimed to reduce the inherent subjectivity of the headroom method. However, to remove the effect of the researcher from this type of research was impossible, although I have attempted to make this possible effect as transparent as possible. My background in research (and limited exposure to commercial endeavours), and the potential impact of this on results, was explored qualitatively in the analysis of interview data. However, the validity of the retrospective case studies may have been improved if the case studies were repeated by another researcher, in order to better explore the subjectivity of analyses. The same could be said for the interview analysis, which

was also conducted by one researcher only. Time and resource constraints inhibited the duplication of research, which may present a worthwhile future research opportunity.

One retrospective case study did duplicate one of four conducted by McAteer (2011) in her thesis on the use of the headroom method for regenerative medicine therapies. In the current thesis, I aimed to replicate as far as possible the context of the developer at the concept stage, which included the information available in the literature as well as the potential time constraint of an early evaluation, and therefore differed from McAteer's approach. Rather, McAteer (2011) provides three detailed health-economic models of the technology's potential cost-effectiveness, and the health benefit required to achieve a certain level of funding (an estimate of which already existed in the literature). The overall results presented are similar (although McAteer concludes that headroom may be sufficient to warrant the treatment if a long-term perspective is taken, whereas I conclude with the same argument but note that NICE seems unwilling to take such a perspective).

#### *10.4.3 (ii) Lack of data saturation*

Saturation is achieved when the researcher no longer obtains new information or insight by pursuing further examples; the concept is often used in qualitative research to determine the appropriate sample size. In both the case studies and interviews, information was certainly corroborated within the samples and trends in the data were apparent, but each case study or interviewee did seem to convey a fresh perspective and an opportunity for learning about the headroom method's application and potential limitations. Saturation therefore may not have been achieved, and further insight may be gleaned from the perusal of additional examples.

#### *10.4.3 (iii) Imperfect follow-up*

The follow-up of retrospective case studies aimed to determine the actual use of the products and their presence on the market. However, as attempts to contact their developers were unsuccessful, this follow-up was also used to determine whether the headroom analysis would have appeared favourable to the developer, by comparing headroom to published evidence on price and/or costs associated with the device. Whilst the decision implication was often intuitive, there was clearly an element of subjectivity in this follow-up, which also lacked details around the actual costs of development and most notably the predictability of these by developers. Indeed, the interview analysis indicated that cost predictions may be difficult for developers without a strong commercial background. The rapid price erosion of medical devices may imply that follow-up was also subject to error.

The headline predictability of market uptake was judged in relation to a product's availability in the NHS. This was because the headroom analyses were conducted with this market in mind, both in the threshold value of a QALY employed, as well as the perspective on the relevant comparators and service cost implications. However, viewed globally, only 2 of the 20 retrospective case studies appeared not to be available anywhere in the world. This demonstrates that the headroom method should be used to provide an appreciation of the potential reimbursement prospects in the UK market, rather than to make the development decisions per se.

#### *10.4.3 (iv) The headroom method as a prognostic test?*

A validation of assessment methods for new product development in the medical sector has been noted to be largely absent from the literature (Bartelmes et al. 2009). This thesis sought to address this for the headroom method, but does not treat such an assessment as a test of diagnostic validity. The reason for this is largely due to the purpose of the headroom method,

which is not exclusively to provide an accurate prediction of future cost-effectiveness, but rather to identify those products that may not be viable. Whilst various statistics have been presented, most notably in relation to the method's proficiency as a rule-out method, these should be interpreted with caution and therefore have not been presented as the headline result of this evaluation. This is due in part to the multiple other context factors and research questions that transpired to be important for each case study, the imperfect nature of the follow-ups, and perspective of the developer which is likely (and has been shown) to extend beyond the UK border.

As noted in the methodology chapter, McCabe and Dixon (2000) provide a review of and recommendations for testing the validity of cost-effectiveness models, which serve to endorse the decision not to treat the headroom method solely as a prognostic test in this evaluation. The authors acknowledge that whilst the overarching purpose of all economic evaluation models is essentially the same—*'to help the decision-maker reach a better informed and rational decision'* (McCabe & Dixon 2000, p. 508)—the specific way in which a model aims to achieve this differs according to the reason for which it is employed. A framework is provided in the paper for assessing validity, which focuses on four main aspects of a model: structure, inputs, results, and the value of the model to the decision-maker. With respect to the first criterion, a brief critical assessment of each case study's structure (the descriptive validity of the economic evaluation presented) accompanied all case studies. In many cases the evaluations were acknowledged not to reflect the whole clinical story, but it was contended that increasing the complexity of the model would not impact the particular decision implication for that case.

The second assessment of validity is of the model's inputs (internal validity) which relates to the selection of data used to furnish the models (McCabe & Dixon 2000). Nuijten (1998)

provides guidance on this topic, and notes that the modeller should *'be able to evaluate the strengths, weaknesses and possible sources of bias that may be inherent in the data used'* (Nuijten 1998, p. 314). In the headroom analyses presented in this thesis, data selection was often opportunistic (I used what I could find), but the quality of data sources was assessed and their selection was based on this assessment where possible. However, no strict guidelines relating to quality were used, and given the potential for bias discussed, internal validity may pose a genuine problem when the method is employed by innovators. An assessment of the third criterion—comparing the results of the model with the real-life outcome (predictive validity)—was facilitated by the retrospective case studies, the results of which were summarised in section 10.3.1. The fourth and final criterion contests that *'the value of the model to the decision maker goes beyond its ability, or otherwise, to produce accurate predications'*, and underlines the need for models to be assessed according to their being *'appropriate to the decision making context'*, *'understandable'*, and *'believable'* (McCabe & Dixon 2000, p. 510). The evaluative approach taken in this thesis has addressed these important factors.

#### 10.4.4 The indirect nature of evidence

The primary limitation of this study, from which the majority of other limitations discussed derive, is the indirect nature of the evidence used to critically appraise the headroom method. The inherent bias of device developers has already been discussed, which raises the question: would a developer ever formulate an unfavourable headroom assessment, or; would they take heed of an unfavourable headroom result? The motivation of interviewees to engage with the headroom method was explored in chapter 9, and was shown for the innovators to revolve mainly around justifying to buyers or funders the value of their products. This casts doubt over the questions posed above, though may reflect the timing of the interaction (well after

true ‘concept’ stage). For those in consulting roles the headroom method was considered to offer an opportunity to rein in the enthusiasm of innovators. The positive views in this regard of the two consultants that claim to use the method are pertinent, although their insight was perhaps underexploited in the interviews, the format of which were kept relatively homogeneous across the whole sample.

As discussed in chapters 3 and 4, the headroom method relies on a NICE decision-making framework which in reality is rarely applied to devices. Therefore the assumption is that local-level purchasers are rational and also consider cost-effectiveness when making coverage decisions. However, previous discussions within this thesis have revealed that this is not always the case, or that at least the perspective from which a cost-effectiveness judgement is made is not always a system-wide one. Other factors certainly influence whether or not a device is successful once launched, outside of cost-effectiveness alone. The retrospective case studies suggest that this situation is not as discouraging for the headroom method as it may seem, as applying the headroom method using the materials provided seems to pick up on the factors influencing uptake. However, the identification of these factors—like headroom calculations—also requires an element of subjective judgement, and therefore it is unclear whether such assessments would have been made by the developer in the same way. As mentioned previously, it is also difficult to know whether these factors would be explored by developers in any case, or whether their identification was facilitated by the headroom method. Although not possible to test through the retrospective case studies, the headroom analysis for the ulcer protector did identify a major competitor of which the innovators had not been previously aware.

In addition to the question of how effectively the headroom method would be used in practice, perhaps an even more fundamental question is *whether* it would be used in practice.

Whilst all interviewees expressed their intention to take the method forward and use it in the future, the success of this cannot be surmised within this project. The difficulty in engaging with industry for the identification of prospective case studies<sup>50</sup> suggests an innate resistance to alter current practice (or may reflect an instinctive secretiveness). Any future progress in understanding the impact of early economic evaluation must derive from research on its use by the stakeholders themselves.

The most important future research questions motivated by the discussion of limitations in this section are summarised below.

#### 10.4.5 Summary of future research questions

The limitations highlighted above in relation to the headroom method's application within this thesis have intimated a number of possible development opportunities and avenues for further research around the headroom method. The incorporation of uncertainty into pre-market value considerations by companies continues to be on the MATCH research agenda (Girling, Chapman, Lilford, & Young 2012;Girling, Lilford, & Young 2011;Girling, Young, Brown, & Lilford 2010). In terms of the very early stage setting considered in this thesis, deterministic sensitivity analysis was often used where input parameters were very uncertain. These sensitivity analyses were exploratory, but a worthwhile avenue of future research may be to investigate the marginal benefit of additional modelling. For example, in many case studies the totality of the clinical story was acknowledged not to be fully represented, but it was contended that further modelling would not alter the implied development decision (and thus

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<sup>50</sup> In the earlier phases of the project, many (unsuccessful) attempts were made to engage with industry and thereby to foster collaborations which could serve as prospective case studies for the thesis. These included: presenting the method and proposing collaboration on a MATCH partners day, placing an advert on the Medilink West Midland's website, and attending / presenting at various industry-facing conferences and forums (e.g. Knowledge Transfer Network conference, ABHI events and research galas).



would not be worth pursuing). However, in cases where the decision implication is only marginally favourable or unfavourable, the value of additional modelling may be much higher. This commercial application of value of information analysis has been discussed briefly by Vallejo-Torres et al. (2008), but could be investigated more formally in the context of very early decision-making.

The development cost analysis proposed in this thesis would benefit from further investigation in terms of its value to device developers. In particular, the time frame over which development costs could acceptably be recovered should be explored. Likewise, appropriate discount rates to apply to headroom valuations (which are likely to differ by developer) could be elicited. Another potential research question is whether other decision factors could be integrated into the headroom method, using multi-criteria decision analysis. Given the qualitative research results presented in this thesis, an important research question to be addressed concurrently would be how such an extension to the headroom method might affect its usability or likelihood of uptake.

If the particular mixed-methods evaluative approach described in this thesis were to be taken forward, the design limitations outlined provide a platform for future research recommendations. A particularly useful research question would be: how subjective is the headroom method? Although this was explored qualitatively in the interviews and illustratively in the case studies, inter-researcher reliability of headroom estimates could be investigated by duplicating case studies (investigator triangulation (Clarke 1999)). The same could be said for the thematic analysis undertaken of the interview data. The biggest barrier to providing concrete performance results in this study was the source of retrospective case studies (the NHSC), which provided a close-to-market sample of medical technologies; this biased the study sample toward successful products, and also limited it to bigger-impact

technologies. A less biased sample of retrospective case studies would therefore be beneficial for future research. However, this may be limited by practical constraints, as it would require businesses to be open about medical technologies that have been abandoned somewhere along the development pathway. More promising, therefore, may be a research strategy which employed numerous prospective case studies, which could be followed over a longer timeframe.

A strategy that would mitigate most of the limitations outlined above would be one which investigated the use of the headroom method among device developers themselves. This study has provided an early indication that the headroom method (as applied in this thesis) may be useful for developers; possible barriers to its use as well as further opportunities have also been identified. In order to further the research and test these findings, direct evidence of the headroom method's use among developers will be required.

## **10.5 Implications**

In the methodology chapter, it was briefly mentioned that evaluations could either be formative (if the aim is to support program improvement) or summative (drawing conclusions on a program's effectiveness) (Scriven 1967). The discussion of results has hopefully demonstrated that this evaluation has contributed to the current state of knowledge in both of these capacities. By outlining the formative and summative results of this evaluation, its implications are summarised.

### **10.5.1 Implications for future applications of the headroom method**

A strong motivation for this project was to explore the feasibility of generating very early-stage headroom estimates (in a way which might be replicable by industry). By applying the

method to a wide spectrum of examples, the study offered methodological insights into; (a) how and for what the method worked best, and (b) how its application might be improved. Future applications of the method should be cognizant of these insights.

The results synthesis presented earlier in this chapter described the form in which the headroom method's application appears to be most effective. It also discussed for whom the method might be useful and in what ways, and highlighted its potential uses outside of its original remit (e.g. to consider entry into new markets or to communicate value with stakeholders). The case studies demonstrated various pre-requisites for the successful application of the headroom method. Firstly, there should be a major marketing opportunity among healthcare providers. The technology and its application should be clearly set out, including the relevant patient population. Additionally, the comparator treatment should be clear. That said, the case studies demonstrated that sensitivity analysis can be used to alter assumptions relating to the relevant treatment comparator (e.g. modelling improvements in current clinical practice or anticipating the emergence of competitors), in order to present alternative headroom estimates or a headroom range.

The case studies revealed what medical technology characteristics were conducive to straightforward evaluation using the headroom method. Technologies whose relationship with current practice can be modelled clearly are most easily assessed: this includes replacement technologies, incremental developments, and in some cases new indications (whose comparator is 'nothing'). Difficulties arise where value is dependent on complex changes in clinical pathways. For such products, health economic benefit is contingent not only upon its main value proposition but also on its cost and resource implications, which may be seen across different parts of the health service and to disparate effect. It is for this reason that many of the diagnostic technologies were excluded from the retrospective case

study sample, and why those that were selected rarely produced an MRP. The E-medICS case study provides a good example of a complex (service delivery) intervention, for which no headroom was delivered. The near-patient COPD monitor also represents a complex intervention, whose potential impact was greatly simplified and whose wider healthcare resource implications may not have been considered sufficiently. For such scenarios, there should in the future be a stronger role for sensitivity analysis.

Around half of the retrospective case studies considered products which would not be used on a per patient basis, and therefore whose value was dependent patient through-put considerations. These implementation/distribution issues were difficult to interpret in the context of the retrospective case studies, and as a result values were not always expressed as MRPs. In future applications of the method, where the developer is engaged with the headroom evaluation, these issues should be explored and incorporated into headroom estimates. Implementation considerations also affect the developer's own cost benefit analysis; where the magnitude of allowable development costs was assessed in this study, uptake was usually considered to be 100%. This should be revised downwards in the future, and should incorporate the developer's expectations of realistic market penetration. Additionally, the developer's internal rate of return should be used to calculate the net present value of the proposed product development project.

The headroom method has been shown to be a flexible tool, for example allowing partial headroom estimates to support investment decisions where these partial valuations are deemed sufficient to cover costs. The method's flexibility may also be important in the context of a changing procurement landscape. In particular, the cost-saving criterion of the medical technology guidance stream within NICE may in the future be incorporated into headroom estimations. In such a setting, headroom valuations would derive exclusively from

expectations of cost impact, whilst investigating the feasibility of at least equivalent health benefit.

### 10.5.2 Wider effectiveness implications

*‘...the more complex reality is, the more dangerous it is to rely on intuitive short-cuts rather than careful analysis.’*

(Williams 2004, p. 14)

The above quotation summarises the danger of relying blindly on the results of a headroom assessment. The method (in its early use at least) proposes to usefully guide resources away from un-lucrative ventures, and so it is in the interest of the user to be realistic. The headroom method has been found to be most effective when a wider perspective is taken, and the materials generated provide the resource for this. By combining headroom estimates with the consideration of important contextual factors identified, the headroom method has been shown—even within this early framework—to helpfully assess reimbursement potential. This should be considered alongside other strategic factors by device developers. Accordingly, just as economic evaluation is employed by decision-makers at the demand-side to help clarify the resource allocation decision rather than to make the decision on its own, the headroom method and the CBA that it facilitates for the developer should be viewed as a useful tool to assist choice rather than to make it:

*‘I take the objective of CBA to be to assist choice (not to make choice, nor to justify past choice, nor yet to delay matters so that some previously chosen course of action has a greater chance of adoption, although I recognise that each of these purposes may also be served by the skilful employment of CBA).*

(Williams 1972, p. 201)

The above quotation also addresses a further role that has been identified for the headroom method through this evaluation, which is to justify a previous development decision or to increase the likelihood of funding or future adoption. Whilst considered by many of the interviewees to represent a valuable function, a word of caution should be issued here. In the

literature review, the development of economic evaluation within the healthcare sector was described, the standards of which were noted to have greatly advanced over time. The use of economic evaluation in the past was more open to subjectivity, and its use as a marketing tool sometimes led to the inappropriate reporting of cost-effectiveness results (Drummond 1991). Whilst this is now better regulated, industry-sponsored cost-effectiveness analyses are still systematically found to report more favourable results than non-industry sources (Chauhan, Miners, & Fischer 2007; John-Baptiste & Bell 2010). Thus, the danger is that the headroom method's use is guided entirely by the user's own agenda, which is not the intention of the method. Employed carefully and honestly, however, it has been shown that the headroom method could assist development decisions and ground these in the potential value of the product.

## **10.6 Conclusion**

The importance of health economics in informing coverage decisions is clear, and has prompted the institutionalisation of CBA in many countries. With the strong technology push from industry and the concurrent strain on the healthcare budget, the role of economic evaluation in maximising the efficiency of spending is critical. However, by the time a comprehensive HTA is undertaken it is too late to modify or terminate the development of medical technologies without huge costs to the manufacturer (Bartelmes et al. 2009). In this thesis I have proposed that, in the very early stages of development, developers face a similar optimisation problem which can also be clarified by considering the decision to develop as a CBA. With development opportunities competing for limited resources, this study set out to evaluate the headroom method according to its capacity to usefully assess market potential.

Research relating to methods of early economic evaluation in the literature lacked a critical lens and a pragmatic focus. By considering the value of the headroom method in terms of its commercial implications, and in relation to the context within which the method's value will be realised, this study has provided an important methodological contribution to a relatively narrow literature base. The mixed-methods design of this study was guided by its research questions, such that each part of the evaluation uniquely contributes to the better understanding we now have of early economic evaluation and its use in practice. When considered together, the results provide a platform for recommendations regarding the future use of the headroom method.

One of the main objectives of this study, as described in the introduction to this thesis, was to find out *whether using the headroom method to explore commercial viability is feasible or even desirable for device developers*. The process of innovation and the accordingly short lifespan of a medical device, as described in chapter 3, mean that commercial viability checks (to be undertaken early and rapidly) are surely desirable. Having initially considered small-scale developers to be the most likely to benefit from the headroom method, the user-related research conducted in this thesis demonstrates that the potential user base is wider than initially anticipated. Involvement in the innovation process can take many forms; this research considered just some of these, but showed that the method may support not only the consideration of development value by innovators (whether these be individuals, health service staff, small companies or large companies), but also by those acting in an advisory capacity. Health-economic value considerations were found to be largely absent from the decision-making processes of the developers interviewed, who suggested that integration of such considerations would be desirable: the gap for the method hypothesised in the early parts of this thesis has been confirmed.

The feasibility of the method's utilisation by developers was also investigated through the case studies and interviews. The method's relatively simple nature was considered to be an asset—and indeed, a prerequisite for its adoption by developers. All but one of the case studies were conducted under the premise of 'headroom in a day', and the method was found to be accessible to developers. However, the practicality of its application may vary according to the user, with those from a research background more readily identifying the relevant data in the literature, and those in commerce having a firmer grasp of development and production costs (to which 'headroom' must be compared). In addition, the strong belief of innovators in their innovations could threaten the objectivity of their early headroom assumptions. The thesis has demonstrated the headroom method's application to a wide range of medical devices, addressing a broad set of clinical problems and change propositions for the health service. Some were more easily assessed than others. In particular, those devices that posed a simple change to current practice were more easily evaluated than those whose health or cost impact was less direct (e.g. diagnostic tests).

Another important objective (and the principal novelty) of this research was to *assess the possible implications of basing development decisions on early expectations of reimbursement value*. This was facilitated by the follow-up of retrospective case studies, where headroom was estimated (based on information that would have been available at an early stage of development) and then followed-up to the present day to compare the headroom outcome with subsequent uptake. (Numerical) headroom assessments predicted NHS uptake with a sensitivity of 92%; the negative predictive value of the method (proficiency as a rule-out tool) was 67% and, overall, NHS uptake was correctly predicted in 82% of cases. These statistics should be interpreted with caution given the close-to-market context of the study sample, which limited its exposure to unsuccessful products. The performance results indicate that



numerical headroom assessments should not be used directly to inform a development decision, primarily due to the narrow perspective with which reimbursement is considered (which was limited to the UK market and to the specific clinical application being considered). It has been shown that early estimates of reimbursement value should be considered alongside the numerous (unquantifiable) factors which may affect the magnitude of that value (factors relating to the appropriateness of early assumptions, and potential changes in the clinical and market context). However, the retrospective case studies demonstrated that these factors can often be predicted from an early stage, and that—by considering them *alongside* the monetary value identified—a good assessment of commercial opportunity can be provided.

The evaluation identified a number of further opportunities provided by the headroom method. As well as informing development decisions, its role was expanded to include identifying and comparing the most relevant sub-populations, informing a product's design, planning the focus of future data collection, and considering entry into alternative markets. Additionally, the method was found to offer a platform to communicate or discuss value. Indeed, its use as a tool for consultants was highlighted, and the headroom method's assessment of the near-patient monitor for COPD has helped to secure funding for its development.

In conclusion, this study finds an important role for the early integration of health economics into decision-making by medical device developers. The method worked most effectively when a flexible and inclusive stance was adopted, suggesting that using a 'back of the envelope' calculation in isolation to rule-out development may be suboptimal. However, this research suggests that the headroom method could offer a practical way to improve the efficiency of R&D spending, by grounding development choices around the potential

healthcare value of a product and by throwing into sharp focus the essential research questions that should be addressed through the development process.

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## **APPENDICES**



## Appendix 1: Pro Forma

Title. *Developer*

<b>1. Description</b>	
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<b>2. Comparator</b>	
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<b>3. Market size</b>	<b>Market size per year:</b>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices *</p> <p><i>Describe any potential costs/savings that you haven't quantified. **</i></p>	<p><b>(Total) <math>\Delta</math>SC=</b></p> <p><b>(Av. Per person) <math>\Delta</math>SC=</b></p> <p><b><math>P_1</math>=</b></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified here**.</i></p>	<p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	
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\* To adjust cost estimates identified to their present value (to the time perspective taken for this form), use the HCHS ‘Pay and Prices’ Index (PSSRU 2010).

\*\* These are so you do not forget about elements of the potential costs / savings you have ignored in the calculations and why. If positive, they could either function as additional narrative support for the device, or if the quantified benefits do not present a sufficiently high MRP, these can be quantified later. If they have the potential to have a negative impact on the economic case, you should consider why these have been left out, and whether they might have an important role to play in the adoption case.

These could also include costs/benefits that NICE do not currently consider as part of a healthcare economic evaluation, but which certainly have a societal impact, such as impact of social care services (this may in fact be incorporated into the remit of NICE’s cost analysis perspective in the future). One potential source for this is: ‘Social Care Online’ (Social care institute for excellence 2011).

## Appendix 2: Template and Resource Guide

# THE HEADROOM METHOD

A TEMPLATE AND  
RESOURCE GUIDE

Amanda Chapman

UNIVERSITY OF  
BIRMINGHAM



## THE HEADROOM METHOD

Before following the structure of investigation outlined in figure 1 (to be read alongside the Pro Forma), it is useful to interrogate the literature and identify the potentially relevant resources that could assist you in answering the questions that will follow. Some may be more relevant than others, depending on the information already collected.

When searching the literature use keywords that are relevant to the technology *and* the clinical area.

The sources that may be of most use in addressing the specific stages of investigation are indicated as a guide alongside fig.1, but are not intended to be definitive.

### RESOURCES

- A. **NHS Evidence:** Draws on many relevant resources. Search results can be filtered by type, e.g. HTAs, care pathways, evidence summaries, guidelines etc. <http://www.evidence.nhs.uk/>
- B. **NHS Choices:** Information for patients. <http://www.nhs.uk/Pages/HomePage.aspx>
- C. **NICE Guidance:** Search NICE guidance by topic (will produce the relevant clinical guidelines/ Technology Appraisals, Interventional Procedures etc.). You can often find a lot of information on clinical practice for a particular condition even if the guidance has been produced in relation to another specific drug / device. <http://guidance.nice.org.uk/Topic>
- D. **Department of Health:** A search of the DH website will identify national targets and strategies. <http://www.dh.gov.uk/en/index.htm>
- E. **National service frameworks and strategies:** Presents the national strategies for certain disease areas (albeit a limited range). <http://www.nhs.uk/NHSEngland/NSF/Pages/Nationalserviceframeworks.aspx>
- F. **World Health Organisation:** Search by topic. General information on condition, cause, diagnosis etc. <http://www.who.int/topics/en/>
- G. **NICE Pathways:** Collates all relevant NICE guidance on certain topics, and presents these visually in pathway form. <http://pathways.nice.org.uk/>
- H. **CEA Registry:** This is an important and useful source of cost-effectiveness studies. Note country of origin and quality score. The studies identified here can help to identify relevant costs and quality of life (QoL) weightings. You can also search QoL weights by topic. <https://research.tufts-nemc.org/cear4/default.aspx>

## THE HEADROOM METHOD

- I. **Cochrane Library:** A useful source which collates Cochrane systematic reviews, clinical trials, HTAs and economic evaluations. If you are trying to find patient benefit estimates, look under the “measure of benefit” subheading on the summary to determine whether it will be relevant. <http://www.thecochranelibrary.com/view/0/index.html>
- J. **PubMed / MEDLINE:** PubMed provides access to the MEDLINE database for clinical studies, economic evaluations, policy issues etc. If you have access to this resource, it is a good place to locate and download studies that have been identified elsewhere. <http://www.ncbi.nlm.nih.gov/pubmed/>
- K. **CRD database:** Centre for Reviews and Dissemination. This includes a central search point for reports from NHS EED (NHS Economic Evaluation Database) and DARE (Database of Abstracts of Reviews of Effects). <http://www.york.ac.uk/inst/crd/>
- L. **NHS Reference Costs:** NHS reference costs is a very large database with key cost schedules for NHS trusts and PCTs. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_123459](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459)
- M. **Euroscan:** Perform a technology search to identify new innovations in the clinical area. <http://www.euroscan.org.uk/outputs/>
- N. **NHSC:** Search technology briefings by speciality or technology type to identify innovations in the area since 2006 (or search the archive for 2000 – 2005) that the organisation have identified as having the potential to make an important impact on patients or health services. <http://www.nhsc-healthhorizons.org.uk/outputs/>
- O. **Google and Google Scholar Search:** Useful for general information searches
- P. **NIHR HTAs:** The NIHR Health Technology Assessment Programme provides a journal series of comprehensive HTAs that have been conducted from an NHS perspective. <http://www.hta.ac.uk/research/HTAJournal.shtml>
- Q. **HES online:** The hospital episode statistics database provides some useful information about the current number of patient episodes, particular procedures, outpatient visits, etc. <http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=889>
- R. **PSSRU Unit Costs of health and social care.** The Personal Social Services Research Unit (PSSRU) provide statistics each year on unit costs for health and social care. This resource is particularly useful for staff costs and specific service costs. <http://www.pssru.ac.uk/uc/uc2011contents.htm>
- S. **Social care online.** This site provides information that could go into the presentation of *additional* benefits of a particular device, that the economic evaluation does not capture. <http://www.scie-socialcareonline.org.uk/default.asp>

## THE HEADROOM METHOD



## 'Finding the numbers' : Extra resources



Market size

The possible sources of data available for identifying the relevant market size are multiple.

Where appropriate, one potentially useful source of data for potential market size is *hospital episode statistics* (HES):

### Market size data

- HES Online

For inpatient data according to Healthcare Resource Group (HRG) code:

<http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=206>

(note: HRG codes are related to the way in which hospitals are paid for the treatment of patients. Treatments are assigned a **Healthcare Resource Group (HRG)**. HRGs are groups of clinically similar activities which consume a similar amount of resources. For costs related to HRG code, see NHS reference cost data below.)

To explore all the available data:

<http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=889>

Particularly useful are 'Main procedures and interventions', and 'Primary diagnosis'.

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The following offers a list of some more specific resources to identify specific healthcare costs, where these are not identified from other studies.

## Cost data

### • Payment by results

The way in which NHS healthcare providers are paid is by a system of 'payment by results' (PbR).

For a simple overview of payment by results, see:

[http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What\\_is\\_pay\\_by\\_res.pdf](http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/What_is_pay_by_res.pdf)

This is a more detailed explanation of the system provided by the DH:

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_128864.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_128864.pdf)

HRGs are the basis of the NHS PbR system, and costs are often reported in relation to these codes (such as NHS reference costs, see below).

### • NHS REFERENCE COSTS

Although the database of NHS reference costs (which is published on a yearly basis) is very large, it offers a wealth of information on NHS costs, if you know exactly what you are looking for:

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_123459](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459)

### •The cost of a hospital bed day

The cost of an 'excess bed day' can give an indication of the cost of a patient day in hospital, according to what the patient is in hospital for. This can be useful in cases where the new device will affect a patient's length of stay in hospital.

These are offered in precise detail in the NHS reference cost database, but the following table provides a summary of these costs according to general speciality.

**Table 1: National average cost per (excess) bed day**

Specialty Code	Specialty	Elective		Emergency	
		Adult	Child	Adult	Child
100	General Surgery	£268	£425	£243	£348
101	Urology	£236	£391	£215	£355
102	Transplantation Surgery	£335	£610	£533	
103	Breast Surgery	£229		£239	
104	Colorectal Surgery	£155		£145	
105	Hepatobiliary Surgery	£181		£139	
106	Upper GI Surgery	£136		£156	
107	Vascular Surgery	£216		£187	
110	Orthopaedics	£282	£614	£241	£406
120	ENT	£268	£361	£275	£368
130	Ophthalmology	£359	£374	£320	£370
140	Oral Surgery	£226		£310	
141	Restorative Dentistry	£158	£347	£101	£198
144	Maxillo-facial Surgery	£284	£1,932	£329	£273
150	Neurosurgery	£197	£517	£193	£365
160	Plastic Surgery	£216	£527	£257	£338
161	Burns Care			£233	£487
170	Cardiothoracic Surgery	£331		£334	
172	Cardiac Surgery	£278	£553	£309	£615
173	Thoracic Surgery	£235		£240	
174	Cardiothoracic Transplant	£486		£476	
180	A&E	£228		£235	
190	Anaesthetics	£136		£136	
191	Pain Management	£255	£205	£175	
300	General Medicine	£200		£175	
301	Gastroenterology	£215	£514	£189	£382
302	Endocrinology	£202	£674	£221	£564
303	Haematology	£244	£521	£239	£503
306	Hepatology	£402		£311	
307	Diabetic Medicine	£148		£159	
308	Blood & Marrow Transplant	£530		£906	
309	Haemophilia	£1,094		£154	
315	Palliative Medicine	£285		£300	
316	Clinical Immunology	£678	£865		£992
319	Respite Care	£327		£137	
320	Cardiology	£335	£489	£225	£530
323	Spinal Injury	£322		£387	
330	Dermatology	£135	£790	£254	£587
340	Respiratory Medicine	£341	£598	£208	£647
341	Respiratory Physiology	£329		£234	
350	Infectious Diseases	£222	£282	£219	£1,773
360	GU Medicine	£282		£269	
361	Nephrology	£153	£417	£171	£419
370	Medical Oncology	£243	£510	£219	£396
400	Neurology	£274	£603	£229	£523
410	Rheumatology	£217	£429	£222	£308
420	Paediatrics		£353		£290
422	Neonatology		£320		
430	Elderly Medicine	£181		£179	
460	Medical Ophthalmology	£101		£133	
501	Obstetrics	£335		£372	
502	Gynaecology	£295		£349	
503	Gynaecological Oncology	£241		£239	
560	Midwife	£171		£340	
822	Chemical Pathology	£311			
999	Joint Consultant	£308		£274	
254	Audiology		£2,326		
290	Community Paediatrics				£457
261	Metabolic Diseases		£3,270		£1,438

This table, presented by Jones (2008), gives the average cost of excess bed days by speciality (the cost of a stay in hospital beyond the expected maximum length of stay for a particular HRG). Beyond the specified stay within a speciality code, these are paid on a per day basis according to these tariffs. These can act as a good estimate that can be used to calculate the effect of increased/reduced hospital stay resulting from the application of a new technology.

## Manipulating the cost data

### •Exchange rates

Where the costs identified are reported in a different currency, HM Revenue & Customs provide the appropriate exchange rates:

<https://www.uktradeinfo.com/TradeTools/Pages/ExchangeRates.aspx>

### •Inflation index

To adjust cost estimates found in the literature to their present value, use the HCHS (Hospital & Community Health Services) 'Pay and Prices' Index:

Year	Hospital & Community Health Services (HCHS)		
	Pay and Prices Index (1987/8=100)	Annual percentage increases	
		Pay and Prices	Pay <sup>3</sup>
1995/96	166.0	4.0	4.4
1996/97	170.6	2.8	3.3
1997/98	173.5	1.7	2.5
1998/99	180.4	4.0	4.9
1999/00	188.5	4.5	6.9
2000/01	196.4	4.2	7.2
2001/02	206.4	5.1	8.3
2002/03	213.8	3.6	5.0
2003/04	225.6	5.5	7.3
2004/05(E)	234.2	3.8	5.3

Source: Personal Social Services Research Unit (PSSRU), Unit Costs of Health and Social Care 2005

Year	Hospital & Community Health Services (HCHS)		
	Pay & Prices Index (1987/8=100)	Annual percentage increases	
		Prices <sup>3</sup>	Pay <sup>3</sup>
2000/01	196.5	-0.3	7.2
2001/02	206.5	0.1	8.3
2002/03	213.7	0.9	5.0
2003/04	224.8	1.5	7.3
2004/05	232.3	1.0	4.5
2005/06	240.9	1.9	4.7
2006/07	249.8	3.0	4.1
2007/08	257.0	1.8	3.5
2008/09	267.0	5.2	3.0
2009/10	271.5 (E)	1.3	3.5 (E)

Source: Personal Social Services Research Unit (PSSRU), Unit Costs of Health and Social Care 2010

$\text{P\&P Index (present year)} \div \text{P\&P Index (year of cost data)} = \text{Inflation rate}$

$\text{£(cost found)} \times \text{Inflation rate} = \text{Present (£) value}$



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Quantifying the benefit to patients of a particular treatment or change in their management pathway can be challenging. The following provides various approaches and sources of information that can help estimate patient health impact, and translate this into a quality of life (QoL) estimate.

### Where the device saves lives...

#### •Life expectancy

If the proposed new technology can expect to reduce mortality (save lives), then in order to value this effect you need to know the life expectancy of that life saved. The office of national statistics (ONS) provides data on the average period expectation of life at any given age:

<http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Interim+Life+Tables>

Under the 'Data' section, click on the appropriate link to access Interim Life tables. The link called 'United Kingdom, Interim Life Tables, 1980-82 to 2008-10' (which was updated on 29/9/11), uploads an excel spreadsheet with the estimated life expectancy at various ages (the 2008-10 tab provides the most up-to-date estimates)

The column labelled  $e_x$  provides the relevant life expectancy statistics, representing the "average period expectation of life at exact age x, that is the average number of years those aged x will live thereafter".

**•Quality of Life weightings for the general population**

If the new technology is expected to save lives and to return a person’s QoL (on a scale of 0 to 1) to match that of the general population, then it is important to weight those life years gained according to QoL experienced, in order to estimate a QALY impact. Kind et al. (1999) conducted a large survey of the UK general population, and provide estimates of the average QoL (using the EQ-5D index) for the general public, according to age (and many other parameters including sex, smoking status, marital status, region, social class, etc).

This report can be found here:-

<http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf>

The following table provides the summary figures of weighted health-state index according to age and sex:

**Weighted Health State Index by Age and Sex**

		Sex		
		All	Males	Females
All	Mean	0.86	0.86	0.85
	Count	3392	1467	1925
	Std Deviation	0.23	0.24	0.22
Age Under 25	Mean	0.94	0.94	0.94
	Count	304	128	176
	Std Deviation	0.12	0.12	0.12
25-34	Mean	0.93	0.93	0.93
	Count	753	330	423
	Std Deviation	0.15	0.16	0.15
35-44	Mean	0.91	0.91	0.91
	Count	561	256	305
	Std Deviation	0.16	0.17	0.15
45-54	Mean	0.85	0.84	0.85
	Count	488	221	267
	Std Deviation	0.25	0.27	0.23
55-64	Mean	0.80	0.78	0.81
	Count	484	196	288
	Std Deviation	0.26	0.28	0.26
65-74	Mean	0.78	0.78	0.78
	Count	488	228	260
	Std Deviation	0.26	0.28	0.25
75+	Mean	0.73	0.75	0.71
	Count	314	108	206
	Std Deviation	0.27	0.28	0.27

MVH National Survey Data 1993  
 Centre for Health Economics  
 University of York

## Where the device affects the quality of life experienced by the patient...

Presented in order of ease and reliability, the following are possible approaches to estimating the impact that a device might have on the QoL of a patient:

- 1) QoL estimates in the literature
- 2) Calculating the value by manipulating the appropriate health states in the EQ-5D questionnaire
- 3) Utility ladder

- **1) QoL estimates in the literature**

The quantification of QoL is complex, and there are many methods that exist that try to do this. For the purposes of a general QoL measurement that can be used across all states of health, NICE consider the elicitation of QoL to be most appropriately estimated by using the EuroQol EQ-5D questionnaire, and the time trade-off method to translate this into a universal QoL measure. This QoL weighting (which will lie between 1 [perfect health] and 0 [death]) is used to calculate QALY impact by multiplying this by the time (in years) for which this impact is sustained.

The simplest way to estimate QoL is to use data provided by other studies (preferably using the EQ-5D, but other methods are sometimes appropriate as well).

- **2) Manipulating the five health dimensions of the EQ-5D questionnaire**

When estimates in the literature do not exist, and the developer has a clear idea of the potential areas of benefit of the product, then it may be appropriate to consider the EQ-5D questionnaire directly. A large UK study conducted by Williams (1995) used people's valuations of various health states according to the five health dimensions of the EQ-5D questionnaire, in order to assign a value to each possible combination of levels (mild, moderate or severe) within each of these five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Dolan (1997) modelled these results and found that the best way to model changes in health state and actual QoL perceived, was to assign a value to each step-change in parameter. We can use these results to estimate the change in QoL of a patient, if it is clear in our minds exactly how the device is likely to affect a person's QoL in relation to one or more of the following parameters:

---

**ANNEXE E THE EUROQOL CLASSIFICATION SYSTEM**

**Mobility**

1. No problems walking about
2. Some problems walking about
3. Confined to bed

**Self-Care**

1. No problems with self-care
2. Some problems washing or dressing self
3. Unable to wash or dress self

**Usual Activities**

1. No problems with performing usual activities (e.g. work, study, housework, family or leisure activities)
2. Some problems with performing usual activities
3. Unable to perform usual activities

**Pain/Discomfort**

1. No pain or discomfort
2. Moderate pain or discomfort
3. Extreme pain or discomfort

**Anxiety/Depression**

1. Not anxious or depressed
2. Moderately anxious or depressed
3. Extremely anxious or depressed

Source: Williams (1995) A measurement and validation of health: a chronicle (Discussion paper 136)

'Full' health, represented by a QALY weighting of 1, is represented by level 1 of all these five parameters.

The combination 11221 represents: 'Some problems performing usual activities', 'moderate pain or discomfort', and no problems with any other health parameter. The aforementioned study mapped each combination of these three levels of five health states, in order to present a QoL value for each combination. The results of this are presented below.

**Means based on time-trade-off valuations**

Dimension	Coefficient
Constant	0.081
Mobility	
level 2	0.069
level 3	0.314
Self-care	
level 2	0.104
level 3	0.214
Usual activity	
level 2	0.036
level 3	0.094
Pain/discomfort	
level 2	0.123
level 3	0.386
Anxiety/depression	
level 2	0.071
level 3	0.236
N3	0.269

Source: Williams (1995) A measurement and validation of health: a chronicle (Discussion paper 136)

Note: Unconscious = -0.402

This table presents the value of all possible deviants from 'full health' (which has a value of 1). The 'constant' 0.081 should be subtracted from any deviation from full health, and N3 (0.269) should be subtracted from the overall value whenever one or more health states are in level 3. For example:

$$11221: 1-0.081-0.036-0.123 = 0.76.$$

$$13312: 1-0.081-0.269-0.214-0.094-0.071 = 0.271$$

These can be used to value the effect of a change in a particular health parameter. If, for example, a new device could plausibly reduce pain/discomfort from level 2 (some pain/discomfort) to level 1 (no pain/discomfort) then this should be valued at 0.123, and should be multiplied by the time (in years) for which this change is sustained.

This should not act as a substitute for a later-stage QoL investigation when the product has been developed. However, it can at an early stage offer some insight into the *potential* value of particular changes to QoL, in cases where this is intuitive.



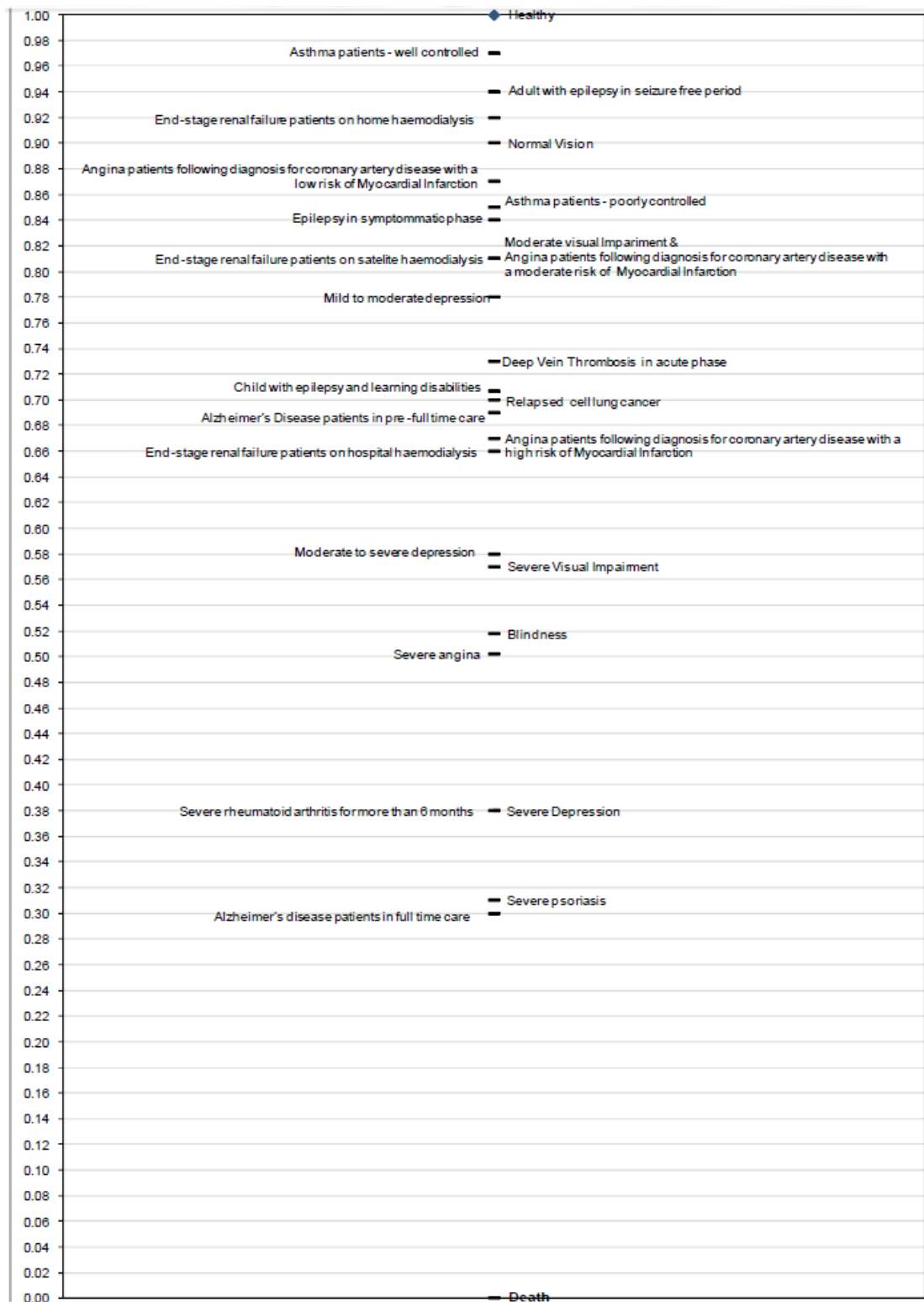
• **3) Utility ladder**

Alternatively, QoL may be estimated by relating the health state in question to others. For example, if it is considered that the QoL associated with the clinical problem of interest might be similar to another, for which a QoL estimate does exist, this could be used as a proxy. McAteer (2011) presents a ladder of various health-related QoL values, so that the clinical area in question may be related to others, and be conceptually placed along this scale.

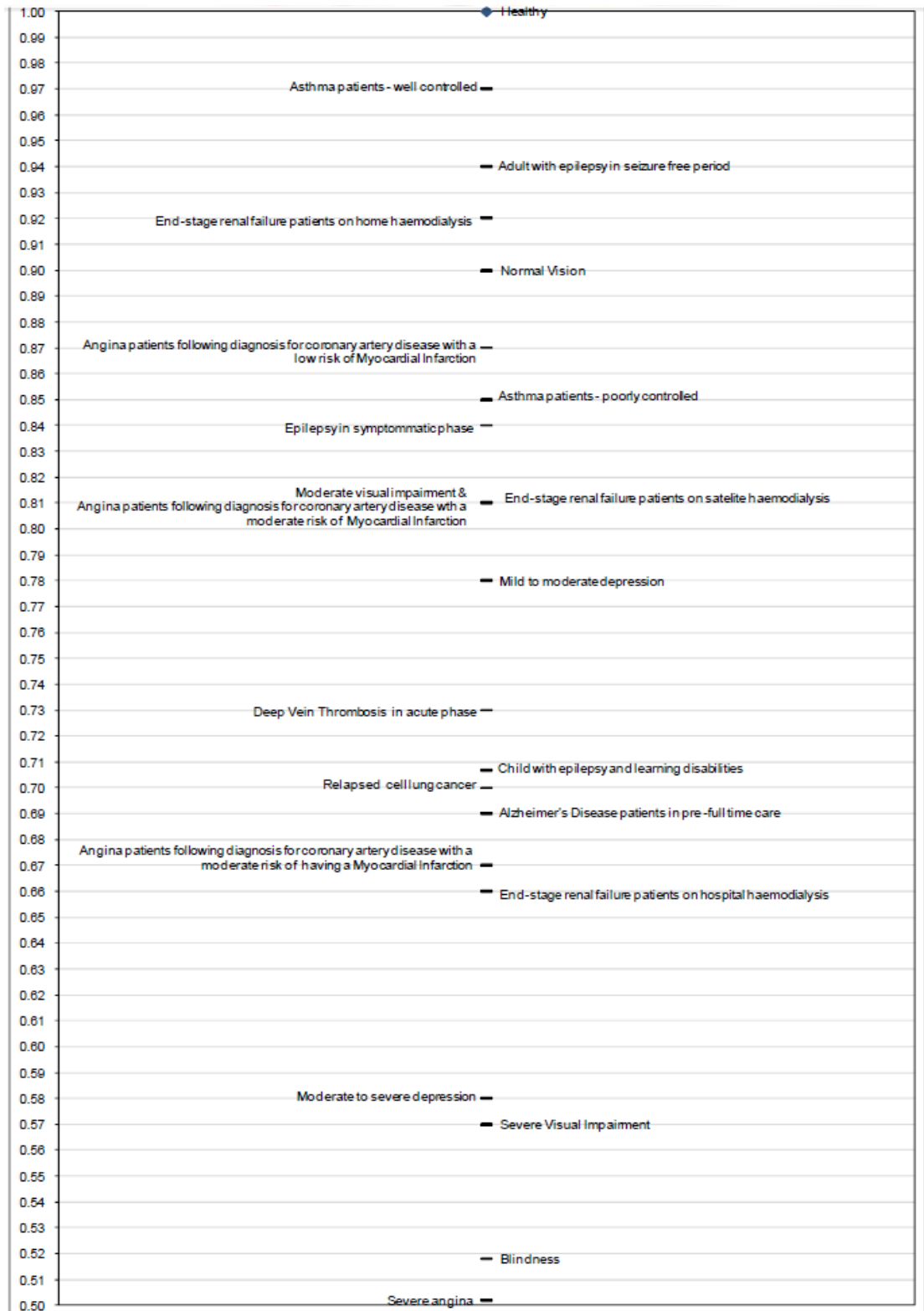
These 'utility ladders' are presented over the next two pages, the first offering a hierarchy of QoL values (all derived from NICE technology appraisals) from 0 to 1, and the next focusing on a spectrum of QoL values from 0.5 to 1.

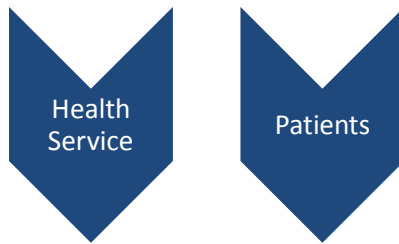
These are taken directly from McAteer's work: McAteer, H. 2011, *The use of health economics in the early evaluation of regenerative medicine therapies*. Ph.D. thesis, University of Birmingham.

# Template and Resource Guide



# Template and Resource Guide





### Discounting for costs and health benefits accrued in the future

In order to reflect the time value of money and health benefit, any impact on costs or health benefit that is accrued in the future must be discounted, at a rate of 3.5% for both costs and QALYS, as per the NICE reference case. This is done in the following way:

If we want to determine the present value of eleven additional life years in a health state of 0.8, the following formula is used:

$$\Delta QALY = 0.8 + \frac{0.8}{1.035} + \frac{0.8}{(1.035)^2} + \frac{0.8}{(1.035)^3} + \frac{0.8}{(1.035)^4} + \frac{0.8}{(1.035)^5} + \frac{0.8}{(1.035)^6} + \frac{0.8}{(1.035)^7} + \frac{0.8}{(1.035)^8} + \frac{0.8}{(1.035)^9} + \frac{0.8}{(1.035)^{10}}$$

$$= 7.46 \text{ QALYs}$$

The same approach is used for costs.

### Appendix 3: Utility weights for COPD

Definition of disease severities: Mild, Moderate and Severe COPD in line with NICE clinical guidance:

Mild: FEV<sub>1</sub> percent predicted ≥80%

Moderate: 50% < FEV<sub>1</sub> percent predicted < 80%

Severe: 30% < FEV<sub>1</sub> percent predicted < 50%

V.Severe: FEV<sub>1</sub> percent predicted < 30%

Year	Journal	Title	Primary Author	COPD- related UTILITY					Source of utility measure
				Mild	Mod	Sev	V. Sev	Exacerbations	
2009	The American Journal of Managed Care	Cost-effectiveness of salmeterol, fluticasone, and combination therapy for COPD (Q.S.: 5)*	Oba (2009)	0.569-0.591. Not split into mild, moderate or severe states.					Utility values were estimated by converting SGRQ (St George’s Respiratory Questionnaire) scores into EQ5D scores.
2009	Respiratory Medicine	Cost-effectiveness of fluticasone propionate/salmeterol (500/50 microg) in the treatment of COPD (Q.S.: 5)	Earnshaw (2009)	0.897	0.755	0.748	0.549	Moderate: 15% ↓ in utility, Severe: 50% ↓ in utility	QALY weights for each disease severity are based on a study by Borg et al. (2004), whose source was a cost of illness study in northern Sweden which used an EQ5D questionnaire. QALY weights were estimated according to UK EQ5D index tariff. Exacerbation implications on utility from Oostenbrink et al. (2005) – who themselves get these from Paterson et al. (2000) and Spencer & Jones (2003).
2008	Thorax	Cost effectiveness of therapy with combinations of long acting bronchodilators and inhaled steroids for treatment of COPD.	Najafzadeh (2008)	Not made explicit.				Moderate: 15% ↓ in utility, Severe: 50% ↓ in utility	Utilities were calculated from the SGRQ scores. Exacerbation implications on utility from Paterson et al. (2000) and Spencer & Jones (2003).

Utility weights for COPD

		(Q.S.: 5)						
2008	Tobacco Control	Cost-effectiveness of the Australian National Tobacco Campaign. (Q.S.: 3.5)	Hurley					Unable to access
2008	Canadian Respiratory Journal	Cost-effectiveness of combination therapy for chronic obstructive pulmonary disease.	Chuck					Unable to access
2008	Current Medical Research and Opinion	Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. (Q.S.: 4.5)	Hoogendoorn					Unable access
2008	Pharmacoecomics	Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. (Q.S.: 4)	Howard et al. (2008)	0.76 - not split into disease severity				Estimated using "various data sources"
2007	European Journal of Health Economics	Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the	Rutten-van Mólken et al. (2007)	-	0.809	0.762	0.655	Utilities based on EQ-5D scores at baseline in a subset of patients randomly accepted in to the UPLIFT trial. Scores valued using the <i>SPANISH tariff</i> (which differ to UK preferences, see Badia et al. (2001)).

Utility weights for COPD

		treatment of chronic obstructive pulmonary disease in Spain. (Q.S.: 5.5)							
2006	Current Medical Research and Opinion	Economic evaluation of tiotropium and salmeterol in the treatment of chronic obstructive pulmonary disease (COPD) in Greece. (Q.S.: 5.5)	Maniadakis						<i>Unable to access</i>
2006	Value in Health	Estimating the cost-effectiveness of fluticasone propionate for treating chronic obstructive pulmonary disease in the presence of missing data. (Q.S.: 5)	Briggs et al. (2006)	Not detailed					SF-36 instrument used and converted to health utility scores.
2005	The European Respiratory Journal	A dynamic population model of disease progression in COPD. (Q.S.: 2)	Hoogendoorn (2005)	0.897	0.755	0.748	0.549		Utility weightings retrieved from Borg et al. (2004).
2005	Value in Health	Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries.	Oostenbrink et al. (2005)	0.897	0.755	0.748	0.549	Moderate: 15% ↓ in utility, Severe: 50% ↓ in utility	QALY weights at each disease severity based on study by Borg et al. (2004). Exacerbation implications on utility from Paterson et al (2000) and Spencer & Jones (2003).

Utility weights for COPD

		(Q.S.: 5)																																									
2005	Pharmacoecomics	Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease.  (Q.S.: 6)	Spencer et al. (2005)	<p><b>Table II.</b> Utility weights by disease stage at baseline<sup>19</sup> and during exacerbations<sup>20,21</sup> for chronic obstructive pulmonary disease</p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="3">Utility weights by disease stage</th> </tr> <tr> <th>mild</th> <th>moderate</th> <th>severe</th> </tr> </thead> <tbody> <tr> <td colspan="4"><b>Mean EQ-5D tariff scores (SE)</b></td> </tr> <tr> <td>Baseline</td> <td>0.81 (0.02)</td> <td>0.72 (0.03)</td> <td>0.67 (0.05)</td> </tr> <tr> <td>Low point for minor exacerbation</td> <td>0.61 (0.02)</td> <td>0.61 (0.02)</td> <td>0.05 (0.05)</td> </tr> <tr> <td>Low point for major exacerbation</td> <td>-0.26 (0.07)</td> <td>-0.26 (0.07)</td> <td>-0.26 (0.07)</td> </tr> <tr> <td colspan="4"><b>Mean modelled utility (SE)</b></td> </tr> <tr> <td>Minor exacerbation<sup>a</sup></td> <td>0.72 (0.02)</td> <td>0.658 (0.03)</td> <td>0.475 (0.05)</td> </tr> <tr> <td>Major exacerbation<sup>a</sup></td> <td>0.519 (0.02)</td> <td>0.447 (0.07)</td> <td>0.408 (0.05)</td> </tr> </tbody> </table> <p><sup>a</sup> Mean value during a 3-month period with an exacerbation. EQ-5D = EuroQOL questionnaire; SE = standard error.</p>				Parameter	Utility weights by disease stage			mild	moderate	severe	<b>Mean EQ-5D tariff scores (SE)</b>				Baseline	0.81 (0.02)	0.72 (0.03)	0.67 (0.05)	Low point for minor exacerbation	0.61 (0.02)	0.61 (0.02)	0.05 (0.05)	Low point for major exacerbation	-0.26 (0.07)	-0.26 (0.07)	-0.26 (0.07)	<b>Mean modelled utility (SE)</b>				Minor exacerbation <sup>a</sup>	0.72 (0.02)	0.658 (0.03)	0.475 (0.05)	Major exacerbation <sup>a</sup>	0.519 (0.02)	0.447 (0.07)	0.408 (0.05)	Mild, Moderate and Severe COPD states based on a different definition, following that described by the American Thoracic Society: Mild: FEV <sub>1</sub> ≥ 50% Moderate: FEV <sub>1</sub> 35-49% Severe: FEV <sub>1</sub> < 35%
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2004	The American Journal of Medicine	Cost-effectiveness of inhaled corticosteroids for chronic obstructive pulmonary disease according to disease severity. (Q.S.: 3)	Sin et al. (2004)	-	1 QALY	0.92 QALYs	0.84 QALYs	↓ of 0.32 QALYs for each episode (mild: 1 week, mod: 2 weeks, sev: 4 weeks)	Definition of mild, moderate and severe as above, using the American Thoracic Society levels.																																		
2004	Value in Health	A computer simulation model of the natural history and economic impact of chronic obstructive pulmonary disease. (Q.S.: 3)	Borg et al. (2004)	0.897	0.755	0.748	0.549	Mild: 5% ↓ in utility, Moderate: 15% ↓ in utility, Severe: 70% ↓ in utility	Source: a cost of illness study in northern Sweden which used an EQ5D questionnaire. QALY weights estimated according to UK EQ5D index tariff. Exacerbation implications on utility: 'Mild and Moderate' based on assumption by "expert panel": J. Wedzicha, A. Gulsvik, and S.D. Sullivan. Severe exacerbation figure derived from asthma data. Definitions of Mild, mod and severe exacerbations: Mild- if the patient can manage in his or her																																		



Utility weights for COPD

									normal environment. Could include phone calls to a doctor that might be followed by a course of antibiotics or oral steroids; Moderate- if the patient must make an unscheduled visit to the doctor; Severe- if the patient requires hospitalization or emergency room visit.
2004	American Journal of transplantation	Cost-effectiveness of lung transplantation in relation to type of end-stage pulmonary disease. (Q.S.: 5.5)	Groen et al. (2004)						Utility scores were collected using the EuroQol questionnaire, but scores were not assigned to each of the different diseases individually, but collected over the whole group, 'averaged', and categorised in relation to pre/post lung transplant.
1999	Intensive Care Medicine	Mechanical ventilation of patients on long-term oxygen therapy with acute exacerbations of chronic obstructive pulmonary disease: prognosis and cost-utility analysis. (Q.S.: 2)	Añón et al. (1999)						Rosser Index score used as an estimate of quality of life. Specific values adopted are not detailed in the paper.
1994	Respiratory Care	Pulmonary artery catheterization in exacerbations of COPD requiring mechanical ventilation: a cost-effectiveness analysis. (Q.S.: 4.5)	Smith						<i>Unable to access</i>

\*Q.S. = Quality Score, as rated by Tuft's CEA registry, on a scale from 1 (low) to 7 (high)

























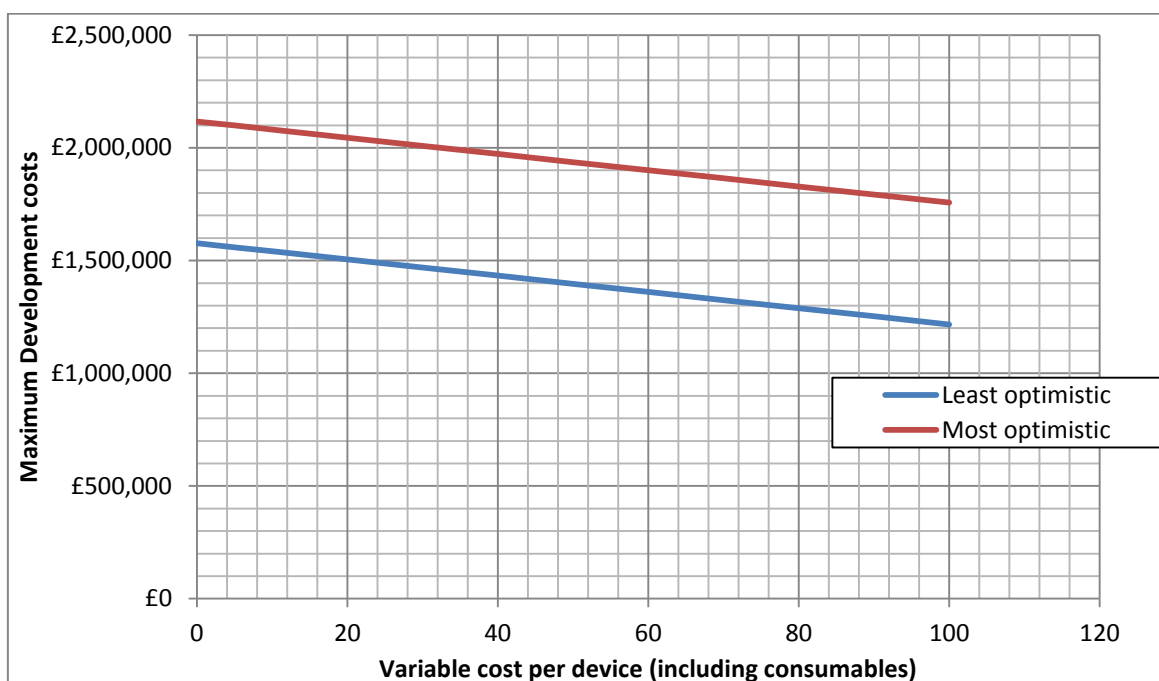




## Retrospective case studies: 1. FibroTest-ActiTest

The headroom for the FibroTest-ActiTest ranges from £438 (when the disutility of liver biopsy is ignored) to £588 (saved disutility included, WTP: £30,000). The calculation presents a 'headroom' per test rather than an MRP per se, as this will need to include the cost of service provision (staff time, laboratory costs, etc). Ideally these costs would have been included in the service cost implications, but there was insufficient information on which to base these estimates. As only a blood test is required, service costs should be minimal.

Some development cost decision analysis was performed, to show the trade-off between various variable costs in relation to maximum development costs, for the most and least optimistic scenarios.



This may be slightly deceiving as the figures calculated corresponded to a 'headroom' rather than an MRP. However, if the likely service costs are included in the variable costs given, then the maximum development costs can be estimated. For example, a variable cost per test of £40 would equate to a maximum development cost of £1.4 million (least optimistic) up to nearly £2 million (most optimistic) (assuming no profit). Clearly, given the nature of this in vitro diagnostic (a blood test whose results are input into a programmed formula), whose variable costs are bound to be small and whose development costs are not likely to be large, the headroom estimate seems very generous.

## Follow-up (FibroTest)

### Headroom Outcome and Market success

#### Does the MRP look realistic? Would it have indicated yes or no to development?

Headroom: £538 (assuming a WTP of £20,000) or £588 (assuming WTP of £30,000) (£438 if we ignore the utility impact associated with not undergoing a liver biopsy). This should be interpreted as a 'unit cost' to the NHS for the test.

Although not verifiable without discussion with the developers of the FibroTest-ActiTest, this seems to be a large value per unit. Presuming a variable cost per test of under £120 per unit, the allowable development costs reach over £1.5 million. Given that the FibroTest-ActiTest is a patented algorithm rather than a piece of kit, these estimates look generous.

The NHSC briefing includes an estimated unit cost (to the NHS) for the FibroTest-ActiTest, which is **£70**. This figure was estimated by the company, so it is assumed to include the estimated price of the technology and the time/person investment necessary for using the test. This indicates that the headroom probably would have seemed favourable.

Interpretive answer: **Headroom Favourable**

#### Has there been a decision made on it by NICE? What was the outcome?

No NICE guidance has been issued relating to this technology.

#### Is it sold in the UK or in other countries? (Or has it in the past) If so, who is it bought by?

Once blood samples have been analysed in the lab, the data obtained (relating to the biomarkers) are downloaded by the biologist into the BioPredictive website (with a registered account), which then returns an immediate report of the results. The laboratories that practice the BioPredictive tests for each country are listed on their website; there are three in the UK. BioPredictive is based in Paris, but laboratories that carry out the test exist in 49 countries across Europe, Africa, South America, North America and Asia (BioPredictive 2011).

It is not clear exactly how wide spread the use of the test is, and who the main customer base may be<sup>1</sup>. The test has certainly been (and continues to be) the subject of much research and many validation studies. Although I cannot find evidence of its systematic use within the NHS, there is certainly an indication in the literature that the test has been used within the NHS to non-invasively test for liver fibrosis (Mardini & Record 2005;NHSC 2004).

FibroTest-ActiTest seems particularly well established in France; the French health authority has approved FibroTest, as well as FibroScan (see next section) as "*first-line estimates of fibrosis in patients with chronic hepatitis C, with recommended reimbursement from the government*" (Halfon,

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<sup>1</sup> Contact has been made with the labs to establish the exact cost of the test, and how many they undertake. An enquiry has been sent to BioPredictive relating to the test's use in the UK. Responses were not received.



*Munteanu, & Poynard 2008*). Liver biopsy is indicated as a second-line estimate, in cases where non-invasive markers are non-interpretable.

### **Have there been investigations into its clinical / cost effectiveness?**

There are many studies looking at the diagnostic value of biomarkers in the prediction of liver fibrosis, not only for hepatitis C patients but also for other liver conditions. BioPredictive provide on their website the titles of 126 scientific publications from 2001 to 2010 relating to their diagnostic tests. The names 'FibroTest' or 'Fibrosure' (as marketed in the U.S.) appear in the title of 54 of these papers. Most report favourable results for the FibroTest, and its use as a substitute for liver biopsy.

A meta-analysis which included 30 studies looking at the diagnostic value of FibroTest in chronic liver disease was produced in 2007. It concluded that FibroTest is an effective alternative to biopsy in patients with chronic hepatitis C and B, Alcoholic Liver Disease, and non-alcoholic fatty liver disease (Poynard et al. 2007).

One cost-effectiveness study was identified, which was based in the U.S and assessed the clinical and economic outcomes of non-invasive strategies in the diagnosis of significant liver fibrosis compared with liver biopsy (Carlson et al. 2009). FibroTest was found to be the most accurate non-invasive strategy, with a sensitivity, specificity and overall accuracy of 84%, 87% and 86% respectively. Compared to liver biopsy, the authors report a cost saving of about \$770 per person, but a 14% decrease in accuracy. They conclude that, compared to liver biopsy, FibroTest could offer short term savings, but that the longer term costs of misdiagnosis might outweigh these. (However, the study compares Fibrotest and the other non-invasive techniques directly to liver biopsy, implicitly assuming a 100% diagnostic accuracy for the latter, which clashes with a general consensus in the literature that important shortcomings of biopsy arise from sampling error and inter-observer variability).

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

Although there have been many publications in the past 10 years investigating the use of non-invasive diagnostic techniques for liver fibrosis, the majority still refer to biopsy as the baseline comparator (and no evidence has been identified of a change in this gold standard for the UK). However, the degree to which biopsy is used as a diagnostic technique pre-therapy seems to be reduced. A technology appraisal by NICE for peginterferon alfa and ribavirin (drugs) for the treatment of HCV indicates that liver biopsy is no longer considered necessary before initiating treatment, which is now given at an earlier stage (NICE 2006c). No other forms of diagnostic aid are mentioned in this guidance.

#### **Are there now many direct competitors?**

There are two main approaches that have been developed to replace liver biopsy and its associated difficulties / risks: the 'biological' approach and the 'physical' approach (Castera 2011).

The FibroTest seems to be the dominant test for the biological approach, being the most frequently studied and the best validated, but others include: Fibrometers (BioLiceScale, France), FibroSpectII (Prometheus Laboratory Inc, USA), ELF (iQur Ltd, UK), and Hepascore (PathWest, Australia) (the

NHSC produced a briefing on ELF – Enhanced Liver Fibrosis Test – in 2008). There are also non-patented scores for liver fibrosis such as the Forns index, FIB-4 and APRI which, although having a slightly lower performance, are free and easy to calculate (Castera 2011).

The other ('physical') approach is Transient Elastography, which measures liver stiffness using ultrasound (the NHSC produced a briefing on this device in 2008). The main Transient Elastography device (developed by Echosens (France)) is FibroScan.

Comparisons of the two approaches seem variable; Castera (Castera 2011) and Degos (Degos et al. 2010) present findings that indicate Fibroscan to be the better diagnostic tool whereas Carlson (Carlson et al. 2009) finds FibroTest to be the most accurate test when compared to Fibrospect II (another biomarker approach) and Fibroscan.

### Conclusions: How useful might the headroom exercise have been?

Results from the headroom analysis suggested that the potential value to the NHS of a non-invasive diagnosis tool for liver fibrosis could probably viably support the development of FibroTest-ActiTest for sale in the UK. That the headroom estimated was very large compared to the actual cost of the test to the NHS, and the cost to BioPredictive of producing the results (simply through a computer-generated algorithm) suggests that if our assumptions had been correct, the product should have achieved widespread success in the UK and be used systematically across the NHS, as it would have represented a better use of NHS resources. Of course, reality is never this simple, and questions 6 and 7 of the headroom pro forma aim to help identify the factors that could influence these parameters.

Unfortunately, the lack of NICE guidance or UK based cost-effectiveness study means we cannot compare this vision with a more recent and better informed decision analysis from a UK healthcare reimbursement perspective. It is clear, though, that BioPredictive has a global focus, and the UK is by no means their only or most important market. The company have a much broader perspective than that taken by the headroom analysis, which considers the case for adoption / sale in the UK (specifically, the NHS). However, a positive endorsement from a UK perspective is likely to translate into a promising case in other settings as well.

The following points offer potential explanations to the question of why the FibroTest-ActiTest is not in widespread use across the NHS, or caveats in the assumptions made that have not held in reality.

1. Many studies have shown the **diagnostic accuracy** of the test not to be equivalent to that of biopsy, as assumed in the headroom analysis. This implies that the cost saving from biopsies avoided should be set against the extra cost and health implications of misdiagnosis, i.e. treating those who do not need to be treated or delaying the treatment of those who need it. This has been attempted by Carlson et al. (2009) who show that this trade-off could swing the cost balance the other way in the longer term.

## Retrospective case studies: 1. FibroTest-ActiTest

2. NICE perform fewer liver biopsies than they did in 2001, due to a **change in clinical practice** whereby treatment tends to be initiated earlier, and often without this sort of testing. This reduces the potential impact (and market size) of the Fibrotest, and makes it less relevant for national evaluation as well.
3. **Direct competitors** have filled the space which was previously less populated. This obviously has implications for uptake.
4. The headroom analysis considered only patients with hepatitis C. The test has now been clinically validated for other liver conditions, thus increasing the potential **market size** (though this has implications for the return on investment decision rather than the marginal analysis used to determine value per patient).
5. I have found no other studies that have considered and quantified the **disutility** associated with liver biopsy. This might suggest this disutility is not important enough to influence decision-making in this area, and that the MRP of £438 might be more appropriate.

All of these points suggest potential problems associated with the headroom method (as applied in this case study), and put into question its prognostic ability (though, it has always been emphasised that the headroom method values the potential market for an idea under optimistic assumptions, and given the uncertainty of developments taking place in the future, this margin is more likely to get smaller than bigger).

So, was the headroom exercise useful, given the subsequent lack of evidence for its widespread use across the NHS? Firstly, the headroom method identified a significant opportunity in this area, and the fact that this product (and others) have and still do sell in many countries, shows that this was an investable space. Secondly, if we compare the 5 points listed above with the points raised in question 6 and 7 of the Headroom pro forma with the 2001 time perspective, we can see that all of those caveats were actually identified as potential threats or changes in the landscape, which should have been monitored through the development process. This may show that the exercise of undertaking a headroom calculation allows the user to usefully identify important areas of investigation and the significant changes in baseline to monitor.

## 2. MARS by Terakiln Ltd.

<p><b>1. Description</b></p> <p><i>Device (Equipment);</i></p> <p><i>New Indication;</i></p> <p><i>IPG follow up</i></p> <p><i>Date of briefing: Jan 2003</i></p> <p><i>Time perspective of this report: 1997<sup>2</sup></i></p>	<p>The Molecular adsorbent recirculating system (MARS®) is a liver support therapy for acute and chronic liver failure. It is a mechanical detoxification system that selectively eliminates both water-soluble toxins and strongly albumin-bound toxins from the blood of patients with liver insufficiency. In other words, it is a blood purification system that filters toxins from the blood stream. Blood from the patient's femoral vein is pumped into the MARS circuit which passes the blood through a membrane, transferring albumin-bound toxins into counter-current albumin-enriched dialysate fluid. Treatment duration is likely to be 6-8 hours. The MARS system will be used with a standard dialysis machine (available in renal units) or continuous venovenous hemofiltration (CVVH) machine.</p> <p>The MARS system will act as a support of liver function for those patients with acute or chronic liver disease, who are waiting for transplantation or capable of spontaneous recovery after some short-term support (and can also act as a temporary supportive role following transplant or liver graft). This could mean shorter hospital stay and better use of donated livers. Mortality from liver failure is 80-100% in the absence of transplantation. In the UK in 1997, 667 liver transplants were undertaken, and 180 patients remained on the waiting list at the end of the year (NHS UK Transplant 2001).</p>
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<p><b>2. Comparator</b></p>	<p>Episodes of acute liver failure are fairly common in chronic liver disease patients, and supportive measures are used in the first instance for these episodes of encephalopathy. The measures include reduction/elimination of dietary protein, or administration of glucose, lactulose and neomycin. Once supportive measures have failed, liver transplantation is currently the only option available, and the definitive treatment for patients with severe liver failure.</p> <p>The MARS liver-assist device can provide therapy for patients where supportive measures have failed, and can act as a bridge to transplantation. Although it is said to provide time for spontaneous liver regeneration or correction of precipitating event, it is not known for how many patients this might be relevant, and as such the MARS system will be viewed upon in this analysis as a bridge to transplantation only.</p> <p>Some estimates suggest that about half patients with fulminant hepatic failure (acute hepatic failure) will die awaiting transplantation (Kamlot, Rozga, Watanabe, &amp; Demetriou 1996). However, it difficult to estimate what proportion of transplant patients in the UK (or on the waiting list) these represent.</p>
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<sup>2</sup> The NHSC briefing says that MARS was launched mid-2000 with diffusion still ongoing, so the time perspective chosen is three years prior to this date, rather than three years prior to briefing as normal (briefings are normally provided within 6 months of launch).

	<p>For this analysis, I will use transplant statistics from NHS organ donation statistics for the year 2001 (NHS UK Transplant 2001)<sup>3</sup>. These offer the outcome of patients waiting for a liver transplant. Of all 954 patients on the waiting list, 70% received transplantation, 17% were still waiting at the end of the year, 6% died, and 7% were removed from the list (the cause of a patient being removed from the list was not indicated in this report, but a 2010 version of the report by the same group indicates that typically patients are removed from the register because they become too unwell for transplant).</p> <p>As the prognosis for severe liver failure is poor in the absence of transplant, it could reasonably be assumed that the mortality rate for those removed from the waiting list (due to deterioration of symptoms) would be high. Adding together those on the waiting list that die and those that are removed, it is possible that a system of liver support could have made a significant impact on 13% of those on the waiting list. Unfortunately, cause of death for those that die waiting for a transplant is not given. I will therefore assume that 10% of the 954 patients on the waiting list that would otherwise have died, might have survived long enough to receive a transplant <i>if</i> they had been given liver support in this bridging period (with the MARS device). I will also run the assumption that 5% of these patients could be saved.</p>
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<p><b>3. Market size</b></p>	<p>If the MARS system were to be used as a bridging therapy for transplantation for all patients, then every year this could equate to around 1,000 patients (there were 954 patients on the waiting list in 2001).</p> <p style="text-align: right;"><b>Market size per year:1,000</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these</p>	<p>If the 10% of waiting list patients that drop off the waiting list every year (due to removal or death) can be kept on the register until a liver transplant is ready for them, then this would increase the demand for liver transplant. However, liver donor supply is clearly restricted and is unlikely to shift significantly in response to changes in demand. Therefore, it will probably be the case that all patients would have longer waiting times until transplant. Although this may in turn increase the risk of death-while-waiting rate, the provision of liver support from MARS will be assumed to offset this.</p>
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<sup>3</sup> Although headline transplant and waiting list statistics for 1997 were found (from the same source), statistics relating to the characteristics and outcomes of transplant / waiting list patients were not found (including information on how many had died waiting for a transplant). As such, the earliest date available for this data is used: 2001. The trend graph for NHS liver transplant activity between 1997 and 2001 is fairly flat, indicating that 1997 statistics may well have shown similar characteristics.

<p>should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p> <p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>If the MARS system were to be offered in ITU (intensive therapy unit) or renal units, then minimal reorganisation / training would be required. As it would be very difficult to estimate the cost of the extra staff time that would be needed, this will have to be considered and accounted for <i>within</i> the headroom sum.</p> <p><i>The potential for the MARS system to offer an opportunity for spontaneous recovery (perhaps reducing the number of transplants required and leading to better allocation of transplants) has been ignored. Savings from fewer transplantations could be significant (a transplant costs between £11,000 and £14,000 per patient).</i></p> <p style="text-align: right;">(Total) ΔSC= - (Av. per person) ΔSC= -  P<sub>1</sub>= -</p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>From a headroom perspective, I will assume that the system is in equilibrium (i.e. the waiting list for transplants is not getting longer and longer all the time). If 10% more people on the waiting list are able to survive until transplant, then the value of the additional benefit of the MARS system would be the value of those lives saved, taking into account their life-expectancy post transplant and for the quality of life they experience in that state<sup>4</sup>.</p> <p>Transplant survival rates are recorded in the liver activity report by the NHS UK Transplant Group (NHS UK Transplant 2001). The group estimate a one year survival rate of 80%, a three year survival rate of 73% and a 64% survival rate at 5 years. This translates into an expected survival time for those receiving a liver transplant of around 10 years (i). This must be adjusted for the quality of life experienced in those</p>
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<sup>4</sup> This actually poses a very complicated problem. One could argue whether it is reasonable to use the value of these extra lives saved when, in real terms, if supply of livers is exactly fixed every year, then the same number of people are being transplanted with or without the device. However, from this simple headroom approach, we can only assume that the system is in equilibrium, and that those kept alive until transplant will (eventually) receive one.

	<p>10 years.</p> <p><u>QoL Estimates</u></p> <p>A report published in 1990 assessed QoL after liver graft. Although the unit of measurement was not an EQ-5D score but the 'Nottingham Health Profile' (a validated HRQoL measurement), results showed HRQoL to be high, and broadly similar to that expected in the general population (Lowe, O'Grady, McEwen, &amp; Williams 1990). Kim (Kim et al. 1997) estimates a QALY weighting of 0.8 following transplant, and Bennet (Bennett et al. 1997) estimate a QoL weighting of 0.5 after first year and 0.7 thereafter. Neither study is clear on how these values were elicited.</p> <p>As an estimate, I will use the middle of these three figures and apply a QALY weighting of 0.8 for the 10 years of expected life following transplant.</p> <p><math>0.8 * 10 = 8</math> QALYs</p> <p>This gives us a discounted health gain for this 10% of patients of 6.89 QALYs per patient (ii), and a total <math>\Delta</math>QALY of 689 QALYs</p> <p>10% of those on the waiting list represents 100 patients, but as the MARS system will be used for all 1,000 patients on the waiting list, the average QALY gain per patient will be <math>(6.89 * 100) / 1,000 = 0.689</math> QALYs.</p> <p style="text-align: right;"><b><math>\Delta</math>QALY=689</b> <b>(Av. per person) <math>\Delta</math>QALY=0.69</b></p> <p>If just 5% more patients could be kept alive until transplant with the MARS system, the figures would transform into the following: <math>(6.89 * 50) / 1,000 = 0.3445</math> QALYs</p> <p style="text-align: right;"><b><math>\Delta</math>QALY=345</b> <b>(Av. per person) <math>\Delta</math>QALY=0.34</b></p> <p>The MARS system is a piece of equipment not for individual use, but to be used for many patients. Therefore, in order to think of a headroom per device, we require an estimate of average health gain per device, for which we need to know how many systems are needed to cover all of these patients (and therefore how many people will be serviced by each device in a year). There is no indication in the briefing notes as to how many patients can be treated by one device. However, this would be an</p>
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<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>essential parameter for calculating headroom per device (the conceptually useful number).  <b>(Av. per device) ΔQALY= ?</b></p> <p><i>Not included in this analysis is the potential for those patients who are currently not suitable for liver transplant (and therefore not on the waiting list), to benefit from liver function support. This would not only lead to a greater relevant patient population, but could provide enhanced quantity/quality of life for these patients.</i></p> <p><i>I have also not incorporated the disutility that may arise from longer waiting times.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [AMBER] A search of the literature identified a paper from 1975 entitled: 'Artificial liver support based on haemoperfusion of adsorbents' (Dunlop et al. 1975). A paper from 1986 also discusses haemoperfusion for this indication (Mito 1986). Although I was not able to access either paper, their existence shows that the idea for this sort of technology is not new. This could mean that:             <ol style="list-style-type: none"> <li>1) If it was a good idea someone would have made a successful product of it before now.</li> <li>2) There might be others developing a similar technology.</li> </ol> </li> <li>• [AMBER] There is much talk in the literature of the acute <i>need</i> for systems that can help to support liver function, whilst patients await transplantation or (ideally) who could recover spontaneously if temporary support were available. Papers with this theme include Nyberg, 1993 (Nyberg et al. 1993), Cattral, 1994 (Cattral &amp; Levy 1994), Jauregui, 1996 (Jauregui, Roy Chowdhury, &amp; Roy Chowdhury 1996) and Fouad, 1996 (Fouad, Mamer, &amp; Shahidi 1996). However, all of these papers talk of the potential for artificial hepatic dialysis that makes use of <i>hepatocytes</i> to enable liver support, a function not dealt with by the MARS system. The MARS system mimics the capacity of the liver for filtering toxins from the blood stream. However, a normally functioning liver also metabolises drugs and synthesises bile and proteins. With the MARS system, this complex task of metabolism and regulation are left to the living hepatocytes within the liver (it is thought that removing toxins</li> </ul>
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	<p>from the blood can improve the environment for hepatocyte regeneration). Liver support devices that are being developed to fulfil these metabolising functions include an extracorporeal liver assist device using human liver cells (Sussman et al. 1992), and a bioartificial liver device containing porcine hepatocytes (Rozga et al. 1994). Sussman (1994,1996) discusses the advantages of biochemical liver assist devices over mechanical devices (i.e. MARS) (Sussman, Gislason, &amp; Kelly 1994;Sussman &amp; Kelly 1996). Although these alternatives have not yet entered the market, it is clear that (long-running) research is being undertaken on these systems, which may allow for increased function as compared with the MARS system.</p>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon?</p>	<ul style="list-style-type: none"> <li>• The principal assumption, upon which all estimations of value are dependent, is that the MARS system has the potential to save lives, by supporting liver function and allowing more people to receive a life saving transplant. This will <i>need</i> to be verified by clinical trials.</li> <li>• In order to estimate the potential of the MARS system to allow for spontaneous recovery (which would be very valuable to the NHS in terms of saved life or reduced demand for liver transplants), the potential magnitude of this should be estimated (i.e. for how many patients might this be relevant?)</li> <li>• Given the large literature base for this technique, the company should be aware of potential competitors or changes in the market.</li> <li>• Research relating to the use of hepatocytes should be monitored carefully, as – if found viable – technologies employing such a function could prove to be more effective than the MARS system in its capacity to aid liver function.</li> <li>• In order to understand the economic and clinical value of a device, the company will need to work out how many patients one device could feasibly service.</li> </ul>
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Notes by AC

(i) Mean survival was calculated in the following way:

$$P(\text{Survive } T \text{ years}) = e^{-d T}$$

Where mean survival = 1/d

- One year survival rate of 80%:

$$0.8 = e^{-d(1)}$$

$$\ln(0.8) = -d$$

$$-0.223 = -d$$

Mean Survival = 4.5 years

- Three year survival rate of 73%

$$0.73 = e^{-d(3)}$$

$$\ln(0.73) = -3d$$

$$0.105 = d$$

Mean Survival = 9.5 years

- Five year survival rate of 64%

$$0.64 = e^{-d(5)}$$

$$\ln(0.64) = -5d$$

$$0.089 = d$$

Mean Survival = 11.2 years

The estimate of a 10 year life expectancy post-transplant has been chosen, as the calculations from the three and five year survival rate are close to this figure. Although the shorter-term risk of death is greater in the first year (presumably from the risk associated with organ rejection), it has been indicated that the MARS system could usefully be used in a temporary supportive role post-transplant, which may help to reduce this risk.

(ii) Calculating discounted QALY gain

Using a discount rate of 3.5% to calculate the value of future health gain, the following formula was used to calculate discounted health gain:

$$\Delta QALY = 0.8 + \frac{0.8}{1.035} + \frac{0.8}{(1.035)^2} + \frac{0.8}{(1.035)^3} + \frac{0.8}{(1.035)^4} + \frac{0.8}{(1.035)^5} + \frac{0.8}{(1.035)^6} + \frac{0.8}{(1.035)^7} + \frac{0.8}{(1.035)^8} + \frac{0.8}{(1.035)^9}$$

$$= 6.89 \text{ QALYs}$$

## Headroom Notes (MARS)

	10% saved	5% Saved
WTP: £20,000 / QALY	£13,800	£6,800
WTP: £30,000 / QALY	£20,700	£10,200

These headroom figures represent the value that using the MARS system on **one patient** presents to the NHS in a **given year** (I have not been able to infer an *MRP* given the absence of a service cost estimate, patient throughput, and device longevity).

As MARS is a piece of equipment, the true value per device would be calculated by multiplying this headroom figure by the number of patients who would use it in a given year. Having calculated a headroom per device per year, this would be multiplied by the expected device lifetime (and subsequently discounted) in order to estimate a true headroom per device. This estimate of maximum willingness to pay would need to cover: the cost to the NHS of the equipment itself ('price'), extra NHS resource expenses (e.g. staff time), consumables (e.g. the albumin and disposable kit required for each use, multiplied by the number of times each patient would need to be treated), and costs for servicing the equipment.

If we were to have all of these inputs, then the true MRP could be estimated and some decision analysis regarding development costs could be undertaken. An interesting aspect of conceptualising the 'headroom' for this particular type of device, is that this value could be recouped through various channels: equipment price, consumables price, and also annual servicing charges. This is likely to be a strategic decision, and could mean dividing total MRP into multiple MRPs, rather than accruing the whole monetary value of the device as one lump sum upon sale of the device.

## Follow-up (MARS)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The MRP for this device was particularly difficult to identify, but what *was* calculated was a headroom per patient. If (unrealistically) one device would be used per patient then, according to these early estimates, the company could reasonably charge £6,600 (5% saved, WTP: £20K) to £20,700 (10% saved, WTP: £30K), which would need to cover all consumables and health service costs. If the device were to last five years, this would become £33,000 to £103,500.

The price indicated for the MARS system is £16,000, with disposable cost per treatment of £1,300 (£1,100 for the kit and £200 for the albumin). The number of treatments per patient is said to be

approximately 3 to 8. A comprehensive service contract is £1,600 per year. Even if we assume that a patient receives 8 treatments, this would cost the NHS (if it lasted 5 years): £16,000 + (£1,300 \* 8) + (£1,600 \* 5) + (health service costs) = £34,400 (+health service costs e.g. staff time). Considering this cost falls short of our *lowest* headroom estimate, and that in reality the fixed capital cost of £16,000 and servicing would be shared among many patients rather than just the one, we can only assume that this headroom looks favourable<sup>5</sup>.

Interpretive answer: **Headroom positive**

### Has there been a decision made on it by NICE? What was the outcome?

In 2004 an Interventional Procedure Guidance was issued (IPG45) on extracorporeal albumin dialysis for acute-on-chronic liver failure, which concluded that the current evidence on safety and efficacy at that time was not adequate to recommend that the procedure be used without special arrangements for consent, audit and research. In the update of this guidance produced in September 2009 entitled 'Extracorporeal albumin dialysis of acute liver failure' (IPG316) the procedure was said to raise no major safety concerns, but that current evidence on its efficacy were still inadequate in quality and quantity. As such, if a clinician wishes to undertake the procedure, they should still inform clinical governance leads, make patients aware of uncertainties, and audit/review clinical outcomes.

Although NICE IP guidance omits specific technology or company names, when looking through the evidence reviewed, it is clear that the majority consider MARS as the system to deliver this dialysis (NICE 2009a). In its guidance, NICE recommend further research be undertaken as to the short and longer term survival of patients 'bridged to transplant', as compared with current practice.

### Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?

Given the volume of clinical trials reported for the MARS system, it is clear that the device *has* been used for a number patients. Even in 2003, according to the NHSC briefing, the MARS system was being used occasionally in 20 UK centres and on a regular basis in 3 centres. A 2009 report commissioned by the North Trent Priorities Process, covering primary care trusts in the North Derbyshire, South Yorkshire and Bassetlaw areas, declared a commissioning policy: that the procedure would be funded for a maximum for four cases per year for the next three year period (Suckling 2009). This was based on that fact that apparently 3 to 4 patients per year with acute liver failure do not respond to standard medical therapy and may be considered suitable. This indicates that the stance used in the analysis may well have overestimated a realistic distribution policy, and that using the liver transplant list may not have been the best estimate of the relevant patient population.

Teraklin Ltd was acquired by Gambro in 2004. On the company website, it is indicated that in the U.S the MARS system is cleared for use in the treatment of drug overdose and poisonings only, and not for the treatment of liver conditions or as a bridge to transplant. It is clear, though, that the MARS

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<sup>5</sup> To the other extreme, we could have assumed that there would be one MARS system per UK liver transplant centre, of which there are 7 (NHS UK Transplant 2001), and in which case the headroom could have been multiplied by around 140!

treatment kit has a global outreach. Research into the use of MARS in practice is undertaken globally, another indicator that the device has widespread interest.

### **Have there been investigations into its clinical / cost effectiveness?**

There have been a great number of studies into the clinical and/or cost effectiveness of the MARS system. A simple search of MEDLINE of 'MARS' AND 'liver' produces 403 studies. On the efficacy side, the NICE review in 2009 showed that, although most studies reported clinical benefits for patients using the MARS system (including increased survival), most effects were not statistically significant.

The CEA registry identifies three cost-effectiveness studies for MARS. The oldest, published in 2006 by Hessel (Hessel 2006) presents a clinical cohort trial with a prospective follow-up of three years. Hessel found that, over the three years, MARS cost 40,000 EUR per patient treated, versus 12,700 for the controls. The three year survival rate was found to be 52% with MARS and 17% in controls (highly significant). He reports an ICER of 47,200 EUR.

The second cost-effectiveness study is by the same author, reporting on study with a larger cohort (149 patients) with a three year follow-up, but having modelled longer-term costs and outcomes. They found an ICER of 43,040 EUR (Hessel, Bramlage, Wasem, & Itzner 2010).

The final cost-effectiveness study on the CEA registry is by Kantola et al, who report on a trial conducted in Finland (Kantola et al. 2010). They find MARS to be both less costly and more effective than standard medical therapy, thus dominating current practice. It cost on average 10,928 EUR less than standard medical therapy. Interestingly, the number of QALYs gained per patient with the MARS system versus standard practice was 0.66 (this was elicited using the 15D generic HRQoL instrument). This is remarkably close to that used in the headroom estimate: 0.69.

A paper by Hassanein et al. (Hassanein, Schade, & Hepburn 2011) reports that nonbiological devices such as MARS, whilst effective in improving severe hepatic encephalopathy, have failed to show improvement in survival in RCTs. They also note that recent pilot studies for biologic devices (incorporating hepatic cells) show improved survival rates in some groups (but RCTs are needed to verify).

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

I have found no evidence to show that clinical practice has changed significantly for patients with acute liver failure, though assist devices such as MARS are becoming more prominent.

#### **Are there now many direct competitors?**

Many clinical trials compare MARS to other devices with a similar function (called liver detoxification albumin dialysis), particularly the Prometheus device. The single pass albumin dialysis (SPAD) is another simple alternative, using standard haemodialysis machines without an additional perfusion pump system.

### **Conclusions: How useful might the headroom exercise have been?**

The seemingly positive headroom for the MARS liver assist device may have suggested development, and the product does seem to be sold across the world. However, there is nowhere near full-scale deployment in the UK, and unfortunately no technology appraisal has been undertaken by NICE to consider its economic as well as clinical impact. This is due mainly to questions of effectiveness.

The MARS liver assist device was viewed upon in the headroom analysis as an aid for liver function. The size of the relevant patient population may have been overestimated for liver disease patients. However, the technology has also been mentioned in relation to renal failure and drug poisoning, which could widen market significantly.

The headroom analysis used increased survival rates as the key clinical and economic driver for its value case. The story was over simplified, and the subsequent clinical data has shown that this parameter is not straightforward. The need to provide evidence of impact on survival of MARS when used as a bridge to transplant was emphasised in the proposed research questions of the headroom analysis. Ten years later, elicitation of this precise parameter was reiterated as a research encouragement by NICE.

The information unearthed by the headroom analysis also uncovered some potential threats to the MARS system in terms of future competitors. This threat remains, and has borne some direct competitors.

Not all clinical studies on the MARS system have shown increased survival (upon which the whole headroom sum was based). There are other factors that were ignored by the headroom analysis and thus un-quantified, including potential reduction in time spent in an intensive care unit.

The headroom analysis undertaken could not identify a true estimate of MRP per device, as I could not estimate the likely lifetime of the device, the number of patients treated per device, or the health service implication in terms of resources. Whilst the developer may be better equipped to estimate such parameters, these may be difficult to predict early on.

### 3. SpeechEasy. *SpeechEasy International* (UK distributor: MedSys)

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Incremental development;</i></p> <p><i>Date of briefing: Sep 2007</i></p> <p><i>Time perspective of this report: 2005<sup>6</sup></i></p>	<p>It is estimated that 1% of adults have a stammer. Most stammering starts in early childhood, and is more common in males than in females. The ‘choral effect’ describes the phenomenon that stammering is usually clearer when a person is singing or speaking in unison with others.</p> <p>The SpeechEasy is a prosthetic device that stimulates this ‘choral effect’ by providing altered-auditory feedback (AAF) of a patient’s own voice to themselves when they talk. This AAF can be in the form of delayed auditory feedback (DAF) or frequency-altered auditory feedback (FAF), and the SpeechEasy can provide a range of settings to combine these two, tailored to each user. It is a wireless device that has three models: one that fits behind the ear, another which sits mainly in the inner ear canal, and a third that sits completely in the ear canal.</p>
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<p><b>2. Comparator</b></p>	<p>Speech and language therapy is commonly used to help deal with stammering, which includes fluency modification techniques (slowed/prolonged speech), vocal fold management, and psychological approaches (counselling etc). Other strategies include anxiety control, hypnosis and narrative therapy.</p> <p>This device is intended as an adjunct to current stuttering<sup>7</sup> therapy. However, the most pertinent comparator for this particular device is an alternative electronic device whose therapeutic goals and means are similar to that of SpeechEasy. The use of AAF to improve stuttering is not novel, and investigations into its effect were published in the 1970s (Pollock, Gregory, &amp; Shaw 1976; Stark &amp; Pierce 1970). Low (1979) first talks of a body-worn AAF device, that broke from previous versions which all required desk-top equipment. Versions of devices providing this function have progressed significantly over the past 25 years. SpeechEasy represents the first available <i>wireless</i> version of AAF devices, allowing for more discrete use.</p> <p>That this sort of device be cosmetically appealing is important, as conspicuous versions could discourage use and may cause some anxiety (a measure of anxiety is included in the health-related quality of life questionnaire EQ-5D). Other versions of AAF devices include models that use a headphone / microphone system (often connected by wires). Prices for these devices range from \$350 to \$3495.</p>
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<p><b>3. Market size</b></p>	<p>It is estimated that 1% of adults have a stammer (around 408,000 adults in England and Wales), though the severity and exact features vary greatly from person to person. There has been no estimate given as to</p>
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<sup>6</sup> More recent date chosen as the device represents a small change to its comparator, so the date is set to two years pre briefing rather than three.

<sup>7</sup> The terms stutter and stammer are used interchangeably.

	<p>the number of patients relevant for this device. The BSA (British Stammering Association) indicates that these electronic devices tend to be more useful for those that suffer more severely from a stammer, but give no indication of the number of people this represents. It is likely that the SpeechEasy could widen the current market for AAF devices given their more discrete nature.</p> <p style="text-align: right;"><b>Market size per year: ?</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>Speech and language therapy is provided by the NHS through specialist clinics. It is not clear to what extent such AAF devices are available on the NHS. The BSA indicate that 'NHS funding for such devices is not generally available' (The British Stammering Association (BSA) 2011). In order to understand what role the technology plays in current clinical practice, if any, I contacted an NHS speech and language therapy clinic (i). A community service that serves the North, East, and Heart of Birmingham localities owns two 'VoiceAmps' (devices that combine voice amplification with an altered auditory feedback function), which are used within therapy sessions to develop a patient's skills. If a patient thinks that such a device could help them in everyday life, then they would have to purchase one. It was noted that the situation with AAF devices varies up and down the country.</p> <p>This brings up two issues. First of all, that the NHS probably represents a very small portion of the potential market for SpeechEasy; such devices are generally used in clinic rather than prescribed for everyday use. Secondly, for those that are used within NHS clinics, there is likely to be little motivation to replace current devices with a more discrete model such as SpeechEasy. As it stands, it seems that the customer-base for SpeechEasy would be the patients themselves rather than the health service.</p> <p>Although indicated as an adjunct to speech therapy, it is suggested that SpeechEasy <i>could</i> eventually reduce the demand for these speech therapy services (which <i>are</i> provided on the NHS). However, to be prescribed systematically by the NHS, this would change the buyer from patient to health service, and change our comparator from 'older version' to 'speech therapy alone'. Being such a small change to previous versions of an AAF device, it is difficult to</p>
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<p>Describe any potential costs/savings that you haven't quantified.</p>	<p>understand why the NHS would decide to pay for these where they didn't before; the potential resource saving from reduced speech therapy is unlikely to be offset by the cost of such a device per patient. As such, the SpeechEasy must be considered as a patient purchase.</p> <p>In light of this, the question becomes not how much the NHS would be willing to pay for the device, but how much <i>patients</i> would be willing to pay.</p> <p style="text-align: right;">(Total) <math>\Delta</math>SC= n/a (Av. per person) <math>\Delta</math>SC= n/a</p> <p style="text-align: right;"><math>P_1 = \text{£}1,827^8</math></p> <p style="text-align: center;"><b>(this is the price of the most expensive existing model. NOTE: This is a patient expense rather than a Health Service expense)</b></p> <p><i>Speech and language therapy is provided by the NHS. It may be that, if SpeechEasy can offer an effective and long term aid for stammer, then the demand for these services may be reduced. However, the device is mainly indicated as an adjunct to current therapy, so this was not quantified in this analysis, but should be considered of potential benefit to the health service.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p>Describe any impact on patient health that you haven't quantified.</p>	<p>If SpeechEasy were to work as well as the most expensive version of what is currently available, which is sold for \$3,495 (£1,827: Pocket Speech Lab by Casa Fortuna Technologies), then people should be willing to pay at least this much for SpeechEasy. However, people are likely to be willing to pay a premium for its more discrete appearance. The question is: how much money could this premium represent?</p> <p>The value of this sort of change in current practice <i>could</i> feasibly be explored and estimated using the tools we use for NHS health valuation (ii). However, whilst interesting methodologically, this cannot be used to estimate incremental WTP for SpeechEasy, as this measure of health related quality of life and its valuation with a 'QALY tariff', have been designed specifically with the NHS and its inherent budget prospects in mind. There is nothing to indicate that this would reflect a patient's WTP.</p>
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<sup>8</sup> Exchange rate (\$1.9129 to the £) obtained from HM Revenue and Customs UK Trade Info for Jan 2005 (HM Revenue & Customs 2011).

	<p>Economic methods that aim to elicit the value a consumer places on particular product characteristics, which could be useful in valuing the magnitude of such a premium include: WTP methods (where individuals are asked to state maximum willingness to pay or willingness to accept) and discrete choice experiments (where the value of particular characteristics of a product are isolated by observing the trade-off between characteristics of commodities and performing a regression analysis). However, such techniques are outside the scope of a headroom analysis.</p> <p style="text-align: right;"><b>ΔQALY= n/a</b> <b>(Av. per person) ΔQALY= n/a</b> (see notes (ii) for theoretical estimate)</p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[AMBER]</b> There is no NICE Guidance of any sort on stammer, indicating that it may not be an NHS priority. As SpeechEasy represents an incremental development to currently available models, it is unlikely to incite funding where it was previously unavailable for similar technologies.</li> <li>• <b>[GREEN]</b> The strong literature base supports the efficacy of such devices, and there is no reason to believe SpeechEasy should be any less effective. Therefore, from a therapeutic perspective, the device is likely to be well received.</li> <li>• <b>[AMBER]</b> There are many makes and models for AAF devices, and the number of direct competitors is not likely to diminish. Although SpeechEasy is the first in-the-ear AAF device, it is unlikely to be so for long, as other companies will follow with yet more versions. Projected market share should reflect this, and the time to make back development costs should also be set with this in mind.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon?</p>	<ul style="list-style-type: none"> <li>• The sound literature base for AAF devices supports their use in people with a stutter. The SpeechEasy device will need to prove that it can perform this function up to the standard of current technologies.</li> <li>• An important parameter to identify is the extent to which patients would value / accept an in-the-ear device. This is the key selling point of the SpeechEasy, and will likely dictate the price that consumers are willing to pay for it.</li> <li>• Investigate the likely lifetime of such a device, as this will inform the length of the development cost recovery period. It is clear from the speed and extent of developments in this market until now that, as in many consumer markets, technology moves on quickly and models are soon outdated.</li> </ul>
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**Notes by AC**

- (i) I emailed a contact supplied on the website of a speech/language therapy centre in Birmingham. I asked him whether devices such as SpeechEasy are provided for patients on the NHS, or whether they are a patient purchase. I received an email in response to my query, advising me of the situation in their clinic:

Dear Amanda

Your request for information on altered auditory feedback equipment has been sent over to me, as Clinical Lead for fluency disorders. I am delighted to hear that you are undertaking some research in to the field of stuttering!

The situation regarding altered auditory feedback devices for adults who stammer probably varies across the country.

The adult community service in Birmingham, which covers the North, East and Heart of Birmingham localities, owns two VoiceAmp devices. These are used in therapy as part of the process for some clients. Clients are supported to use the device in the session, and can develop their skills in using them. If they decide that the device could benefit them in their everyday life, they would have to purchase one.

I hope this is useful.

- (ii) Interestingly, one of the 5 health dimensions in the EQ-5D questionnaire relates to level of anxiety / depression. Comparing SpeechEasy to 'Pocket Speech lab' (and assuming it works just as well), the only health-related quality of life parameter likely to be affected would be a one-level shift in anxiety (resulting from using a more discrete device), from moderately / slightly anxious or depressed, to slightly / not anxious or depressed. The effect of this on total utility weighting should be easy to estimate.

Williams (1995) lists all possible combinations of the EUROQOL classification system, and used interviews from a cohort of 3395 people in the UK to estimate each and every combination. Each of the 5 health parameters contains three options: No problems,

Moderate / some problems, or extreme problems. Dolan (Dolan 1997) models these results and provides a coefficient for each parameter (and the effect of a change in these on overall QoL)

Using this scale, we could estimate the value of a shift-change in level of anxiety. For example, if all other health parameters (mobility, self-care, usual activities, pain/discomfort) are held constant at 1 (no problems), a shift from moderately anxious to not anxious would be worth 0.152 (1 [with SpeechEasy] – 0.848 [with more visible device]) in a quality of life tariff. If we imagine that the person does not return to 'full health' at baseline (in the model, there is a 'constant' which represents the reduction in health state for anything under 1: full health), then this change would be 0.071. Multiplied by £20,000 or £30,000, this would incite a WTP by the NHS of £3,040 - £4,560, or £1,420 - £2,130 per year.

## Headroom Notes (SpeechEasy)

No calculation made

## Follow-up (SpeechEasy)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

Rather than estimating a definitive maximum reimbursable price, in this instance, the headroom method has only provided a narrative argument for SpeechEasy over other similar AAF devices. The MRP has thus been expressed as the price of the most expensive current technology (£1,827) plus some premium that consumers should be willing to pay for the discrete nature of SpeechEasy as compared with other models. The headroom method provides no means with which to estimate this premium.

Without knowing the cost of transforming the AAF function into such a small device, it is hard to know what a realistic MRP would be. According to the NHSC briefing (2007), the actual price of SpeechEasy ranges from \$4,100 (£2,050) for the behind the ear model to \$4,900 (£2,450) for the completely-in-the-ear-canal model. The SpeechEasy website now indicates that prices range from \$4,100 to \$5,100 (£2,550 using the same conversion rate) (SEInternational 2011). This price includes initial fitting and development of the mould to fit each person specifically, as well as ongoing device adjustments.

This seems to fit well with the expectation that the company should be able to charge a price equivalent to the most expensive alternative, plus a premium for the discrete design. For the most expensive model (completely hidden), this premium seems to have been estimated at £623 - £723.

Interpretive answer: **Headroom lacked sufficient detail to answer this**

### **Has there been a decision made on it by NICE? What was the outcome?**

No NICE guidance relates to stammering.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

SpeechEasy is a U.S. based company, but with providers around the world, including all over North and South America, parts of Africa and Asia, and much of Europe. The website of Europe's distributor MedSys indicates that the product is available in the UK.

The British Stammering Association (BSA) make the SpeechEasy device available to its members for free for a five day trial, so people can see if it works for them.

SpeechEasy has received a lot of international press, and among other media outlets has received air time on the Oprah Winfrey show, and SpeechEasy was also featured on the program 'Inside Out' for the BBC in 2009.

Searching 'stammer' on the NHS choices website indicates AAF devices as a treatment option for stammer, but that these are still not provided on the NHS.

### **Have there been investigations into its clinical / cost effectiveness?**

There have been a number of small trials for the SpeechEasy device, most of which are favourable. Armson (2006) reports on a trial (in laboratory conditions) with 13 people, which finds SpeechEasy to be beneficial to all patients in at least one of three speech tasks, though degree and pattern of benefit varied greatly across participants (Armson, Kiefe, Mason, & De Croos 2006). O'Donnell et al. (2008) tested SpeechEasy on seven adults who had responded positively to the therapy in a laboratory setting, to see if the benefit would hold in situations of daily living (O'Donnell, Armson, & Kiefe 2008). Five out of seven participants experienced some instances of reduced stuttering with the device compared to without. SpeechEasy was also found to have (moderately) favourable results by Armson & Kiefe (2008) and Pollard et al. (2009) as well (Armson & Kiefe 2008;Pollard, Ellis, Finan, & Ramig 2009).

No cost-effectiveness analyses were identified.

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

It seems (through information retrieved from the web, the BSA and a Birmingham-based speech and therapy clinic) that AAF devices still do not attract systematic NHS funding.

#### **Are there now many direct competitors?**

There are still many competitors in the market and, as anticipated, these have also developed and moved forward their technological developments, making them direct competitors to SpeechEasy.

As an example, the competitor 'next best' device which was used in the headroom analysis which cost \$3,495—the Pocket speech lab by Casa Fortuna—is now, according to their website, an 'obsolete model now marked down for clearance', and costs \$995 (CasaFortunaTechnologies 2011). They have developed a very small version AAF which they sell for \$2,495 (though it doesn't fit

completely within the ear, and requires a small box nearby), and they have also developed an iPhone app which features AAF.

### **Conclusions: How useful might the headroom exercise have been?**

As an NHS perspective could not be taken for this device, the headroom approach did not allow the isolation of an MRP; this is a shortcoming of the headroom method. The eventual price set for SpeechEasy does seem to have aligned itself with expectations from the headroom exercise, and the research questions were pertinent. Whether, though, this has anything to offer beyond what a company would have been investigating anyway, is probably unlikely.

#### 4. SLF bypass graft. *Tayside Flow Technologies*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Incremental development;</i></p> <p><i>No NICE follow-up</i></p> <p><i>Date of briefing: Sep 2009</i></p> <p><i>Time perspective of this report: 2006</i></p>	<p>Peripheral arterial (or vascular) disease (PAD) is the narrowing of the peripheral arteries (primarily in the legs), leading to insufficient blood supply to the muscles and other tissues. It can cause leg pain and weakness when walking, but in advanced cases can develop into pain at rest.</p> <p>Critical limb ischaemia is when claudication progresses to Fontaine classification stages III (ischaemic rest pain) or IV (ulceration, gangrene or both). About 150-200 per million of the population in the UK progress to this critical limb ischaemia stage every year (Beard 2000). It is for these patients that revascularisation techniques are considered. In 2000 it was estimated that critical limb ischaemia cost over £200 million a year in the UK alone (Beard 2000).</p> <p>Spiral laminar flow (SLF) describes the normal spiral pattern of blood flow through the arteries (because of the twisting of the heart on its axis). This movement increases total pressure and velocity of the blood. Stenosis (narrowing) of the vessels interrupts this spiral flow and places pressure and stress on the vessel wall.</p> <p>The SLF peripheral bypass graft is a man-made graft which has a flow inducer at the distal end which restores natural SLF (and so reduces the laterally directed forces and turbulence caused by stenosis). This should reduce neointimal hyperplasia (NIH) (thickening of a blood vessel, a natural response to vessel injury and a cause of vessel occlusion), and thus reduce the incidence of vessel occlusion.</p>
<p><b>2. Comparator</b></p>	<p>Management of PAD includes self-help measures such as smoking cessation and regular exercise, and the use of antiplatelet agents. When PAD becomes more severe or persistent, options include: percutaneous transluminal angioplasty (PTA) or—the most relevant comparator for the SLF bypass graft—bypass surgery with autologous saphenous vein or synthetic graft. In a small number of cases amputation might be necessary.</p> <p>It is thought that where the flow of blood becomes non-spiral due to stenosis, the turbulent energy can increase dramatically (by about 700%) (Stonebridge et al. 2004). Lowering these forces acting on the vessel wall could reduce hyperplasia and subsequent occlusion. It is proposed that the SLF graft could achieve this stabilising effect. The SLF bypass graft is itself a man-made synthetic polytetrafluoroethylene (ePTFE) graft, but unlike traditional ePTFE grafts, has a flow inducer at the distal end which should improve graft patency (the chance of a graft remaining open). It is said to be an alternative to traditional ePTFE grafts or autologous vein grafting.</p>

Retrospective case studies: 4. SLF bypass graft

	<p>Prosthetic grafts are usually considered only when an autologous vein is not available for revascularisation, as vein grafts are known to have higher patency rate than prosthetic grafts (Cheshire et al. 1992; Eidt et al. 2006; Fisher et al. 2003; Londrey et al. 1991; Panayiotopoulos et al. 1997; Pereira et al. 2006)<sup>9</sup>.</p> <p>There was no estimate in the NHSC briefing as to degree of improvement that could be expected for the SLF graft over other ePTFE grafts. An optimistic but reasonable assumption for the purposes of this analysis could be that the SLF graft will work <i>as well as</i> an autologous venous graft (but will be used when a venous graft is not available)<sup>10</sup>.</p>
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<p><b>3. Market size</b></p>	<p>I have found no estimates in the literature regarding the number of patients undergoing a PAD bypass procedure every year. Nor have I found the proportion of patients for which autologous vein grafting is not possible.</p> <p style="text-align: right;"><b>Market size per year: ?</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p>	<p>In the literature, vessel occlusion has been found to be common for PAD bypass grafts. In most studies, graft material <i>has</i> been found to be an important factor in patency rates, and the general consensus is that patency is improved with vein grafts over prosthetic ones. However, the degree of this improvement varies, with some saying that vein and ePTFE patency rates are broadly similar, going as high as 70 to 80%, where others find much lower patency rates. Panayiotopoulos, in a UK prospective analysis of bypass grafts between 1991 and 1995, finds three year patency to be 55% for vein grafts and only 24% for ePTFE grafts (around half) (Panayiotopoulos et al. 1997). They estimate the cost to the health service of a successful bypass to be £4,320, and the cost of a failed bypass surgery which warrants later amputation to be £17,066.</p> <p>Whilst it seems feasible to estimate the change in cost to the health service of doubling patency rates for those who must use PTFE grafts (making them</p>
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<sup>9</sup> Although most studies estimate a much higher patency rate for vein grafts, one paper raises the question of whether the two graft options have been fairly compared, as ePTFE is usually used in trials when a venous graft is not an option; the risk factors and extent of arterial disease in the two treatment arms could be very different (Panayiotopoulos & Taylor 1997).

<sup>10</sup> This assumption has not been elicited from the developers own appreciation of the graft's potential (which was not expressed in the NHSC briefing), but from an appreciation gained from the literature of the disadvantages and reduced patency rates of ePTFE grafts. It would be unreasonable to assume that the SLF graft would achieve 100% patency, so assuming a patency rate equivalent to that of a venous graft (which would be the surgeon's first option anyway) seems appropriate.



<p>Use HCHS index to inflate estimates to current prices</p> <p>Describe any potential costs/savings that you haven't quantified.</p>	<p>similar to patency rates of venous grafts), to do so would mean understanding the number of graft revisions that take place, and how many go on to be amputated.</p> <p>Cheshire et al. estimate a patency rate of 72% for vein grafts and 48% for ePTFE grafts. Unfortunately the article is not accessible, but the abstract implies that the initial cost to the health service of both vein and ePTFE graft is \$6898, which increases to \$15,024 and \$20,416 respectively when considering the (three year) follow up period, due to higher reintervention rates for ePTFE grafts (Cheshire et al. 1992). This theoretically means we could value a technology that increases patency rates of ePTFE grafts up to that of vein grafts could be worth about \$5400 to the health service, per unit, over a three year time horizon (£4,400 after having inflated to today's (2006) prices and converted from U.S. \$ to the £).</p> <p>Given the paucity of data, any calculation made here would seem tenuous. However, to think of this problem logically, and given the assumption made, the case for development is compelling. From the literature, we have gathered that there is a big efficacy gap between ePTFE grafts and venous grafts. If we think that the SLF graft can work as well as venous grafts (the fact that it is proposed as a possible replacement for venous grafts implies that the developer believes this to be the case), then patency rates can be increased. This means fewer cases of graft revision (or amputation). The one estimate identified suggests that the cost saving potential for the NHS of this could be about £4,400. Even if this figure were actually to be far more modest, one can surmise that, as the SLF graft is a reasonably simple device that represents a <i>small change</i> to current ePTFE grafts, development costs shouldn't be huge. As there are many versions of the ePTFE grafts on the market (assumed to be in profitable business), then the <i>extra</i> reimbursement that could be achieved from producing a product that worked better could surely more than cover the cost of the modified mechanics of the SLF graft.</p> <p style="text-align: right;">(Total) <math>\Delta SC =</math> (Av. Per person) <math>\Delta SC =</math></p> <p style="text-align: right;"><math>P_1 =</math></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>It has been argued above that the economic case for a graft that works better than current prosthetic grafts is a strong one. As it represents an incremental modification to current grafts, its increased cost per unit (if any) is unlikely to outweigh this potential.</p> <p>It is clear that patients would only <i>benefit</i> from a reduced vessel occlusion rate. Having established that the grounds for development are clear on its economic merit alone, there is no need to quantify its benefit to patients.</p> <p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p> <p><i>The increased quality (and perhaps quantity) of life from reduced vessel occlusion and graft revision has not been quantified.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[AMBER]</b> There is much innovation in this area, including other modifications of ePTFE grafts which, if found to be better than current versions, could change the baseline.</li> <li>• <b>[AMBER]</b> One such development is the introduction of herapin-bonded grafts, which could improve resistance to thrombosis. A clinical investigation has been published on the incremental effectiveness of ePTFE grafts that are bonded with herapin over standard ePTFE grafts. Early patency and limb salvage results are promising, but longer term RCTs are required to confirm this (Bosiers et al. 2006).</li> <li>• <b>[RED]</b> The Distaflo graft by BARD is another graft that, like the SLF graft, has been developed to reduce intimal hyperplasia by improving hemodynamics (blood movement) at the distal end of the graft (Fisher et al. 2003). The 'Miller cuff' is also described for this purpose. It has been found to have an improved patency rate for below-the-knee bypass (Griffiths, Nagy, Black, &amp; Stonebridge 2004).</li> <li>• <b>[AMBER]</b> It has already been found that precuffed grafts have benefits for improved haemodynamic forces which suppress hyperplasia and improve patency rates (Fisher et al. 2001b;Fisher et al. 2001a).</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon?</p>	<ul style="list-style-type: none"><li>• Does it work as well as we thought it would? There is a wide body of literature aiming to assess the patency of different graft types. In order to introduce and establish a viable new product in this market, the SLF graft must prove to work better than current ePTFE grafts.</li><li>• Are there any other upcoming graft types for this indication, and how do they compare to SLF?</li></ul>
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## Headroom notes (SLF bypass graft)

No calculation made

## Follow-up (SLF bypass graft)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

An MRP was not identified for this product, but an intuitive case was made for its development.

Interpretive answer: **Headroom positive**

#### **Has there been a decision made on it by NICE? What was the outcome?**

A clinical guideline for lower limb peripheral arterial disease is in progress; Tayside Flow Technologies is not on the stakeholder list.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

The SLF bypass graft is CE marked and received FDA approval in 2009 (Bloomberg 2009). The company indicate that they are selling and marketing their SLF grafts in more than 20 countries across the world. The United States seems to represent a big market for Tayside Flow Technologies, with as many as 10 distributors over there. At the end of 2010, the SLF graft had already been used by 55 surgical centres in the USA (Tayside Flow Technologies 2010b). Tayside Flow Technologies has since been renamed Vascular Flow Technologies (Vascular Flow Technologies 2013), and has expanded. The company confirm that their SLF bypass graft is used within various NHS hospitals (confirmed through telephone communication with the company, whose headquarters are in Dundee, Scotland).

### Have there been investigations into its clinical / cost effectiveness?

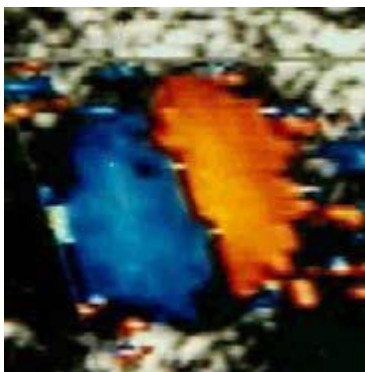
There have been many clinical investigations into the patency of different graft types, much along the same lines as those published before 2006. Cost-effectiveness analyses in this area are still few in number.

One HTA considers the cost-effectiveness of balloon angioplasty versus bypass surgery, and finds that for those with a life expectancy of under two years, angioplasty is the more cost-effective solution, but where life expectancy exceeds two years, bypass is the best option (as patients are likely to experience the longer term benefits)(Bradbury et al. 2010). However, they also indicate that patients for whom a *vein* bypass is not possible would be better off attempting balloon angioplasty first, and advise that surgeons should view prosthetic grafts as a last resort. This could represent a move away from revascularisation using prosthetic grafts in PAD.

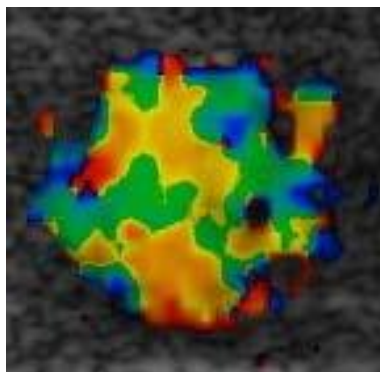
The literature relating to spiral laminar flow and its role in vessel occlusion has already been presented, showing the theoretical link between SFL and increased patency. As for the SLF graft itself, no studies were identified, but the company provide the results of some preliminary trials on their website. Forty patients were implanted with the SLF graft, and ten (randomly selected) were subsequently assessed using ultrasound and were found to *have* this spiral flow pattern. The primary patency rate at 1 year was 88%. Another trial achieved 96% primary and secondary patency (at 11 months) for a cohort of 36 patients in 2009-2010 (Tayside Flow Technologies 2010a). Another finds 78% patency rates at 24 months (Tayside Flow Technologies Ltd. 2011).

The following pictures show images of blood flow within a normal artery, one with vessel occlusion, and following an SLF graft:

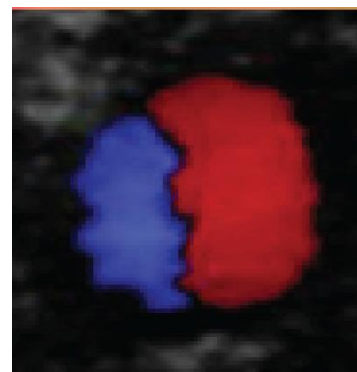
Natural blood flow within a healthy artery



Turbulent blood flow from a non SLF graft



Natural blood flow from an SLF graft



The clinical function of the SLF graft seems to have been demonstrated. There are early indications that this leads to reduced vessel occlusions, but this needs independent confirmation by larger trials.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

A Cochrane review published in May 2010 outlines the evidence for the various graft types for femoro-popliteal bypass surgery: autologous vein, polytetrafluoroethylene (ePTFE) or Dacron (another type of prosthetic material used for grafts) (Twine & McLain 2010). They conclude that vein bypass is the most effective, followed by the synthetic materials, but that using a vein cuff leads to improved patency rates over ePTFE alone. There was no mention of the SLF graft specifically within the ePTFE group.

Current practice does not seem to have changed significantly since 2006.

### **Are there now many direct competitors?**

In one large retrospective study published in 2009, herapin-bonded ePTFE grafts were found to have patency rates that were not significantly different from those of autologous saphenous vein grafts (Daenens et al. 2009). The Distaflo graft continues to be marketed, and BARD have since developed other version of their ePTFE bypass graft. No other grafts were identified which propose the restoration of spiral laminar flow.

## **Conclusions: How useful might the headroom exercise have been?**

The main conclusion drawn from the headroom analysis was that, if the patency rates of the SLF graft could be shown to be equivalent to those of vein graft, then the economic case for product development would be strong. Early clinical investigations have shown promising results, and the company seem to be successfully expanding into markets across the world.

As the headroom analysis really hinged on the clinical case for the SLF graft (the gap for which was identified in the literature), it is difficult to say whether this headroom analysis would have been *useful*, even if it wasn't wrong. The clinician to first develop this would have had this clinical case as the driving force for his research, and in this instance the economic case to follow was an obvious one (given the non-existent impact on service cost of actually implanting the graft, and the clear health service and patient benefit of increased graft patency).

## 5. Meniett. *Medtronic Xomed*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Another Option;</i></p> <p><i>IPG in development;</i></p> <p><i>Date of briefing: July 2003</i></p> <p><i>Time perspective of this report: 1999<sup>11</sup></i></p>	<p>Ménière’s disease is a condition of the inner ear which can affect hearing and balance. It is thought to be linked with excess fluid in the inner ear, which affects pressure. The main complaints of patients suffering with Ménière’s disease are: attacks of rotary vertigo (room spin), hearing loss, tinnitus (ringing in the ear), and a feeling of fullness / pressure in the ear. Although the disease is progressive, symptoms can fluctuate significantly and unpredictably, making it difficult to observe the effects of treatment. Generally, attacks of vertigo tend to be more frequent in the first few years, and following this, reduced frequency of attacks is accompanied by a sustained deterioration in hearing.</p> <p>Meniett is a non-invasive, portable patient-administered device for Ménière’s disease which delivers intermittent low-pressure pulses into the inner ear through a tympanostomy tube (grommet), which must first be inserted into the inner ear with the patient under local anaesthesia. The low-pulse generator is to be used three times a day until remission of symptoms, for patients who do not respond to medical therapy.</p>
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<p><b>2. Comparator</b></p>	<p>Certain drugs can be used to improve symptoms of vertigo, and vestibular rehabilitation is used in some cases. However, for those refractory cases where patients do not respond to medical therapy, an ablative or surgical procedure may be used to control symptoms.</p> <p>The Meniett low-pressure pulse generator is to be used <i>instead of</i> ablative treatment or surgery where medical therapy has failed.</p> <p>Research into the use of pressure as a treatment for patients with Ménière’s disease has been undertaken for many years. There are many early studies dating back to the 1970s and 80s which find changing air pressure within the ear to have an effect on hearing (Densert, Ingelstedt, Ivarsson, &amp; Pedersen 1975;van Deelen, Hulk, &amp; Huizing 1987). Two academics with the name of Densert (O and B, who often co-author papers) have been prolific in this area since 1975 to the present day<sup>12</sup> (Densert 1987;Densert et al. 1997;Densert &amp; Densert 1982;Densert, Sass, &amp; Arlinger 1995;Densert, Ingelstedt, Ivarsson, &amp; Pedersen 1975). The papers tend to show that pressure pulses to the middle ear improve electrocochleographic recordings (a technique of recording stimulus-related responses or electrical potentials of the inner ear / auditory nerve).</p> <p>According to the NHSC briefing note, ablative treatment with aminoglycosides (called local intratympanic gentamicin), where an injection is given locally into the ear to deaden the inner ear, is the</p>
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<sup>11</sup> Product was launched in 2002

<sup>12</sup> Barbara Densert writes an introduction to the Meniett device in the journal of Acta Otolaryngol in 2000 (Densert, Arlinger, & Odkvist 2000)

	<p>‘treatment of choice’ for refractory cases. Surgical techniques that are not destructive to hearing are endolymphatic sac surgery and vestibular nerve section. Destructive treatments such as labyrinthectomy are occasionally used in severe cases. Pfeiderer (1998) reports that the local intratympanic gentamicin procedure is an effective treatment for patients with unilateral Ménière’s disease, and is associated with low morbidity and good hearing preservation, and indicates it is a potentially superior alternative to surgical treatment (Pfleiderer 1998). Atlas (1999) reports on a study in which 84% of the 83 patients showed complete vertigo control, and another 6% showed ‘substantial’ vertigo control. As a group, there was no statistically significant change in hearing parameters at 24 months (Atlas &amp; Parnes 1999). Many other studies also show this to be the treatment of choice, and that these injections provide significant vertigo control, without the significant cost of a more invasive surgical procedure (Hirsch &amp; Kamerer 1997).</p> <p>Some other studies talk of endolymphatic surgery as the treatment of choice, achieving (some degree of) vertigo control in 96% of cases, and gentamycin injection being an effective back-up treatment (Watanabe et al. 1995).</p> <p>We can surmise that the treatment of Ménière’s disease in refractory cases is far from formulaic. However, there does seem to be varied opinion, and scope for various procedures to be used as options, depending on clinician and patient preference.</p> <p>The NHSC briefing gives no indication of if/ by how much treatment of patients will <i>improve</i> by using the Meniett device as compared to current ablative / surgical procedures that conserve hearing. Therefore, I assume that the Meniett will work <i>as well as</i> other procedures.</p>
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<p><b>3. Market size</b></p>	<p>The Meniett device is thought to be applicable for one third of patients who do not respond to medical therapy (there is no source or explanation attached to this assertion, so this estimation is thought to come from the manufacturer). The number of those affected by Ménière’s Disease is difficult to estimate, but this is thought to correspond to a relevant patient population for the Meniett device of between 172 and 3,432 patients (based on the Meniere’s Society estimates of total incidence).</p> <p style="text-align: right;"><b>Market size per year: 172 – 3,452 patients per year</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in</p>	<p>Although local intratympanic gentamicin (ablative injection into the inner ear) seems to be the reference standard, it is clear that surgical options are also considered for the treatment of these patients with refractory symptoms.</p>
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<p>previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p> <p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>The headroom method usually takes the 'gold standard' in current practice to be the relevant comparator. As there are so many different treatment options, we can only assume that, if the Meniett works just as well as / better than treatments that <i>are</i> currently funded by the NHS, then the health service should be willing to invest the same amount in this new device, especially if it is found to be better accepted by patients.</p> <p>Information regarding the cost of procedures for Ménière's disease is not readily available on the internet. A cost estimate of surgical alternatives: endolymphatic sac surgery, vestibular nerve section and labyrinthectomy are presented in the NHSC briefing: £750 to £1,500. No reference is given as to the source of these costs, so I assume that these estimates are from the developer's own knowledge base. These surgical techniques are said to be accompanied by a hospital stay of around three days. It is not absolutely clear whether the resource implication of these three days hospital stay are included within the £750-£1500 estimate, but intuitively I will assume that they are not, considering the cost of three days in hospital would make up a large portion of this estimate, and also given that costs indicated in the NHSC briefing for other procedures (namely, the grommet insertion for the Meniett device) is later revealed not to include hospital costs.</p> <p>Those service costs <b>saved</b> (per patient) by replacing surgery with Meniett treatment would be:</p> <ul style="list-style-type: none"> <li>• £1,500 for avoiding the surgery itself (taking the higher of the estimate range), and</li> <li>• 3 days hospital stay, valued at £201 per day =£603 (i)</li> </ul> <p>Total saved per patient: £2,103</p> <p>Those extra service costs that must be <b>incurred</b> when switching from clinical practice to the Meniett device:</p> <ul style="list-style-type: none"> <li>• Grommet insertion: £428</li> <li>• Hospital costs (estimated one day): £201</li> </ul> <p>Total incurred per patient: £629</p> <p><b>(Total) ΔSC= £253,528 to £5,088,248</b>  <b>(Av. Per person) ΔSC= £1,474</b>  <b>P<sub>1</sub>= (included in above estimate)</b></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>As outlined above, there is no indication in the NHC briefing that the Meniett device will work better than current procedures.</p> <p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p> <p><i>If treatment with the Meniett device were found to be more acceptable for patients, this could offer an increased incentive for its use. If the quality of life loss from the surgical procedure itself were to outweigh the frequent daily use of the Meniett device, then this could be quantified, and translated into a WTP for the health service, potentially adding to the headroom.</i></p> <p><i>If the Meniett device could <b>enhance</b> rather than simply preserve hearing, then this could also have an impact on the reimbursement opportunity.</i></p>
<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products</p>	<ul style="list-style-type: none"> <li>● <b>[RED]</b> Local intratympanic gentamicin (injection into the ear) seems to be well supported by the literature. Although a cost estimate couldn't be found, it is likely to be much less costly than surgery. If this is to become more widespread, this might displace other treatment options.</li> <li>● <b>[GREEN]</b> Considering that all other treatment options for patients with refractory Ménière's disease are fairly invasive / destructive, a treatment option which is minimally invasive could present an attractive proposition to patients and clinicians. This may not be captured in a headroom calculation.</li> <li>● <b>[GREEN]</b> Early research into pressure therapy for Ménière's disease indicates that it <i>could</i> actually improve hearing, rather than simply preserve it.</li> <li>● <b>[AMBER]</b> As noted above, the use of pressure therapy has been under investigation for many years. This could mean that direct competitors</li> </ul>

<p>being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<p>may emerge.</p>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>• The headroom analysis has been based on assumption that it will work as well as surgical techniques (in terms of vertigo control and hearing preservation). This must be investigated in trials. If it transpires that it could work <i>better</i> than current surgical techniques, the headroom should be adjusted accordingly, as current estimates could have underestimated its value (potential for a positive effect on hearing could be a big factor here, if found to be significantly affected by the Meniett pulse generator).</li> <li>• Would the device be well tolerated by patients? Its minimally invasive nature could be attractive (perhaps adding a premium to the reimbursable price), but this should set against patients’ feelings towards the frequency of treatment required for therapy using the Meniett pulse generator (3 times daily until remission, and thereafter depending on duration and severity of symptoms). If this treatment schedule were to be indicated for a long time, a one-off surgical intervention may seem more attractive.</li> <li>• Would the Meniett pulse generator be procured on a per patient basis (for home use, as indicated), or might the devices be made available centrally in primary care? This could increase the value per device, though practicalities must be considered, given the optimal frequency of treatment.</li> <li>• Is there scope for the Meniett to be a patient purchase? It may well be that the value to patients of this minimally invasive procedure outweighs what the NHS might be willing to pay for it.</li> <li>• Be mindful of other emergent devices using the same sort of technology, which deliver pressure therapy for sufferers of Ménière’s disease.</li> </ul>
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### Notes by AC

- (i) Identifying the average cost of an excess bed day (either in general or for individual specialities) represents one way in which hospital bed day costs can be estimated. Having not been able to find any such estimates predating 1999 (from the Department of Health or any literature within the clinical area), I use the table presented by Jones (2008), for speciality-specific national average cost per (excess) bed days. For ENT, this is £268 for adults. Jones uses the NHS Reference Cost database for 2006-07. Using the HCHS Pay&Prices index, this would be worth the following in 1999 prices:

HCHS P&P Index 1999/00: 188.5

HCHS P&P Index 2006/07: 249.8

Deflation rate:  $188.5/249.8 = 0.75$

Cost of ENT bed day:  $£268 * 0.75 = £201$

Although from a practical perspective, this particular resource did not exist in 1999, it is thought that given time and experience within the area, this would have been a findable number.

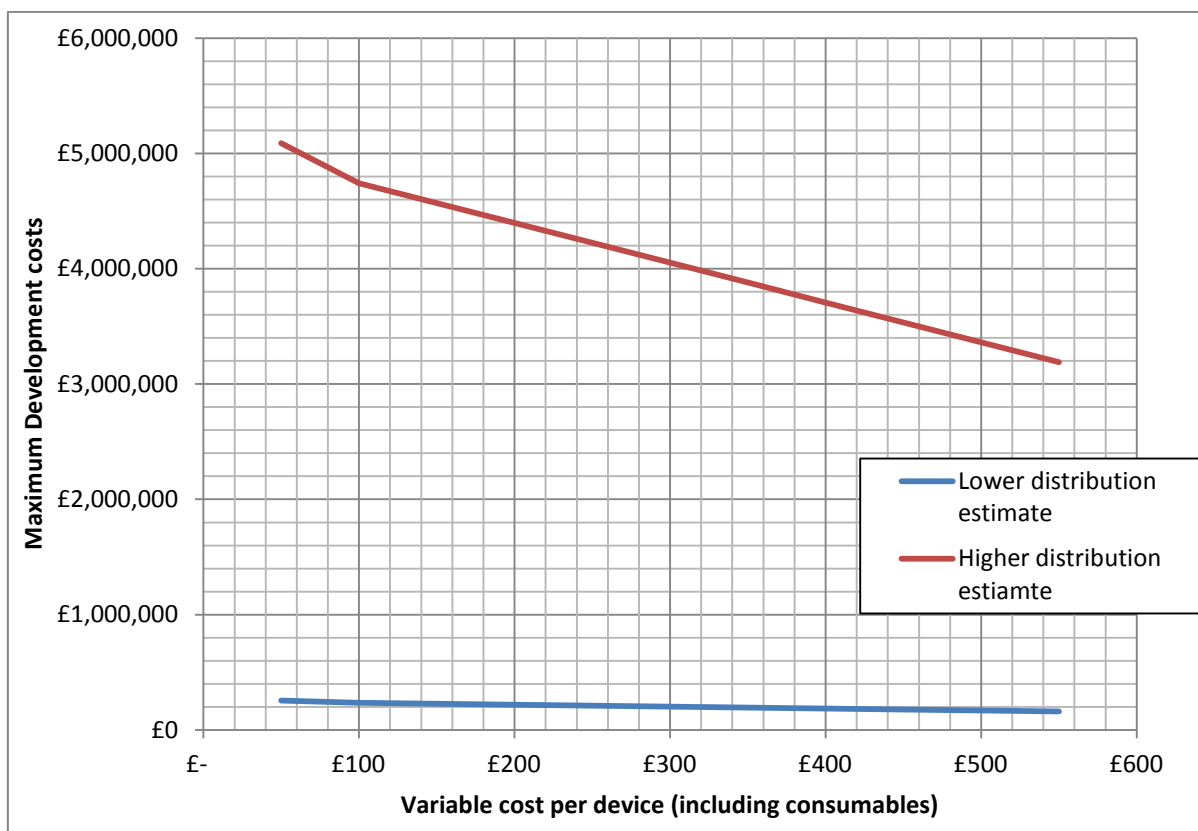
### Headroom Notes (Meniett)

MRP: £1,474

It must be noted that the value created by disinvesting in the one-off surgical procedure is, (unlike most headroom analyses for pieces of equipment that have been undertaken), not a yearly value. Therefore, the assumption we are making here is that the Meniett pulse generator will last a patient's lifetime.

It is indicated that only a small amount of patient training is required, and that this is provided by Medtronic. The cost of this training must be included in this price (the device is said to have no maintenance costs).

The huge gap between the lower and upper estimates of market size reflect the high uncertainty in the number of people suffering from and being treated for Ménière's disease. However, given the MRP estimated of £1,474, the following graph shows the relationship between variable cost per unit and maximum allowable development costs, if this price can be achieved when the Meniett pulse generator is put on the market, assuming the lower distribution estimate of 172 (blue curve) and the higher estimate of 3,452 (red curve).



In the case of a small market size, the allowable development cost does not vary greatly according to variable cost, and ranges from about £160,000 when variable cost per unit is £550, to about £250,000 if a unit cost of £50 could be achieved. The wider distribution could support much larger development costs, ranging from £3.2 million to about £5 million, given the variable costs presented here.

It should be noted that, as this device is indicated as ‘another option’ the relevant market size is difficult to estimate, and will depend greatly on patient and clinician preference. The analysis presented above is illustrative of potential market size, according to the NHSC briefing.

## Follow-up (Meniett)

### Headroom Outcome and Market success

#### Does the MRP look realistic? Would it have indicated yes or no to development?

The MRP, indicated by the estimated magnitude of disinvestment in current surgical procedures (and considering the extra health service investment required to undergo the grommet insertion), was **£1,474** for the Meniett low-pressure pulse generator. The allowable development costs were also estimated, at various levels of unit production (variable) cost.

It was acknowledged that surgical intervention represents one group of treatment options for patients with Ménière’s disease who have refractory symptoms (not responding to medical therapy),

but that other interventions (e.g. the injection of gentamicin into the ear) were also used, and are probably cheaper. However, it was thought that if the case for surgical intervention was sufficient to warrant their use and reimbursement on the NHS, then this higher reimbursement opportunity would represent the price up to which the health service should be willing to pay for an equivalent treatment.

The Meniett device was priced, at launch, at £2000. This is clearly *above* the MRP estimated. We cannot tell whether, from the company's perspective, this MRP of £1,474 would have appeared early on to be sufficient to cover development and unit cost of production, and therefore, cannot say for sure whether this would have suggested a go or a no-go development decision. When price turns out to be below MRP, we can reasonably assume that it would have provoked a 'go' decision; this case is less clear, as we do not know by how much actual price exceeds what they could actually afford to charge, and also what their prediction of this might have been. However, if the NHS does fund the device at a price of £2,000, then: either the headroom approach is flawed, or the assumptions employed to calculate the MRP appear to have underestimated its potential.

Interpretive answer: **Headroom decision unsure. Possibly negative**

#### **Has there been a decision made on it by NICE? What was the outcome?**

An interventional procedures guideline is currently 'in progress' by the NICE IPG team (expected to be published November 2011), for 'Micropressure therapy for refractory Ménière's disease'. An overview was compiled in April 2011 and provisional recommendations were subsequently made in July 2011 (subject to potential revision after the public consultation). Having examined the literature upon which provisional recommendations are made, all trials refer to the Meniett device as the system used to deliver this therapy.

Provisionally, NICE state that the current evidence on the safety and efficacy of micropressure therapy is inadequate in quantity (NICE 2011f). As such, it should only be used with special arrangements for clinical governance, consent, and audit or research. They encourage further research into the therapy.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

At the time the NHSC briefing was produced (July 2003), thirty Meniett devices were in use in the NHS. It was also stated that several had been purchased privately.

A forum set up in 2008 on the Ménière's Disease UK website, shows some patients exchanging thoughts on the Meniett device (Meniere's Disease UK Forum 2008). The (small number of) patients in this forum have mixed reviews regarding the efficacy of the device; it seems that most patients bought the product themselves (sometimes after trying it on loan from a consultant).

Pressure therapy is not included among the list of treatments for Ménière's Disease on the NHS Choices website. The section of Medtronic's website dedicated to the Meniett device refers specifically to the U.S. market, and indicates that the device is mainly a patient purchase and may not be covered by medical insurance. They do not provide information about the global reach of product sales.

## **Have there been investigations into its clinical / cost effectiveness?**

### **Well tolerated by patients?**

The first UK study into the effectiveness of the Meniett device was presented by Buchanan in 2010 (Buchanan, Rai, & Prinsley 2010). Thirty retrospective questionnaires indicated that the device was well tolerated by patients, useful, and minimally invasive. Only 19 of the patients (63%) felt it had alleviated their vertigo and tinnitus.

### **Clinical effectiveness**

Most clinical studies for the Meniett device show positive results regarding vertigo control, though many of these are quite small, or with a short follow up period (Barbara et al. 2001; Densert & Sass 2001; Dornhoffer & King 2008; Huang, Liu, Gao, & Zhou 2009; Thomsen, Sass, Odkvist, & Arlinger 2005). Although many studies found that a (usually small) proportion of patients tested did not respond to the therapy, I have come across none that report negative effects. Although some early trials indicated a significant positive impact on hearing, a recent study by M. Barbara finds this not to be the case (Barbara et al. 2010).

No individual clinical study compares the Meniett device directly with other treatment options.

A Cochrane review to assess the effects of the Meniett device on the symptoms of Ménière's disease is underway but has not yet been published.

### **Cost effectiveness**

I could not find any cost-effectiveness studies relating to the Meniett device, or indeed to any other treatment for Ménière's disease. In 2003 Bjerne published an article relating to the *social* cost of Ménière's disease (Bjerne & Agerberg 2003). Though the treatment was unrelated to the Meniett device, Bjerne showed that the societal cost of Ménière's disease (in terms of time off work) is significant.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

A national survey of UK otolaryngologists regarding the treatment of Ménière's disease was undertaken and presented by Smith in 2005 (Smith, Sankar, & Pfliegerer 2005). Smith concludes that a wide range of medical and surgical management techniques are undertaken, much of which has little or no evidence base. He notes in particular that there is an increasing trend in the use of intratympanic gentamicin, which is now used by two thirds of correspondents, despite only being introduced to UK clinical practice 10 years previously. The Meniett device, and pressure therapy in general, is not mentioned in this report.

In the headroom analysis, the Meniett device was presented as an alternative to surgery (as this was considered the most expensive of the options available to clinicians, and thus the maximum reimbursement opportunity). In the Interventional Procedures Guidance outline document, the specialist advisers consider intratympanic gentamicin (the injection), or placement of the grommet

alone, to be the most pertinent comparators. Changing the baseline comparator to this intervention could have brought the headroom down further.

Studies into the effectiveness of intratympanic gentamicin tend to be very positive, some recent ones being Delgado (Delgado, Rodrigo, & Peña 2011) and Katzennel (Katzenell, Gordon, & Page 2010). A Cochrane review conducted in 2011 concludes that intratympanic gentamicinid is effective (produces significant reduction in vertigo complaints), but that it does carry a risk of hearing loss. I could not find any cost or cost-effectiveness analyses (Pullens & van Benthem 2011).

### **Are there now many direct competitors?**

Given the attention that pressure therapy has received in the literature for many years, the headroom pro forma brought up the possibility of other devices being developed for the same purpose. I have identified one other device that delivers low pressure pulse therapy, and is similar to the Meniett device: the P100-Menièr, by Enttex (Enttex 2011). The manufacturer claims that this manually operated hand-held device works just as well as the Meniett device, but costs a fraction of the price. One clinical trial compares the two devices, and finds that both to be equally successful, and confirms the efficacy of pressure therapy for sufferers of Ménière's disease (Franz & van der Laan 2005). However, the P100 was the preferred device given its significantly lower cost.

In the literature considered by NICE's interventional procedures group, the only device for which evidence was presented was Meniett by Medtronic. This suggests that Meniett is still the dominant technology in the market, or that the P100 has not been around long enough to have undergone many clinical effectiveness studies.

### **Conclusions: How useful might the headroom exercise have been?**

We cannot draw firm conclusions regarding the development decision that would have come out from the headroom analysis had it been undertaken early on in the lifecycle of the Meniett device. What we do know is that the MRP was significantly below the subsequent asking price, even though we took as a comparator the most expensive of treatment options.

Clinical studies exploring the effectiveness of the Meniett device are favourable, but not decidedly more so than other treatment options, including the less expensive injection therapy. According, then, to the headroom framework, the health service should not be willing to pay above this MRP of £1,474, unless:

- 1) Some Meniett benefits were left unquantified.
- 2) Procurement decisions made by the health service are not always strictly rational (in the sense that NICE consider decisions to be rational).
- 3) The device could be used by more than one person, thus boosting the per unit value (though this doesn't seem to be the case, given its impracticality – the NICE IPG document also regards the Meniett device for home use).

However, the Meniett device does not seem to have achieved many sales to the NHS, according to anecdotal evidence on chat forums, the paucity of UK-specific research and trials that have been

undertaken, and the failure of pressure therapy to be mentioned at all in a 2005 national survey of otolaryngologists (although the NHSC briefing indicated that 30 were in use in the NHS in 2003).

Pressure therapy has not been recommended by NICE in a recent interventional procedures guidance document, though this was based on its insufficient clinical support in the literature (quantity of, rather than results). As the IPG group look only at safety and efficacy rather than issues of cost-effectiveness, one would assume that, had the evidence been sufficient to support the therapy from a clinical perspective, then it would have been recommended to clinicians. This puts into question the influence of cost-effectiveness issues on purchase decisions (though simply knowing that a procedure is safe and effective may not guarantee that it will actually be procured and incorporated into routine clinical practice). Unlike TAs, there is no obligation to fund procedures based on a positive IPG.

So, would the headroom exercise have been useful? Results wise, the headroom analysis delivered an unconvincing case for Meniett, which has been followed by poor health service uptake. However, the device is still available for purchase, and seems to be a viable product for Medtronic. This could be for a number of reasons:

- 1) The headroom method, and indeed health economics in general, has difficulty in estimating the value patients and clinicians place on parameters (preferences) that are not directly related to health and health costs, but which *may* indeed affect willingness to buy, and even willingness to pay.
- 2) Given its minimally invasive nature, it is reasonable to assume that this might be something patients are willing to pay for, in order to potentially avoid more destructive means to control their symptoms. Indeed, the Meniett device seems mainly to *be* a patient purchase.

Both of these factors were outlined in the research questions that were identified in the process of the headroom analysis, and this highlights the importance of this section of the pro forma (other issues raised by the research questions also turned out to be pertinent, namely emergent competitors and the use of intratympanic gentamicin in clinical practice). The factors that emerge from sections 6 and 7 of the headroom pro forma should be considered by the developer in conjunction with the concrete number output (MRP), as this could invariably affect the product's uptake and thus its potential as a viable investment. This has come through as the major lesson from this example. Although the not-entirely-convincing headroom was followed by a not-entirely-convincing health service uptake (a positive result for the headroom method itself), separate factors such as the possibility of Meniett being a patient purchase (which was identified in the research questions) have made this a viable, investable product.



## 6. AmpliChip CYP450. Roche Diagnostics Ltd.

<p><b>1. Description</b></p> <p><i>Diagnostic;</i></p> <p><i>New Indication;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: Sep 2007</i></p> <p><i>Time perspective of this report: 2004</i></p>	<p>Tamoxifen is the most commonly used form of hormonal treatment, and is widely used as an adjuvant therapy for patients with early-stage oestrogen receptor positive (ER+) breast cancer. It acts by blocking the tumour's ability to use oestrogen (which provides stimulus to the cancer cells).</p> <p>There is a CYP450 marker gene—CYP2D6—that is thought to influence the rate at which a patient can metabolise tamoxifen (Dehal &amp; Kupfer 1997). Poor metabolisers tend to show poorer clinical outcome in terms of disease recurrence and survival, than do extensive or ultra-rapid metabolisers.</p> <p>The AmpliChip CYP450 is a laboratory array-based prediction test that can detect variations in this gene, and thus identify those breast cancer patients that would not benefit from tamoxifen treatment. The clinical pathway of these poor metabolisers may then be more appropriately managed.</p> <p>The AmpliChip is based on a polymerase chain reaction, and is to be used on the GeneChip microarray platform (from Affymetrix Inc). The test uses whole blood and takes 8 hours.</p>
<p><b>2. Comparator</b></p>	<p>There is no comparator for the AmpliChip device itself, as there is currently no prognostic test for response to tamoxifen (that does not use tumour cells).</p> <p>Five years of tamoxifen represents the standard adjuvant treatment for breast cancer (adjuvant therapy aims to prevent recurrence). However, Aromatase inhibitors (AI) provide an alternative hormonal treatment, which rather than blocking the tumour's ability to use oestrogen as tamoxifen does, actually reduces the amount of oestrogen that the body produces. Three types of AIs have market authorisation in the UK: Anastrozole, Exemestane and Letrozole. They are more expensive than tamoxifen, and are sometimes used after tamoxifen has not been effective (Campos 2004). Where patients are predicted by the AmpliChip to be poor metabolisers of tamoxifen, it may be that AIs are used instead.</p>
<p><b>3. Market size</b></p>	<p>I could not find any estimates in the literature of the number of patients currently treated with tamoxifen who may be poor metabolisers of the drug (not surprising, as there is no routine test currently available to test for this). However this test is proposed to be performed on all users / potential users of tamoxifen. In England and Wales there were 39,214 new cases of breast cancer diagnosed in 2003. Tamoxifen is considered for those 75% of breast cancers that are ER+. This gives a <i>potential</i> market size of up to around 29,500 per year.</p> <p style="text-align: right;"><b>Market size per year: 29,500</b></p>

<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p> <p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>Many clinical studies find tamoxifen to be an effective (Early Breast Cancer Trialists' Collaborative Group 1998) and a cost-effective (Cykert, Phifer, &amp; Hansen 2004;Smith &amp; Hillner 2000) way to reduce breast cancer recurrence and increase survival for breast cancer patients.</p> <p>The hypothesis upon which the worth of the AmpliChip CYP450 is based is that the prognosis of patients determined (by the CYP2D6 gene) to be poor metabolisers is not significantly improved by tamoxifen, and so whose treatment regime should be re-thought.</p> <p>Megestrol acetate used to be the standard second-line treatment after tamoxifen, but this has been replaced by AIs.</p> <p>More recently, attention has turned to AIs and their use as an alternative <i>first line</i> treatment, i.e. instead of tamoxifen. There are many studies which propose that AIs are more <i>effective</i> (costs aside) than tamoxifen (Bonnetterre et al. 2001;Fentiman 2004;Goss &amp; Strasser-Weippl 2004).</p> <p>Yearly costs of tamoxifen and the three AIs are the following:</p> <ul style="list-style-type: none"> <li>-Tamoxifen: £31</li> <li>-Anastrozole: £894</li> <li>-Exemestane: £1,080</li> <li>-Letrozole: £1,084</li> </ul> <p>Some early investigations consider the <i>cost-effectiveness</i> of AIs as a first-line adjuvant treatment versus tamoxifen. A UK-based study finds letrozole to be a cost-effective alternative to tamoxifen as a first-line hormonal therapy with a cost per QALY gained with letrozole between £2,927 and £3,969 (the two authors of this paper are sponsored by Novartis Pharmaceuticals UK, the manufacturers of letrozole) (Karnon &amp; Jones 2003). A cost-utility study of AIs from the perspective of the Italian national health service concludes that anastrozole and letrozole are both cost-effective alternatives to tamoxifen for first-line therapy (Marchetti, Caruggi, &amp; Colombo 2004). A computer simulation study by Hillner estimates that the cost-effectiveness of adjuvant anastrozole is acceptable for patients who are expected to live 12 years or longer (Hillner 2004). Another U.S. study finds that anastrozole compared with tamoxifen produces a higher quality-adjusted time to disease</p>
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	<p>progression, <i>and</i> lower healthcare resource utilisation (due to reduced hospitalisations, chemotherapy, outpatient visits etc.), thus making anastrozole the cost-effective option (Simons, Jones, &amp; Buzdar 2003). Other studies also provide support for AIs as a cost-effective alternative to tamoxifen (Dranitsaris, Verma, &amp; Trudeau 2003).</p> <p>Leaving to one side issues of treatment cost-effectiveness for now — In order to understand and calculate the overall benefit and cost per patient of using the AmpliChip test to personalise chemoprevention, the following information would be required:</p> <ul style="list-style-type: none"> <li>• What proportion of patients is likely to be poor metabolisers, and thus switched to treatment with AI from tamoxifen (all patients would be tested with AmpliChip, but not all will have their treatment changed as a result)?</li> <li>• How many people treated with AI <i>currently</i> are likely to be good metabolisers of tamoxifen, and thus indicated for tamoxifen treatment by AmpliChip (the NHSC briefing indicates that savings could be made in this direction)?</li> <li>• How much worse is the prognosis (in terms of disease recurrence and survival) for poor metabolisers of tamoxifen compared to good metaboliser tamoxifen users? Without knowing this, we don't understand the baseline situation properly (presumably poor metabolisers respond to tamoxifen, just not <i>as well</i> as good metabolisers).</li> </ul> <p>Without this information, we cannot estimate the likely impact of AmpliChip CPY450 on health care costs.</p> <p>Some studies, outlined above, have shown that AIs are more cost-effective than tamoxifen. If this is the case and if this can be proven beyond reasonable doubt, then first-line adjuvant treatment with AI may become routine clinical practice, in which case there would be no need for a test of tamoxifen metabolism. There are two caveats to this:</p> <ol style="list-style-type: none"> <li>1) If poor metabolisers were to be taken out of the cohort of patients receiving tamoxifen (achievable using the AmpliChip), then the (average) perceived effectiveness of tamoxifen may rise. This would change the effectiveness</li> </ol>
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	<p>comparison between tamoxifen and AIs, and perhaps make tamoxifen the more cost-effective option for good metabolisers.</p> <p>2) Tamoxifen has been used for many years for the adjuvant treatment of breast cancer, with proven results. Given this, and the fact it is the much cheaper option, changing clinical practice entirely may be met with some resistance.</p> <p style="text-align: right;"><b>(Total) ΔSC=?</b> <b>(Av. Per person) ΔSC=?</b></p> <p style="text-align: right;"><b>P<sub>1</sub>=?</b></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>The literature provides estimates of the utility experienced by patients receiving hormonal therapy for breast cancer if they are responding to treatment (utility: 0.8) or if their breast cancer is progressing (utility: 0.6) (Marchetti, Caruggi, &amp; Colombo 2004). However, for the same reasons as those bullet pointed above in box 4, we cannot estimate the likely change in patient outcomes if we do not know in what way tamoxifen prescription or effectiveness might change as a result of the AmpliChip. What might also need to be taken into account is the unwillingness of some patients to take tamoxifen due to its potential side effects (Port, Montgomery, Heerdt, &amp; Borgen 2001) (in the United States it has been estimated that as little as 5% of patients eligible for tamoxifen choose to take the therapy, due to fear of side effects (Ozanne &amp; Esserman 2004)). This could potentially be improved by the AmpliChip device, as one study shows tamoxifen self reported side-effects to be related to tamoxifen metabolism (Gallicchio et al. 2004). This could <i>add to</i> the potential rise in overall effectiveness of tamoxifen that may result from removing the poor metabolisers from the cohort of tamoxifen users.</p> <p style="text-align: right;"><b>ΔQALY=?</b> <b>(Av. per person) ΔQALY=?</b></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national</p>	<ul style="list-style-type: none"> <li>[AMBER] When searching the literature I came across some studies that investigate the relationship between gene expression and the benefit of tamoxifen in ER+ breast cancer patients. Bièche et al. find that 7 out of the 27 genes investigated were found in significantly higher levels in ER+ breast tumours than in normal breast tissue (Bièche et al. 2004).</li> </ul>
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<p>objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<p>However, only the NAT1 gene was found to have prognostic significance for relapse free survival, thus a candidate predictor of tamoxifen responsiveness. Another investigation finds the CYP3A gene to be the predominant determinant of tamoxifen metabolism, along with CYP2D6 which has some catalyzing effect (Desta, Ward, Soukhova, &amp; Flockhart 2004). These may call into question whether the CYP2D6 gene in isolation is the most useful predictor of tamoxifen metabolic function.</p> <ul style="list-style-type: none"> <li>• <b>[RED] AIs tend to be supported in the literature.</b> This supports the notion that patients for whom tamoxifen does not work should have their treatment pathway adjusted, and AIs seem like an effective alternative for these patients. However, if it is decided that AIs are definitely the most cost-effective option for patients, then this could curtail the need for a tamoxifen diagnostic test such as AmpliChip.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• No headroom has been calculated here, as not enough information was available in the briefing or the literature upon which to base any meaningful assumptions for costs and health outcomes. The 'developments' section above allows us to articulate how the clinical and research context into which the new device will fit, may have an impact on the feasibility of the new product. The two major issues are:             <ol style="list-style-type: none"> <li>1) Is the CYP2D6 gene the most appropriate marker of tamoxifen response?</li> <li>2) With the growing body of research supporting AIs as the adjuvant therapy of choice, will tamoxifen continue to be prescribed? The developer should bear in mind these factors when deciding whether to proceed with development.</li> </ol> </li> <li>• The AmpliChip CYP450 is based on indirect evidence, that links: a) genotype with tamoxifen metabolism and b) genotype with outcome. In order to prove itself to be a useful test, a <i>direct</i> link between tamoxifen metabolism and outcome must be made.</li> </ul>
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	<ul style="list-style-type: none"> <li>• If it is decided that the case for development is strong enough, the following things need to be investigated in order to provide a sound clinical and economic case for AmpliChip (these are the things I did not know that prohibited a preliminary economic evaluation from being undertaken):             <ol style="list-style-type: none"> <li>1) Around what proportion of patients is likely to be poor metabolisers of tamoxifen?</li> <li>2) How many people treated with AI <i>currently</i>, are likely to be good metabolisers of tamoxifen?</li> <li>3) How much worse is the prognosis (in terms of disease recurrence and survival) for poor metaboliser tamoxifen users compared to good metaboliser tamoxifen users?</li> <li>4) Is the overall effectiveness of tamoxifen likely to rise as a result of AmpliChip's ability to isolate those that are poor metabolisers and direct them to an alternative treatment? If so, would this increase the cost-effectiveness of tamoxifen in relation to AIs?</li> <li>5) What effect might a reduction in side effects have on the cost-effectiveness of tamoxifen?</li> </ol> </li> <li>• The CYP2D6 gene relates not only to the metabolism of tamoxifen, but also other types of drug. This means that potential applications of AmpliChip may extend, into other disease areas. This would clearly have a large impact on the commercial opportunity provided by AmpliChip.</li> </ul>
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## Headroom Notes (AmpliChip)

No headroom calculated. Not enough information to make useful assumptions.

## Follow-up (AmpliChip)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

A headroom analysis in numbers was not achieved for this device. There were too many unknown parameters for any useful assumptions to be made. The process revealed a few key questions and developments in the area that should have been key considerations in the decision to develop.

Of particular importance was the emergence of AIs as the adjuvant treatment of choice for patients with breast cancer. The universal acceptance of this should mean that there would no longer be a

place for tamoxifen in clinical practice, and therefore no need for a pharmacogenetic test for this application.

According to the NHSC briefing, the UK cost of AmpliChip is £200 per test.

Interpretive answer: **Headroom unknown – substantial threats identified (see ‘research questions’)**

### **Has there been a decision made on it by NICE? What was the outcome?**

The AmpliChip was considered for potential technology appraisal by NICE but was rejected by the panel.

There are many NICE guidance documents relating to breast cancer treatments, showing the continual development in the clinical area and its importance to the health service.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

On Roche’s website, the AmpliChip CYP450 test is indicated as providing ‘comprehensive detection of gene variations for the CYP2D6 and CYP2C19 genes’ (Roche 2011) (this second gene was not mentioned in the NHSC briefing, so might be a new addition, or one that is not relevant to tamoxifen specifically). Specific clinical applications are not mentioned, but Roche indicate that these genes play a role in the metabolism of 25% of all prescription drugs.

The NHSC indicate that, by 2007, the AmpliChip was already being used in psychiatry, cardiology, and pain management. Indeed, searching for AmpliChip in the clinical literature returns studies pertaining to psychiatry in greater number than any other clinical indication. Given the diverse countries of origin of research, the AmpliChip seems to have a global reach.

### **Have there been investigations into its clinical / cost effectiveness?**

The changing landscape of hormone therapy prescription was highlighted in the headroom analysis as being of key importance for the feasibility of such a test as AmpliChip. Many early studies indicated that aromatase inhibitors (AIs) are probably a cost-effective alternative to tamoxifen; if this had turned out to be the case and tamoxifen were no longer used as first-line adjuvant therapy for ER+ breast cancer, then there would be limited use for a test that measures the tamoxifen metabolic potential of a patient. A technology appraisal conducted by NICE in November 2006 on hormonal treatments recommended anastrozole, exemestane and letrozole (the three AIs with UK market authorisation) as possible treatments for women with ER+ breast cancer (post-menopausal) (NICE 2006d). Having reviewed the relevant literature and data submitted by the manufacturers, NICE find all three to be cost-effective alternatives to tamoxifen (all had ICERs under £20,000, given the most probable assumptions considered by the experts). They do not, however, suggest that tamoxifen be removed from standard clinical practice.

Ramón y Cajal et al. (2010) find that genotyping patients using the AmpliChip CYP450 according to CYP2D6 variants, is associated with improved disease free survival of those patients (Ramón y Cajal et al. 2010). Serrano et al. also note the relevance of pharmaco-genomics (using the AmpliChip CYP450) for tailoring tamoxifen treatment (Serrano et al. 2011). The use of (measuring) CYP2D6

genetic variants for personalising treatment strategy for breast cancer patients is also supported in a review conducted by Brauch & Jordan (Brauch & Jordan 2009).

A study by Abraham et al. finds that the reported association between CYP2D6 genotype and treatment response in breast cancer may not be valid, according to the results from the case-cohort study examined (Abraham et al. 2010).

As indicated in the headroom pro forma, the AmpliChip is based on indirect evidence that links genotype with tamoxifen metabolism, and genotype with outcome. The MHRA indicate that the evidence linking poor metaboliser genotypes with tamoxifen treatment outcome is mixed and inconclusive, and therefore **do not** recommend genetic testing before treatment with tamoxifen (MHRA 2010). One technology evaluation published in 2008 also say that the hypothesis that CYP2D6 poor metabolisers have reduced tamoxifen metabolism, and have poor outcomes as a *direct* result, is not yet supported by evidence (BlueCross BlueShield Association 2008). A systematic review published in September 2011 on 'The clinical and cost-effectiveness of genotyping for CYP2D6 for the management of women with breast cancer treated with tamoxifen' concludes that the data is limited and conflicting, and it is therefore not possible to recommend pharmacogenetic testing (Fleeman et al. 2011).

### Has the landscape described changed significantly?

#### **What is current gold standard clinical practice now? Has this changed?**

There is still no form of pharmacogenetic predictive testing in standard clinical practice for breast cancer management.

#### **Are there now many direct competitors?**

I have not found any direct competitors in my searches, though the NHSC briefing mentions that another CYP2D6 test is available for research purposes (TaqMan Allelic Discrimination Array from Applied Biosystems).

### Conclusions: How useful might the headroom exercise have been?

The headroom evaluation did not produce any numbers with which to consider the development opportunity. The task did, though, bring to light some important factors for its development case.

Although AIs have been found to be cost-effective, this does not seem to have pushed tamoxifen out of the market, and tamoxifen still seems to be the reference standard of treatment for women with ER+ breast cancer (Fleeman et al. 2011). Although the evidence so far has not been sufficient to allow AmpliChip to be recommended, it is clear that the interest in idea of pharmacogenetic testing remains; this is evident from the substantial body of research that is still being undertaken on this topic.

Something that was also brought up in the research questions was the applicability of the test to other disease areas. It seems that this has turned out to be very important for the success of AmpliChip, given its limited use for breast cancer.



## 7. Agento I.C. Bard Limited.

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Incremental Development;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: Jan 2009</i></p> <p><i>Time perspective of this report: 2005<sup>13</sup></i></p>	<p>Ventilator associated pneumonia (VAP) (a subset of hospital-acquired pneumonia), can occur in patients that require mechanical ventilation in hospital. Mechanical ventilation (MV) is delivered via an endotracheal tube (ETT); when this becomes colonised with bacteria, the patient can breathe these bacteria into their lungs, thus causing VAP which can lead to feverish symptoms and low body temperature (though diagnosis can be difficult). Those patients who receive MV for 24 hours or longer are particularly susceptible to VAP. The presence of the mechanical device inhibits first line defences against such an infection by providing access to the airways for bacteria, and eliminating the cough reflex.</p> <p>The Agento I.C. is a silver-coated ETT, which has been designed to prevent VAP in patients who require prolonged MV (24 hours or more). Silver is widely known for its antimicrobial properties, reducing bacterial adhesion, and blocking biofilm formation (which offers a protective environment for bacteria).</p>
<p><b>2. Comparator</b></p>	<p>The comparator device for the Agento I.C. is a <b>standard ETT</b>. The company estimate that the cost of these range from £1.50 (for those used for short-term use) and £55 (those used in a specialist intensive therapy unit).</p> <p>Other means of preventing VAP include altering body position (semi-recumbent positioning), and oral antiseptics.</p> <p>Silver and its antimicrobial qualities have been researched in other clinical contexts for many years. For example, the use silver for urinary catheters has been found to significantly reduce the adhesion of bacteria that cause urinary tract infections (Ahearn et al. 2000;Gabriel, Sawant, Simmons, &amp; Ahearn 1995). It has also been used to promote healing for burns (Dunn &amp; Edwards-Jones 2004). One study tests ETTs that were internally coated with silver-sulfadiazine and chlorhexidine in polyurethane and used in mechanically ventilated sheep for 24 hours. Compared with those sheep that were intubated with uncoated ETTs, all 8 of which were heavily colonized with bacteria after the 24 hours, those with silver treated ETTs largely showed no growth of bacteria (7 out of 8 – the one remaining showed low growth) (Berra et al. 2004)<sup>14</sup>. Before making assumptions on how the Agento IC might impact the occurrence of VAP, it is appropriate to first identify the incidence and impact of VAP in current clinical practice (where patients are mechanically ventilated using standard ETTs).</p>

<sup>13</sup> For devices that represent an incremental development of an existing model, a two year date back is usually employed. However, having come across a paper relating to the device from 2006, I have chosen 2005 as my reference date.

<sup>14</sup> No company was mentioned in this report, so it is unclear whether this might have been early tests for Bard's ETT or not.

	<p>The incidence of VAP among mechanically ventilated patients is difficult to estimate, given the hazy diagnostic criteria and because it could overlap with other lower respiratory tract infections. The NHSC estimate that it could range between 10% and 30%. The largest and best designed study I have found for VAP incidence and outcome is from 2002 by Rello et al., who present an analysis of VAP from a large U.S. database study (Rello et al. 2002b). The study sample included patients that were admitted to an ICU (not admitted with pneumonia already), and received MV for more than 24 hrs (9,080 patients in all). This seems appropriate as the Agento IC is indicated for use in ICU, for those needing ventilation for 24 hours or more. These were the main findings on interest:</p> <ul style="list-style-type: none"> <li>• VAP developed in 842 patients (9.3%)<sup>15</sup>.</li> <li>• 63.2% of VAP developed within 48hrs; 16% within 48 to 96hrs; 20.8% after 96 hrs</li> <li>• <i>Case-control analysis</i>: There was no statistically significant difference in hospital mortality among patients with and without VAP. (30.5% vs 30.4% respectively). <i>No attributable mortality</i>.</li> <li>• Patients with VAP had significantly longer duration of MV (14.3 ± 15.5 vs 4.7 ± 7.0 days); greater number of ICU days (11.7 ± 11.0 days vs. 5.6 ± 6.1 days); longer hospital length of stay (25.5 ± 22.8 days vs. 14.0 ± 14.6 days)</li> <li>• Mean billed hospital charges: \$104,983 with VAP, \$63,689 without</li> </ul> <p>As this was a case-control analysis, the specific outcomes <i>attributable</i> to VAP could be identified. Other studies report mortality rates for VAP patients at around 30% (Kollef et al. 2005) (the NHSC indicate that estimates range between 24-50%). However, this may be misleading as those needing MV are likely to have relatively poor outcomes and substantial risk of death anyway. Like Rello, Bregeon (Bregeon et al. 2001) also finds VAP <i>not</i> to be an independent risk factor for death, though some others disagree (Kollef, Silver, Murphy, &amp; Trovillion 1995). As such, I will not assume that the Agento IC would have an impact on mortality, though this may be a conservative assumption.</p> <p>Using Rello's estimates, the <i>attributable</i> effect of VAP on some important outcome parameters are: 9.6 addition days of mechanical ventilation, 6.1 additional days in ICU, 11.5 additional days in hospital, leading to a total additional cost per VAP patient of more than \$40,000 to the health service.</p> <p>The properties of silver and its use in other clinical indications to date give reason to believe that the Agento IC could reasonably have a substantial impact on the incidence of VAP. Without knowing the exact potential for VAP avoidance, I will calculate the value of the Agento IC under three scenarios:</p>
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<sup>15</sup> This is the lowest incidence rate that I have come across, but seems to be the most reliable.

	<ol style="list-style-type: none"> <li>1) VAP is completely avoided (unlikely, but represents the upper limit of potential effectiveness)</li> <li>2) VAP burden is reduced by half</li> <li>3) VAP burden is reduced by 25%</li> </ol>
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<b>3. Market size</b>	<p>The NHSC briefing contains an estimate of ICU patients on ventilation in England, Wales and Northern Ireland of 62,000 per year (out of 122,000 admissions to critical care units in total). This estimate was said to be from a source supplied by the company, so I will use this figure.</p> <p style="text-align: right;"><b>Market size per year: 62,000</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>Given the paucity of UK data on costs, I will assume a cost saving per avoided VAP episode of \$40,000. Although this sum was calculated in the context of intensive care units in the U.S., it is the best estimate that I have found. Converted to pounds and inflated to 2005 prices, this represents a cost saving of £31,113<sup>16</sup> (see note (i)).</p> <p>The company estimate that those ETTs used in specialist ICUs cost the NHS £55 per unit.</p> <p>I assume that the Agento IC will be used for all 62,000 patients in critical care that are mechanically ventilated<sup>17</sup>.</p> <p>Given our three scenarios (100%, 50% and 25% reduction in VAP incidence), the impact on service costs are calculated below, using the following information:</p> <ul style="list-style-type: none"> <li>• MV patients per year: 62,000</li> <li>• Incidence of VAP in MV patients ≈ 10%</li> <li>• Additional service cost for VAP: £31,113</li> </ul> <p>1) 100% reduction in VAP:  <math>(62,000 * 10%) * £31,113</math>  <math>= £192,900,600</math></p> <p>2) 50% reduction in VAP:  <math>\frac{1}{2} (62,000 * 10%) * £31,113</math></p>
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<sup>16</sup> Exchange rate (\$1.4497 to the £) obtained from HM Revenue and Customs for Jan 2002 (HM Revenue & Customs 2011). This was then inflated to 2005 prices using HCHS Pay&Prices Index. See note (i) for workings.

<sup>17</sup> It is thought that the Agento IC will be used for those who are ventilated for 24 hours or more. Without having access to the source of this figure, I cannot discern whether this figure corresponds to those ventilated for over 24 hours (the target market indicated by the company, and the situation for which the estimates from Rello pertain), or all those that are ventilated in ICUs for however long.

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>=£96,450,300</p> <p>3) 25% reduction in VAP:  <math>\frac{1}{4} (62,000 * 10%) * £31,113</math>                  =£48,225,150</p> <p>These estimates should be divided by 62,000 to get the value per patient.</p> <p><b>Scenario 1: 100% reduction in VAP</b>                  (Total) ΔSC= £192,900,600                  (Av. Per person) ΔSC= £3,111</p> <p><b>Scenario 2: 50% reduction in VAP</b>                  (Total) ΔSC= £96,450,300                  (Av. Per person) ΔSC= £1,556</p> <p><b>Scenario 3: 25% reduction in VAP</b>                  (Total) ΔSC= £48,225,150                  (Av. Per person) ΔSC= £778</p> <p style="text-align: right;"><b>P<sub>1</sub>= £55</b></p> <p><i>The estimate of cost saving per VAP episode retrieved from Rello et al (Rello et al. 2002b), is thought to contain all relevant costs, and be generally equivalent to what such costs would be in the UK. This estimate should be updated if any more relevant data becomes available.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>The exact impact of VAP on patient health is very difficult to estimate, because the morbidity caused by the underlying illnesses that have led them to be mechanically ventilated is probably high and varies greatly from patient to patient (this is also a reason why the effect of VAP on mortality is difficult to estimate).</p> <p>The only estimate that I have found is from two cost-effectiveness analyses of VAP treatment with linezolid, which use a QALY weighting of 0.92 for patients for the years that follow mechanical ventilation, until death, which they (arbitrarily) reduce by a further 10% ('to be conservative') to get 0.83 (Grau et al. 2005;Shorr, Susla, &amp; Kollef 2004). Having traced the source of the 0.92 figure, the basis of this does not seem reliable as the study actually</p>
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	<p>relates to mechanical ventilation of those admitted for acute respiratory failure due to pneumonia (or acute respiratory distress syndrome) in the first place, and this comes from a 6 month follow up survey, and seems to simply assume that all patients were in perfect health (QoL weighting of 1) at baseline (Hamel et al. 2000).</p> <p>We would ideally like an estimate of the QoL loss experienced by patients in those days in hospital during which they were suffering from VAP.</p> <p>One study that considers the cost-effectiveness of pneumococcal conjugate vaccination in England and Wales uses a QALY loss of 0.006 per inpatient pneumonia episode (not VAP specifically) (Melegaro &amp; Edmunds 2004). Tracing the source of this estimate brings up a cost-effectiveness study for the pneumococcal vaccine in US navy and marine corps by Vold Pepper and Owens (Vold Pepper &amp; Owens 2000). Because the literature at the time (2000) did not include any assessments of utility for (hospitalised) pneumonia, they estimate this on the basis of comparisons with other health states, at 0.85 (utility loss of 0.15). Although the baseline for mechanically ventilated patients is likely to be well below 1 (full health), we can use this utility loss of 0.15 during the VAP episode to estimate the likely QALY loss of patients experiencing VAP whilst being mechanically ventilated, versus those not acquiring VAP.</p> <p>Patients experiencing VAP on average spend an additional 11.5 days in hospital compared with non-VAP mechanically ventilated controls (Rello et al. 2002b). If these extra days (due to VAP) are experienced in a utility state that is 0.15 lower than their non-VAP counterparts, then that would lead to a QALY loss of 0.005 per VAP patient (<math>0.15 * 0.035</math> years).</p> <p>In other words, there would be a gain of 0.005 QALYS per avoided VAP patient (as per cost estimations, the three scenarios consider an incidence rate of 0%, 5% and 7.5%).</p> <p><b>Scenario 1: 100% reduction in VAP</b></p> <p style="text-align: right;"><b>ΔQALY= 31</b> <b>(Av. per person) ΔQALY= 0.0005</b></p>
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<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p><b>Scenario 2: 50% reduction in VAP</b>  <math>\Delta QALY=15.5</math>  <b>(Av. per person) <math>\Delta QALY= 0.00025</math></b></p> <p><b>Scenario 3: 25% reduction in VAP</b>  <math>\Delta QALY= 7.75</math>  <b>(Av. per person) <math>\Delta QALY= 0.000125</math></b></p> <p><i>This estimate should be revised if any quality of life data pertaining to VAP specifically, and based on actual clinical investigation come to light.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [GREEN] Hospital acquired infections have and continue to be recognised as important contributors to patient and service costs, and therefore measures to reduce such infections will be well received and are likely to be viewed as a priority.</li> <li>• [AMBER] There has been lots of research undertaken to investigate the factors and actions that can reduce VAP incidence (e.g. semi-recumbent positioning of patients in their beds, use of antibiotics, etc) (Dodek et al. 2004; Kollef 2004). Putting all these into place may improve baseline management of VAP, and thus reduce the potential impact of the Agento IC. For example, one study considered the effect of an educational initiative which involved a self-study module for ICU nurses and respiratory care practitioners on risk factors and prevention strategies for VAP. Fact sheets and posters were posted across ICU to reinforce the information. Across the four hospitals in the study, the combined VAP incidence dropped by 46% following the intervention (Babcock et al. 2004).</li> <li>• [GREEN] The Agento IC represents a straightforward and easy way to reduce VAP in mechanically ventilated patients. Rello (Rello et al. 2002a), in a survey based study of international experts, investigated <i>why</i> physicians do not follow evidence-based guidelines for the prevention of VAP; he found a non adherence rate of 37%. The most common reasons were disagreement with interpretation of clinical trials, inavailability of resources, and</li> </ul>
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	costs. He found that nonadherence was largely uninfluenced by degree of evidence (Rello et al. 2002a). The Agento IC would be an easy way to improve outcomes, without changing clinician behaviour (which seems to be a particular stumbling point in this area).
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>• The majority assumptions on the current state of affairs for VAP incidence, outcome, and cost, come from one American study. These should be revised and updated if more relevant (UK?) data comes to light.</li> <li>• The market size of 62,000 may overestimate the market for Agento IC, as it is not known what proportion of these are mechanically ventilated for 24 hours or over.</li> <li>• Currently, research has shown that the recommendations in place for reducing VAP are not very well implemented. Over time, this may improve. The result of this on the baseline situation should be monitored (i.e. if uptake improves, then the relative impact of the Agento IC may become smaller).</li> <li>• Research must be undertaken to ascertain the likely impact of Agento IC on VAP incidence.</li> </ul>
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### Notes by AC

- (i) The cost saving of \$40,000 needed to be converted into pound sterling, and then inflated to 2005 prices  
 Exchange rate Jan 2002 (HM Revenue & Customs 2011): \$1.4497 to the £ ≈ £27,600

$$\begin{aligned} \text{HCHS P\&P Index Inflation rate} &= \text{P\&P Index (present year)} \div \text{P\&P Index (year of cost data)} \\ &= 240.9/213.7 \\ &= 1.127 \end{aligned}$$

$$£27,600 * 1.127 = £31,113$$

### Headroom Notes (Agento I.C)

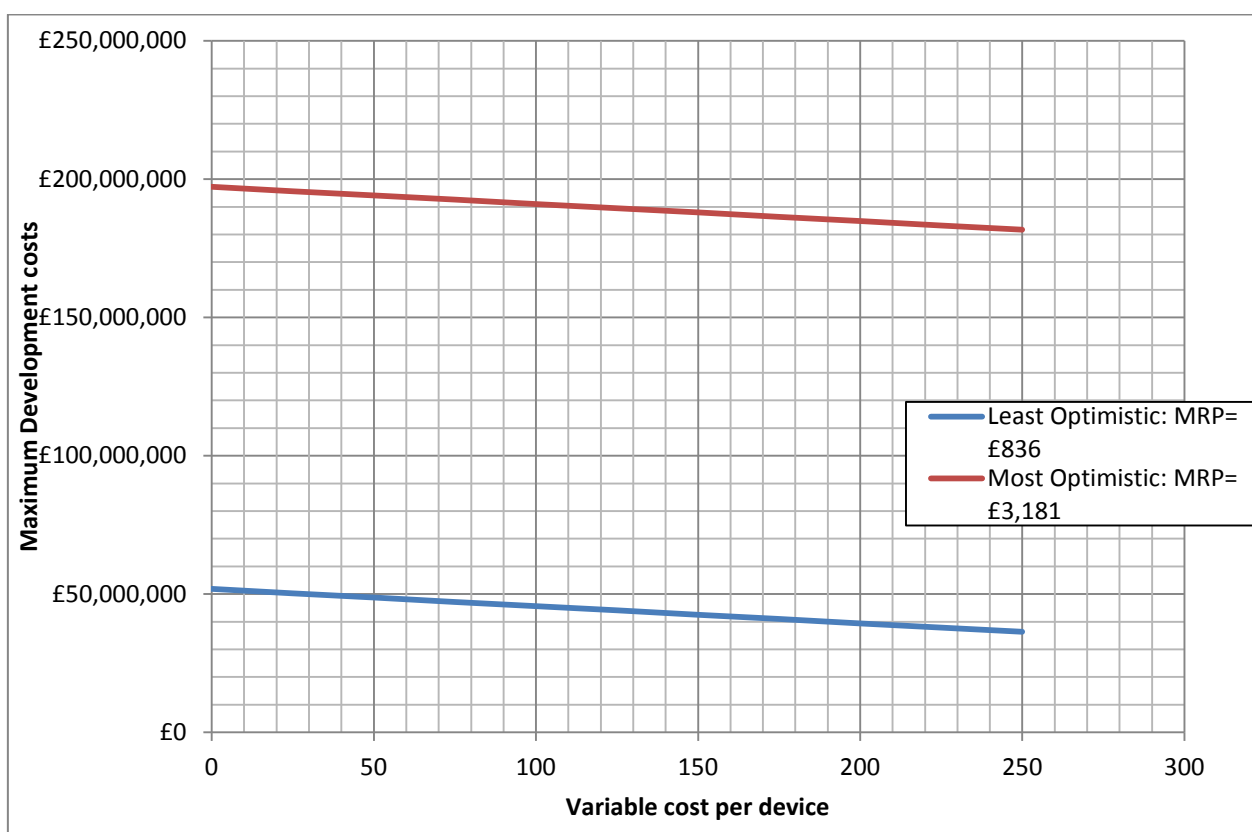
	MRP	
	WTP: £20,000	WTP: £30,000
100% reduction in VAP	£3,176	£3,181
50% reduction in VAP	£1,616	£1,619
25% reduction in VAP	£836	£837

## Retrospective case studies: 7. Agento IC

In this case, I was able to estimate both the impact on service costs of the Agento IC as well as the potential impact on patient quality of life; this has allowed me to calculate an MRP for the Agento IC, given the assumptions specified.

These 'assumptions' cover a wide spectrum of effectiveness for the Agento IC, ranging from a 25% reduction of VAP incidence for mechanically ventilated patients, to a 100% reduction in VAP incidence (VAP eliminated). It is likely that the developer would pin-point a more precise estimate of potential effectiveness, based on their expertise in the area. However, the MRPs estimated range from £836 (25% reduction in VAP; NHS WTP £20,000) to £3,176 (100% reduction in VAP; NHS WTP £30,000). It is likely that the developer would have made assumptions that would result in an MRP between these two prices.

In order to practically consider whether this represents sufficient potential to warrant development, the trade-off between development costs and variable costs for both the least and most optimistic scenarios are presented;



Because of the low variable costs chosen (relative to MRP), the large development costs do not vary a great deal in response to changes in these variable costs. These are of course speculative, and simply aim to demonstrate the likely magnitude of return at different variable costs. This is based on the assumption that the Agento IC would be used on 62,000 mechanically ventilated patients. As indicated in the headroom pro forma, this may be an overestimation of the market. It also assumes that all development costs are recovered within a year.



## Follow-up (Agento IC)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The estimated MRP for the Agento IC lay somewhere between £836 and £3,181 (a large difference, that reflects my uncertainty of potential product performance. If the product were to cost below £836 to produce then, so long as the unit cost for production was not at the very top of this range, the investment opportunity for this product is likely to have been considered attractive. The headroom analysis estimated the allowable development costs for given variable costs, and these ranged a great deal depending on how optimistic we are about the potential effectiveness; if the Agento IC were to cost £100 to make, maximum allowable development costs would be between £45 million and £190 million. This seems large considering that it incrementally develops a current medical device. Profit prospects would therefore be large.

The actual price for the Agento IC has been difficult to obtain. However, I did find one American website (Great Medical Supplies 2011) which prices a box of 10 at \$2,201, indicating a price per device of about \$220—around £145 (it may well be that prices charged to a health service would be somewhat lower than the price charged online). A 2009 publication that considers the cost-effectiveness of silver coated endotracheal tubes considers the device to cost \$90 in their model, the source of which is stated to be “an assumption” (Shorr, Zilberberg, & Kollef 2009). Despite the fact that neither of these sources provides confidence in the exact price of the Agento IC, they indicate that the device seems to have been priced well below our most pessimistic scenario for the headroom analysis, of £836.

Interpretive answer: **Headroom positive**

#### **Has there been a decision made on it by NICE? What was the outcome?**

No NICE guidance has been issued in the Agento IC. NICE did produce a patient safety guidance document in 2008 for ventilator associated pneumonia, but alternative ETTs were not mentioned in the guidance (this would have been pre launch in the UK) (NICE National Patient Safety Agency 2008).

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

Bard received clearance from the US Food and Drug Administration to market the Agento IC in November 2007 (BARD 2007). The Agento IC and its launch in the USA is reported in its 2008 annual report, but in no subsequent annual reports (C.R.Bard Inc. 2008). The NHSC briefing indicated that the device was expected to receive CE marking by mid-2009, but I haven't been able to find evidence of this. Additionally, Bard do not seem to be in the list of brands for endotracheal tubes on the NHS product supply chain catalogue. Research and trials that I have identified for the device seem mainly to be based in the U.S., but I have also come across Spain as a site for clinical trials. The Bard customer services team confirmed by telephone that the Agento I.C. is not sold in the UK.

## Have there been investigations into its clinical / cost effectiveness?

### Clinical effectiveness

Some early studies that considered the effect of Agento IC on bacteria colonization of an ETT reported favourable results (Rello et al. 2006).

The biggest and most cited clinical trial has been the North American Silver-Coated Endotracheal Tubes trial (NASCENT), the results of which were published in 2008 (Kollef et al. 2008). This RCT was conducted in 54 centres of North America, and included 9,417 patients screened between 2002 and 2006 (this indicates that my headroom perspective date of 2005 was too late and that BARD would actually have conducted such an early economic evaluation before 2002). They found that the silver-coated ETT was associated with a 36% relative risk reduction in VAP (4.8% versus 7.9%), but no statistically significant impact on hospital / ICU stay, duration of intubation, or mortality was found.

Bard uses the findings from this trial in their product information literature, citing the fact that the Agento IC reduces the incidence of VAP by 36% (48% risk reduction within 10 days of intubation) (BARD Medical Division 2008).

A protocol has been written for a Cochrane review of effectiveness studies for the silver-coated endotracheal tube, but this has not yet been published. I did not find any estimates of quality of life associated with VAP.

### Cost effectiveness

In 2009, Shorr et al. produced a cost-effectiveness analysis for the Agento IC (Shorr, Zilberberg, & Kollef 2009). They use the findings of the NASCENT trial to model the effectiveness of the device, but use cost saving estimates from another study (Warren et al. 2003). Indeed, the NASCENT trial found no statistically significant impact of the Agento IC on hospital length of stay, whereas the cost saving figures from the study used (Warren et al. 2003) base the attributable cost of VAP on reductions in length of hospital stay; there is some contradiction here. Shorr's cost-effectiveness study uses the 'assumption' that the Agento IC costs \$90, and that a normal ETT costs \$2 (based on 'expert opinion'). The assumed marginal VAP cost is \$16,620, and the break-even cost of the Agento IC was found to be \$388.

In response to a 'letter to the editor' in JAMA, the author of the NASCENT trial paper, Kollef, discusses the reasons for the statistically insignificant impact on hospital stay, and proposes that it is due to the lower than expected incidence of VAP (around half of most other published estimations) (Kollef 2008). He goes on to present a break-even cost (from a healthcare perspective) for the Agento IC using, like Shorr, the cost of VAP from another study (\$25,072); the break-even cost estimated is \$678.

### My assumptions

We can see just from these two cost-effectiveness studies (which base their effectiveness estimates on the same trial) that there is a very wide spectrum of costs presented in the literature for VAP, which would present a very different value for the Agento IC. The attributable cost of VAP that I

found and used for the headroom calculation (\$40,000 per case) was much higher than other estimates I have found since. Unsurprisingly, this relatively high estimate of attributable VAP cost is that which the company itself now also uses in the Agento IC product information. *Since* completing the headroom analysis, I have come across one cost of illness study that was published in 2003 (so which could have been considered when completing the pro forma using the time perspective taken), which produces a much lower estimate of cost attributable to VAP. After adjusting for severity of illness, Warren (Warren et al. 2003) finds an incremental cost per VAP episode of just \$11,897. If I had used this estimate instead, the headroom would have been reduced by about 70%.

I assumed an incidence of 10% of mechanically ventilated patients. One UK estimate of incidence for an intensive care unit in Sheffield was 18% for all mechanically ventilated admissions, indicating that I may have underestimated this parameter (Lwin A, Temple A, & Heap M 2008). Though the incidence level reported in the NASCENT trial is quite low (7.9% at baseline), other sources tend to report incidence rates at around the 15% mark.

Additionally, I used the price of a standard ETT estimated by the company and reported in the NHSC briefing of £55. In one cost-effectiveness study, a \$2 ETT price is used, based on 'expert opinion' (Shorr, Zilberberg, & Kollef 2009).

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

Initiatives to reduce the time that patients spend with mechanical ventilation are being implemented across the health service with varying degrees of success (Blackwood et al. 2010). These measures are increasingly prioritised; VAP is a large contributor to healthcare acquired infection in the NHS.

Evidence-based research has progressed in this area, and the 'bundling' of care practices known to reduce the risk of VAP has been found to decrease its incidence (O'Keefe-McCarthy, Santiago, & Lau 2008). However, there is substantial variation in VAP prevention strategies across the UK (NICE National Patient Safety Agency 2008).

NICE have issued a patient safety solutions document for VAP recommending that patients should be positioned with their upper body elevated, and that oral antiseptics should be included as part of the oral hygiene regimen for patients receiving mechanical ventilation (NICE National Patient Safety Agency 2008).

The diagnosis and management of VAP in the UK in 2007 is summarised in a paper by Hunter et al (Hunter, Annadurai, & Rothwell 2007). They report widespread variation in diagnosis methods, and over utilization of antibiotics.

Torres et al write a special article on 'Defining treating and preventing hospital acquired pneumonia: European perspective' (Torres A, Ewig S, Lode H, & Carlet J 2009). They provide a table of recommended measures for prevention of VAP, according to what experts in Europe believe to be best practice. Silver-coated endotracheal tubes are among the 'additional measures which might be

helpful in distinct settings and populations'. This report was produced in 2009 (CE marking for the Agento IC was said in the NHSC briefing to be expected mid 2009).

### **Are there now many direct competitors?**

I have not come across any direct competitor to the Agento IC; all trials / published articles for silver-coated endotracheal tubes, where the company or product has been mentioned, have all been in reference to Bard's Agento IC.

## **Conclusions: How useful might the headroom exercise have been?**

The headroom calculated for the Agento IC was very high, and is likely to have indicated a positive development decision. By presenting its value to the health service under various levels of effectiveness, we were able to examine the impact this would have on MRP. Even at the lowest effectiveness estimate of 25%, the investment proposition still looked attractive (the actual effectiveness of the Agento IC found in clinical trials is higher than this). It is clear from the wide spectrum of cost estimations that VAP is a particularly difficult disease to accurately monitor and review in clinical trials, probably due to diagnostic difficulties. Such challenges in trial design are outlined by Niederman (Niederman 2010). Although subsequent estimates in the literature on the cost-effectiveness of the Agento IC have been more modest than that estimated in the headroom analysis, they have still shown that the Agento IC is likely to represent a cost-effective purchase.

Although the headroom method indicated that the Agento IC would generate substantial value to the health service, and the more recent literature also indicates that the Agento IC is cost-effective, the *purpose* of the headroom method is to estimate future cost-effectiveness in order to present the opportunity for *uptake*.

The Agento IC is not sold in the UK. Without knowing why, this makes drawing conclusions about the usefulness of such an exercise difficult. The 'developments' in the clinical context identified in the pro forma and the research questions articulated may have been useful. The method's use to demonstrate the value of the Agento IC at various levels of effectiveness may also have been helpful.

## 8. Cooling Cap. *Olympic Medical Corp.*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>New Indication;</i></p> <p><i>Follow up NICE IPG 347.</i></p> <p><i>Date of briefing: Dec 2000</i></p> <p><i>Time perspective of this report: 1997</i></p>	<p>Perinatal asphyxia is the deprivation of oxygen to a newborn baby, usually resulting from an interference with blood flow to an infant’s brain during delivery. It can be caused by placenta issues, maternal blood pressure, uterine rupture or umbilical cord complications. Hypoxic damage (damage resulting from deprivation of oxygen) can affect most organs in the infant, but the most common and serious risk is brain damage (hypoxic-ischaemic brain damage). Neonatal encephalopathy is another clinical term associated with this condition. It is estimated that about two in every thousand babies born in England will have some degree of asphyxia (Volpe 1995) (the incidence rises dramatically in preterm neonates).</p> <p>Perinatal asphyxia is a significant cause of infant death and impairment of neurological development; it is the cause of about 20% of all cerebral palsy cases (Patel &amp; Edwards 1997). Other outcomes include mental retardation, learning disability and epilepsy (Vannucci 1990).</p> <p>The Olympic Medical Corp ‘cooling cap’, which is to be initiated within 6 hours of birth and for up to 48 hours, aims to bring down the baby’s core brain temperature in an effort to prevent continuing damage to the brain cells and their environment. Although (whole body) cooling is not systematically used in clinical practice, it has been found to have a positive impact on cerebral outcome in newborn animals. The cooling cap provides focal cooling on the baby’s head, and is the first commercial product for neonatal cooling.</p> <p>The cooling cap will be used for neonates believed to have hypoxic-ischemic brain damage, but this can be difficult to determine. Certain indicators are thought to help determine the outcome. Some frequently used indicators have been found to be non-specific, for example obstetric information and clinical examination. Simple electroencephalographic methods (EEG), magnetic resonance spectroscopy and MRI can have positive predictive values when used soon after birth (Patel &amp; Edwards 1997). One study finds EEG to have excellent sensitivity (94.7%) but a less satisfactory specificity (68.4%) (Selton &amp; André 1997). The NHSC briefing indicates that an aEEG device (amplitude integrated EEG), which is a cerebral function monitor, would be used to screen for eligibility for treatment with the cooling cap. Although this will play a role in the overall pathway change from introducing the cooling cap into clinical practice, I will consider this to be external to this particular analysis, and simply assume that it does the job for which it is intended correctly.</p>
<p><b>2. Comparator</b></p>	<p>The NHSC briefing indicates that there is no comparator treatment for the prevention of birth asphyxia leading to permanent damage, or the treatment of hypoxic brain damage; they indicate that so far other techniques have proved unsuccessful.</p> <p>Indeed, a 1990 review of current management strategies for perinatal</p>

	<p>hypoxic-ischaemic encephalopathy reported that these ranged from no therapy at all, to the extensive use of a variety of medications to treat brain swelling, such as fluid restriction, sedation, hyperventilation, and others (Vannucci 1990). There is no uniform standard of care, and inappropriate drugs are often prescribed. Seven years later, the situation remains largely the same. An article by the same author but written in 1997 indicates that, one by one, drugs that appeared promising have been discarded, such that ‘no agent has proven useful to ameliorate perinatal hypoxic-ischaemic brain damage in the clinical setting’ (Vannucci &amp; Perlman 1997).</p> <p>Vannucci and Perlman estimate that approximately 15-20% of asphyxiated infants who exhibit hypoxic-ischaemic encephalopathy die (during the newborn period), and 25% of survivors will exhibit permanent neurological deficits (Vannucci &amp; Perlman 1997).</p> <p>The cooling cap does not symbolise a revolutionary new clinical method; the significance of brain temperature has long been recognised to influence the outcome of cerebral ischaemia. For example, experiments on rats have shown that cooling of the brain by just a few degrees has a protective effect against brain damage after transient ischaemia (stroke) (Busto et al. 1987). Similarly, outcomes of brain cooling in rats have been tested after experimental traumatic brain injury; mortality was significantly reduced in those cooled to 30 degrees C, and long-term behavioural defects were also reduced (Clifton et al. 1991). Induced hyperthermia of the brain (raising the temperature by as little as one or two degrees) has been found to have the opposite effect, accentuating brain damage (Vannucci &amp; Perlman 1997). The use of systemic cooling in patients undergoing heart surgery has long been recognised and employed to protect their brains from ischaemic damage (Greeley, Ungerleider, Smith, &amp; Reves 1989; Vannucci &amp; Perlman 1997). So, the relationship between brain temperature and outcomes is well supported in the literature.</p> <p>Hypoxic-ischaemic brain damage in relation to perinatal asphyxia <i>specifically</i> has also been investigated in early experiments on animals. Induced hypothermia has been found to reduce brain damage in newly born rats (Yager, Towfighi, &amp; Vannucci 1993; Young, Olenginski, Yagel, &amp; Towfighi 1983) and pigs (Laptook et al. 1994). Additionally, <i>focal</i> cooling of the head has been found to be effective in rats (Towfighi et al. 1994) and sheep (Gunn et al. 1997). One study has shown that brain temperature measured in newborn babies is related to level of brain injury in that baby (Simbruner, Nanz, Fleischhacker, &amp; Derganc 1994).</p> <p>The NHSC briefing does not indicate that the cooling cap would be more effective than whole body cooling (with cold air or a cooling mattress— which would probably be cheaper). However, we do know that whole body cooling is not part of standard clinical practice at this time. Also, it could be assumed that selective head cooling would reduce the adverse</p>
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	<p>effects of hypothermia for babies<sup>18</sup>.</p> <p>Without having found any effect estimates of infant cooling on neurological outcome, I do not know the degree to which this could affect death / impairment. However, the long term costs and morbidity of hypoxic ischaemia are so high that any improvement in outcome for those babies is likely to have a high value to the NHS. This is discussed further below.</p>
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<p><b>3. Market size</b></p>	<p>Asphyxia affects about two in every one thousand babies born in England every year. This equates to around 1,200 babies (out of 600,000 born in England per year). In the NHSC briefing, it is indicated that all 1,200 would probably be eligible for aEEG screening, and out of these an estimated 600 babies may benefit from treatment with the cooling cap.</p> <p style="text-align: right;"><b>Market size per year (NHS England): 600</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>The cost to the NHS of hypoxic-ischaemic brain damage as a result of birth asphyxia is likely to be huge, though I have not found a direct estimate. Cerebral Palsy, a potential outcome for babies that suffer from perinatal asphyxia, is thought to cost \$503,000 per new case (based on 1992 U.S. data, which includes both direct medical costs and indirect costs such as specialist education services and lost productivity) (Centers for Disease Control and Prevention (CDC) 1995).</p> <p>Additionally, brain injury following birth asphyxia is a common cause of litigation (Goldsmith 1989); lawsuits taken out against the hospital often result in very large financial settlements. These can cost the NHS millions of pounds per case.</p> <p>The likely health service impact of avoiding even a small percentage of hypoxic-ischaemic brain damage in newborns would be difficult to quantify but must be very large. Savings are likely to be seen in medical costs of treatment, nursing care, physiotherapy, transportation, and the provision of many other services, as well as pay-outs following court cases for perinatal asphyxia that resulted from mistakes made by clinicians.</p>
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<sup>18</sup> One study conducted in 1978 on the effectiveness of neonatal transport found that those babies that arrived in hospital with a core temperature of below the optimal (36 to 37 degrees C) had a significantly higher mortality rate (Gunn & Outerbridge 1978).

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p><i>The cost of brain injury to families and social care services is huge. The impact of childhood brain damage on parents' work and family finances was investigated in one paper; trouble maintaining regular work schedules, and resulting financial problems were a big problem for families with children suffering brain injuries (Osberg et al. 1997).</i></p> <p style="text-align: right;"> <b>(Total) ΔSC=</b>  <b>(Av. Per person) ΔSC=</b>    <b>P<sub>1</sub>=</b> </p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>As well as the substantial health service costs of hypoxic-ischaemic brain damage, the QALY loss to the infant can be huge.</p> <p>Birth asphyxia is a major cause of neonatal mortality; a recent study conducted in India found a neonatal mortality among asphyxiated neonates of 24.7%, which was 35 times that of the non-asphyxiated population (Paul, Singh, Sundaram, &amp; Deorari 1997).</p> <p>The adverse QoL outcomes of neonatal encephalopathy are widespread. A retrospective cohort study in the Oxford Regional Health Authority found that children with cerebral palsy at age 5 who have the condition as a result of neonatal encephalopathy were more likely to have developed spastic quadriplegia, have visual impairment and to be non-walking compared to those without neonatal encephalopathy (Gaffney et al. 1994). Another study finds subtle learning differences (particularly in auditory pathway, attention, and short-term recall) in school children who had moderate hypoxic-ischemic encephalopathy at birth versus the mild encephalopathy group (Robertson &amp; Finer 1993).</p> <p>An intervention that could reduce the incidence of hypoxic-ischaemic brain damage and thus reduce the incidence (or degree) of cerebral palsy, mental retardation, and neonatal death that can follow, would be highly regarded and would likely incite a very high willingness to pay (especially as the patients in question are babies, with all of their 'life years' ahead of them).</p> <p style="text-align: right;"> <b>ΔQALY=</b>  <b>(Av. per person) ΔQALY=</b> </p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[AMBER]</b> Cooling as a way to reduce neurological damage is not a new idea, though this is the first commercialisation of such a technique. Research into the effect of cooling on neurological damage has used other means to reduce the core brain temperature. Some experiments tested selective head cooling, using a tube coiled around the head of an animal with cold water running through it. Therefore, even if proven effective, there are other ways to achieve perform cooling, and that other products could be developed.</li> <li>• <b>[RED]</b> Whole body cooling may be as effective in reducing core brain temperature, and is likely to be cheap to perform.</li> <li>• <b>[GREEN]</b> As indicated by the overview of literature supporting cooling methods, the technique and its clinical benefit is recognised. Whole body cooling is apparently an effective way to bring down core brain temperature. Why, then, has it not been brought into clinical practice already? It may be that the development of a specific product for this indication is what it needed in order for it to be integrated into clinical practice across the NHS.</li> <li>• <b>[AMBER]</b> Other possible treatments for hypoxic-ischaemic brain damage are under investigation. Some pharmacologic agents which are under experimental investigation are: oxygen-free radical inhibitors and scavengers, excitatory amino acid antagonists, calcium channel blockers, inhibitors of nitric oxide production, monosialogangliosides, glucocorticosteroids, and combination therapy. Nonpharmacologic interventions under investigation (aside from induced hypothermia) include hyperglycemia, carbon dioxide and hypoxic preconditioning (Vannucci &amp; Perlman 1997). If any of these are found to be effective, they could alter the incremental effectiveness of the cooling cap which, at this time, is being compared to <i>no treatment</i>.</li> <li>• <b>[GREEN]</b> There is likely to be strong societal pressure for the introduction of technologies that can save the lives / improve the outcome of babies at risk of brain damage.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>• Given the fact that cooling is an established technique, the potential of the cooling cap for perinatal asphyxia as a viable medical device and commercial opportunity could hinge on the following:             <ol style="list-style-type: none"> <li>1) Are other products for the same purpose being developed?</li> <li>2) Is this commercial product a sensible / attractive alternative to non-commercial cooling? What is the price differential likely to be?</li> </ol> </li> <li>• If the cooling cap is found to have the same effect on core brain temperature as whole body cooling, what are the benefits of selective head cooling? To what extent does induced hypothermia present a risk to newborns? (Anecdotal evidence presented above suggests that small reductions in a newborn’s body temperature can have an impact on mortality).</li> <li>• How many devices would be required per hospital? It may be that 600 cases per year would require the cooling cap, but how many would need to be purchased in order to ensure adequate coverage?</li> <li>• How much would the aEEG testing cost for those estimated 1200 babies per year who are likely to need the screen if this were to become common practice?</li> </ul>
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### Headroom Notes (Cooling Cap)

Given the lack of current (clinically proven) alternatives for newborns with hypoxic-ischaemic brain damage, the cooling cap seems to be a ‘no brainer’ from a headroom perspective (its potential health economic case is clear, if it works as we think it will and if our comparator (no treatment) does not change). The potential impact of perinatal asphyxia on outcomes and costs makes this case seem obvious, without having to articulate the numerical value of this (which the literature does not supply readily). A long term view will need to be taken to realise the full value of such a product.

The literature indicates that it will work, but the pertinent question is whether it works better than whole body cooling which, whilst not currently part of standard clinical practice, may offer a cheap easy way to realise the same therapeutic benefit. This must be a key consideration when deciding whether to develop the product, as if it is thought that whole body cooling *could* feasibly become part of routine clinical practice, then the cooling cap must prove to work better than this (or be cheaper- which is unlikely). Alternatively, the company would have to have some confidence in the fact that by selectively cooling the head only, outcomes for the baby would be improved or the risks reduced.

If a headroom were to be calculated in the future, the number of cooling caps needed to cover all those babies at risk would need to be considered, as well as the longevity of the device. The likely market share should also be considered given the likelihood that other means of cooling may also have a place in clinical practice.

## Follow-up (Cooling Cap)

### Headroom Outcome and Market success

#### Does the MRP look realistic? Would it have indicated yes or no to development?

As indicated in the headroom notes, the (unquantified) MRP for the Cool-Cap (now its official name) would have been very high. The indications in the literature of potential effectiveness were very positive. The associated costs, morbidity, and mortality associated with hypoxic-ischaemic brain damage due to perinatal asphyxia are large, meaning that the value of this device would be high.

This was based on the assumption that:

- 1) The strong body of research into cooling as a way to reduce / prevent brain damage would translate into favourable effectiveness results for the Cool-Cap.
- 2) The comparator, which in 1997 was 'no treatment', would remain so. It was identified that whole-body cooling using mattresses or cool air may achieve similar results, and if this was found to be more acceptable / affordable than the Cool-Cap, then the business case could be at risk. The two caveats to this are that:
  - a. Selective head cooling could reduce the risk to the baby posed by hypothermia, by achieving a reduction in core brain temperature without subjecting the rest of the body to low temperatures.
  - b. A concrete device designed specifically for this indication may be what is needed to raise the profile of therapeutic cooling, and clinicians may prefer the Cool-Cap to other methods of cooling

Although I have been unable to find the actual price of Cool-Cap, I feel that, from a headroom perspective, this was a 'no brainer', but the decision should have been made with consideration of the 'developments' and 'research questions' presented.

Interpretive answer: **Headroom positive**

#### Has there been a decision made on it by NICE? What was the outcome?

In 2007, 'Whole body cooling for the treatment of neonatal hypoxic ischaemic encephalopathy' was considered by the Interventional Procedures team but deemed 'Not In Remit' as it was not an interventional procedure. Three years later in 2010 NICE produced IPG347 on 'Therapeutic hypothermia with intracorporeal temperature monitoring for hypoxic perinatal brain injury: guidance' (presumably overcoming the remit issue by describing the way in which temperature is monitored) (NICE 2010c). NICE pronounce that current evidence on the safety and efficacy of

therapeutic hypothermia is adequate to support its use in the NHS. They go on to briefly present the evidence from the literature of decreased mortality following cooling as well as reduced incidence and severity of neurodevelopmental disability. They describe hypothermia to usually be induced by cooling the whole body with a blanket or mattress or sometimes by cooling the head only with a purpose-made cap. Having looked through the sources of evidence used, those considering a cooling cap refer exclusively to the Olympic Cool-Cap.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

The Olympic Cool-cap received FDA approval in December 2006 (FDA 2006b); Olympic Medical Corp. was merged into Natus Medical Inc. in December 2007 (both American companies) (Bloomberg 2008). Although information provided on their website is focused toward an American audience, the Cool-Cap is used within the NHS (though it is not clear to what extent). There have been many clinical trials testing cooling methods (see next section). A study from 2009 looking at how cooling is managed in the UK *outside* of clinical trials follows hospitals that had been involved in the TOBY trial (Total Body Hypothermia for Neonatal Encephalopathy trial); a few of these infants were treated with the Cool-Cap (Azzopardi et al. 2009b).

Considering the positive trial results, and the fact that improving the outcomes of babies at risk of long-term brain damage (and death) is a poignant issue, there has unsurprisingly been a lot of press and media coverage on this issue (Kaiser 2004;One True Media 2011;VanderbiltHealthNews 2011). The British media specifically have also reported on the big potential impact of cooling, with headlines like 'Cooling cuts baby brain damage' (Walsh 2009), 'Cooling "cure" averts infant brain damage' (Laurance 2009), 'Cooling babies could reduce brain damage' (Alleyne 2009) and 'Cold cuts baby brain damage' (NHS Choices 2009).

Clinical trials for the device are international in location, suggesting a global reach.

### **Have there been investigations into its clinical / cost effectiveness?**

#### *Clinical effectiveness*

There have been many clinical trials for the use of cooling in human neonates with perinatal asphyxia and suspicion of hypoxic-ischaemic brain damage since 1997 (the time perspective taken for the headroom analysis). As in the animal trials, cooling for newborn infants has been shown to have a positive impact on mortality and neurodevelopment, with no adverse effects. A Cochrane review published in 2007 confirmed this, though reported that adverse events linked to hypothermia included an increase in the need for intorope support (of borderline significance) and significant increase in thrombocytopaenia. They conclude that the benefits outweigh the risks (Jacobs et al. 2007). A 2010 meta-analysis draws the same conclusion, stating that moderate hypothermia is associated with a consistent reduction in death and neurological impairment at 18 months (Edwards et al. 2010). The biggest cooling trial undertaken in the UK is the 'TOBY' trial, which was a multicenter randomized trial comparing intensive care plus total-body cooling for 72 hours versus intensive care alone. The results showed that induction of moderate hypothermia in infants who had perinatal

asphyxia did not significantly reduce the combined rate of death or severe disability, but did improve neurological outcomes in survivors (Azzopardi et al. 2009a).

As for Cool-Cap specifically, the results of the biggest trial to estimate clinical effectiveness was by Gluckman et al, published in 2005 (Gluckman et al. 2005). They conclude that the cool-cap could reduce disabling neurodevelopmental sequelae of neonatal encephalopathy, except in the most severely encephalopathic infants.

I have found no study that compares head cooling with whole body cooling directly.

#### *Cost-effectiveness*

A cost-effectiveness study of therapeutic hypothermia after cardiac arrest finds cooling to be cost-effective (cost-effectiveness ratio of \$47,168). The cost and benefit improvement is likely to be *more* favourable when used for babies, especially as cooling has also proved to have a significant impact on mortality.

One cost-effectiveness study for cooling, which combines the effectiveness estimates of the TOBY trial, NICHD trial and Cool-Cap trials, and costs found from the TOBY trial, find that the probability that cooling is cost-effective is finely balanced at 18 months, but increases to 99% when the throughput of infants was increased to reflect national incidence of neonatal encephalopathy, or when a longer time horizon was taken (which is probably appropriate for this intervention) (Regier et al. 2010).

A U.S. study published in 2008 simulates the cost-benefit scenario of various strategies of deployment of selective head cooling and aEEG use for treatment allocation (Gray, Geva, Zheng, & Zupancic 2008). They find that the package of aEEG and selective head cooling is an economically desirable intervention.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

Clinical practice has changed substantially in response to clinical trials and general awareness of cooling as an effective way to improve neurological outcome for asphyxiated babies. Whereas before there was no routine treatment, induced hypothermia is becoming increasingly common.

A survey conducted in 2009 by Ponnusamy et al. questioned all 214 neonatal units in the UK with regards to the availability of cerebral function monitoring (CFM) and hypothermia therapy (Ponnusamy et al. 2010). CFM was available in 41% of units, and 28% had dedicated cooling equipment. 16% of those without CFM were planning to acquire it, and 14% of those without cooling equipment were planning to procure it soon. In level three units CFM and cooling equipment availability was 87% and 78% respectively. There is no indication in the report what *type* of cooling equipment is used in these units.

Olympic Medical now produce and sell their own cerebral function monitor, the Olympic CFM 6000 (their own aEEG device to diagnose hypoxic-ischaemic damage and indicate whether cooling is appropriate (Natus 2011)).

Whole body cooling is probably more widely used in the UK than selective head cooling. Robertson et al. estimate that under 3% of units in the UK use selective head cooling (though the source of this estimate dates back to 2007) (Robertson, Kendall, & Thayyil 2010). Robertson also suggests that servo-controlled devices, which have only recently come to the market, offer improved stability of temperature and minimal nursing input compared to other whole body cooling devices (such as the Criticool™ and the Tecotherm servo).

Though comparative data does not exist, the company highlight the benefit of the Cool-Cap: that the baby is not subjected to the adverse effects of hypothermia during treatment. However, Azzopardi reports that clinical complications that had arisen during the cooling period (using whole body cooling) were not considered related to the hypothermia therapy (Azzopardi D et al. 2009). It is thought that eventually the cool-cap may provide cooling therapy *portably* (for example in ambulances) (Kaiser 2004) – this may be more feasible with this device than other means of cooling.

#### Are there now many direct competitors?

There has been continued research into whether any pharmacologic agents can prevent mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Recent reviews show that alloupurinol (Chaudhari & McGuire 2008), naloxone (McGuire, Fowlie, & Evans 2004), anticonvulsants (Evans, Levene, & Tsakmakis 2007), and dopamine (Hunt & Osborn 2002) still do not have sufficient evidence to support any clinically important benefit.

In their hypothermic therapy guidance, NICE also reiterate that no other specific pharmacological agents or interventions have been shown to prevent neuronal damage. In the literature, the only commercial device I have come across for selective head cooling is that of Olympic Medical Corp (now Natus). This is consistent with the declaration on their website that the Cool-Cap is the only device for this indication with FDA approval (Natus 2011).

Commercial devices that have been developed to allow for whole body cooling include:

- Blanketrol cooling blanket (Cincinatti Sub-Zero);
- CritiCool whole body cooling system (Criticool, Charter Kontron, Milton Keynes, UK), and;
- Tecotherm (Tecotherm, Inspiration healthcare, Leicester, UK).

I have also come across the use of simple ice /gel packs, fans, and water bottles.

### **Conclusions: How useful might the headroom exercise have been?**

The Cool-Cap was an example of commercialising a device for which the mechanism of action already has an established clinical case, but turning it into a marketable product. The question of whether it would work *better* than other methods has not been answered explicitly by the literature to date, but current practice and research indicate that other means of cooling may be just as effective as the Cool-Cap.

When comparing the therapeutic benefit of the cooling cap to 'no treatment' (which was current practice in 1997), the headroom for development was really a 'no brainer'. The evidence for cooling that has been produced over the past decade supports the notion that both clinically and economically, cooling is the optimal form of treatment for newborns with suspected hypoxic-ischaemic encephalopathy. The media has probably served to propel changes in clinical practice with increased vigour and speed.

To our knowledge, the Cool-Cap was the first commercial device for this indication. An interesting parameter in this example is clinician preference. From a health economic perspective, effectiveness and costs alone dictate the cost-effectiveness of one intervention over another. Comparing the Cool-Cap to no intervention led to a straightforward positive case, but if we were to have considered that cheap alternatives were just as effective, the cool-cap may have been dominated. However, as therapeutic cooling did not yet have a place in widespread clinical practice, a commercial device may have been what was needed to raise awareness and promote wider support for the intervention. The fact that the Cool-Cap was the *first* commercial device, may have benefited the company and provided support for the development case; the research interest generated and the clinical trials undertaken would mean that the company could make early contacts and alliances with individual hospitals/clinicians. This is not the case with new or alternative versions of currently 'established' devices, as there would be limited need for trials.

As is the nature with devices, especially in an area where the therapeutic benefit is known and the methods of cooling are multiple, the market has become crowded with competitors. This was highlighted as a significant and likely threat for the development opportunity. It is clear though that different devices which achieve the same therapeutic effect but by different means can co-exist in the same market. This exemplifies the fact that customer choice (in this case that of the clinician) is of importance here. It may reflect clinician's having different ideas/interpretations of clinical effectiveness, or a predisposition toward gadgets.

So, the headroom method and the signals it provided with regards to the commercial opportunity of cooling *and* the external threats to that opportunity, turned out to be applicable. Would a headroom analysis have been needed to give us this information? Maybe not.

## 9. ChondroCelect<sup>19</sup>. TiGenix NV

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Incremental development;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: Aug 2008</i></p> <p><i>Time perspective of this report: 2006</i></p>	<p>Cartilage damage is associated with knee pain, knee swelling, knee locking, and giving way of the knee joint. It can be caused by injury (and is often a result of sporting activity), or can happen spontaneously (osteochondritis dissecans). It mostly occurs in young adults. Incidence is not very well known, but it is estimated that about 10,000 patients in the UK suffer from cartilage damage that warrants repair (NICE 2005b) .</p> <p>ChondroCelect is a somatic cell therapy product, which will be developed from a patient’s own cartilage-forming cells (from a lesser weight-bearing area of the joint), and expanded ex-vivo prior to implantation. It is administered as part of an ‘autologous chondrocyte implantation’(ACI)<sup>20</sup>. The procedure consists of three steps, which are performed over 4 to 6 weeks:-</p> <ol style="list-style-type: none"> <li>a) An arthroscopy is undertaken to assess the cartilage lesion and to take a biopsy from a lesser-weight bearing part of the joint</li> <li>b) Cells are harvested from the cartilage biopsy and expanded to make ChondroCelect.</li> <li>c) Arthrotomy: a biodegradable cover (a periosteal cap or collagen membrane) is joined over the cartilage defect, under which the cultured cells (ChondroCelect) are injected.</li> </ol> <p>The combination of ChondroCelect (the product) and ACI (the procedure) is called Characterised Chondrocyte Implantation (CCI™).</p>
<p><b>2. Comparator</b></p>	<p>There is no one uniform approach to managing knee cartilage defects. Options include:</p> <ul style="list-style-type: none"> <li>• Symptomatic relief</li> <li>• ACI. Also available is ‘MACI’: Matrix-guided ACI. This is where the extracted chondrocytes are cultured within a collagen matrix before being implanted. Implantation can be done by arthroscopic injection (less invasive, uses a collagen membrane so avoids the need for a periosteal cap).</li> <li>• Microfracture: This is a marrow stimulation technique, and involves breaching the sub-chondral bone to cause bleeding. The blood clot that develops is thought to create the right conditions for stem cells to build new tissue</li> </ul>

<sup>19</sup> There is some disagreement around the appropriate classification of somatic cell therapy/tissue-engineered products; at least from a regulatory perspective they pose quite different issues from devices and medicines. Regulation of European Parliament on such products classify them as ‘advanced therapy medicinal products (ATMPs)’. In a summary of the new directive, it is said that ‘a Committee for Advanced Therapies (CAT) will be established within the European Medicines Agency (EMA) to provide scientific advice on ATMPs of which at least two members must have medical devices expertise’(Department of Health 2008) . This exemplifies the unique nature of tissue engineered products that means they lie somewhere between a device and a medicine. The NHSC classify them under medical devices, which is the reason for its inclusion.

<sup>20</sup> The NHSC document refers to this procedure once as ‘autogenous cartilage implantation’ procedure (ACI), though I cannot find this term used anywhere else. The company itself refers to the ChondroCelect as being used for ‘autologous chondrocyte implantation’.



	<ul style="list-style-type: none"> <li>• Mosaicplasty: Cylinders of normal cartilage and bone are removed from non-weight-bearing areas of the affected knee, which are then placed into the areas of effective cartilage. Mosaicplasty was reviewed by NICE as an interventional procedure in 2006, which concluded that there are no major safety concerns for the procedure but that data on long-term efficacy was inadequate (NICE 2006b)</li> <li>• Knee lavage</li> <li>• Knee replacement.</li> </ul> <p>NICE produced a technology appraisal for ACI in 2000. This was revisited in 2005, and became: ‘TA89 Cartilage injury – autologous chondrocyte implantation (ACI) (review): Guidance’(NICE 2005b) . ACI was <i>not</i> recommended for treating knee problems caused by damaged cartilage (unless designed to produce good quality research data for the procedure). The re-appraisal made the following modifications to the original guidance:</p> <ul style="list-style-type: none"> <li>○ The recommendation that ACI should not be used for routine primary treatment was expanded to include <i>all</i> treatment levels.</li> <li>○ <i>All</i> patients receiving ACI should be enrolled in clinical studies</li> <li>○ Patients should be fully informed of the uncertainties about the long term effectiveness and potential adverse effects of the procedure.</li> </ul> <p>The ACI procedure described in this NICE technology appraisal seems identical to that described for ChondroCelect. When describing the ‘Innovation and/or advantages’ of ChondroCelect in the NHSC briefing, it is said to be (if licensed) the “first advanced autologous chondrocyte therapy product developed for this indication”<sup>21</sup>. We can only assume that the cell culturing technique differs to those used already for this procedure, leading to more effective cultured chondrocytes (ChondroCelect), and thus improved effectiveness.</p> <p>NICE considered four relevant RCTs in order to ascertain ACI effectiveness: two comparing ACI to Mosaicplasty and two comparing it to Microfracture. Compared with Mosaicplasty, one trial showed equivalent results whilst the other found greater improvement in knee function and symptoms in the ACI group (this difference was statistically significant). Compared with Microfracture, one trial found that after two years, a slightly greater number of ACI patients experienced less pain compared with Microfracture, but the physical component of the SF-36 was improved more with Microfracture. The other shows no statistically</p>
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<sup>21</sup> By the time this (the NHSC briefing) had been written, the NICE technology appraisal for ACI had been available for three years, and the original appraisal had actually been issued five years before that. Whilst the brief does not indicate what it is that makes the ChondroCelect any different to ready-established ACI procedures, it can only be assumed that what makes this the first “advanced” ACI must be something in the cell culturing process (perhaps these details are omitted for reasons of confidentiality). The NHSC briefing also neglects to mention that the ACI procedure was *not* recommended by NICE.

	<p>significant difference.</p> <p>A Swedish longer-term observational study found that ACI had good or excellent results in 82% to 92% of patients.</p> <p>NICE conclude that the clinical effectiveness evidence for ACI is inconclusive.</p> <p>The HTA that was undertaken to support the NICE guidance was published in late 2005 (Clar et al. 2005). They state that microfracture is the ‘current standard treatment of cartilage defects’. Combining this with mosaicplasty’s problem of damage to donor sites meaning that the procedure is limited to smaller lesions (Clar et al. 2005), and that in their 2006 guidance on mosaicplasty NICE declare that effectiveness data for mosaicplasty was insufficient, I will assume that microfracture is most appropriately considered the ‘gold standard’ in clinical practice’<sup>22</sup>.</p>
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<p><b>3. Market size</b></p>	<p>Although incidence is not well known, it is thought that 10,000 patients in the UK suffer cartilage damage that warrants repair. It is anticipated that 9-12% of these patients would be suitable for treatment with ChondroCelect.</p> <p style="text-align: right;"><b>Market size per year: 900 to 1,200</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>ACI is thought to offer relief of symptoms in the short term, and reduced incidence of subsequent osteoarthritis and later knee replacement in the long term. For all of the associated benefits (both in terms of health and health service cost) to be incorporated, a long-term view must be taken.</p> <p>In NICE’s technology appraisal, four companies are mentioned in relation to the ACI procedure, which provide the cell culture service. They estimate the cost by company, which includes the cell culturing, shipping, and training of hospital staff. They also provide details of the one trust that use in-house methods of chondrocyte culture: The Robert Jones and Agnes Hunt Orthopaedic &amp; District NHS Trust (RJAH) is Oswestry.</p> <p>Genzyme Ltd UK and Ireland: £4,000-£5,000                  BBraun/TeTec AG: £4,000                  Verigen UK Lts: £3,200                  Geistlich Biomaterials: £3,500                  RJAH: £2,000                  (It was noted that acquisition cost may vary according to local agreements). NICE then added to</p>
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<sup>22</sup> Additionally, the HTA for ACI finds mosaicplasty to be dominated by ACI and microfracture in nearly all scenarios.

	<p>this the health service costs involved. They chose to use the Verigen UK cost of cell culture in their cost model.</p> <p>NICE undertook illustrative modelling of the cost-effectiveness of ACI, and argue that there was insufficient evidence to produce a <i>robust</i> cost per QALY. They modelled cost-effectiveness in the short (2 years), medium (10 years) and long term (50 years) (the latter being the most speculative). It is only when taking a 50 year time horizon that ACI appeared cost-effective, but as the relative effectiveness of ACI was still experimental, NICE concluded that there was insufficient information on which to base long term effectiveness and quality of life gain estimates.</p> <p>The HTA report that informed this analysis provides more detailed information behind that modelling. Even though the modelling was illustrative because of the lack of long term data on ACI, the HTA team used what they thought to be reasonable assumptions; these well-informed ‘guesses’ fit the purposes of a headroom calculation.</p> <p>The report provides explicit costs for each procedure, which include procedural costs (length of stay, theatre time, physiotherapy) and cell culture cost for ACI (at £3,200). For arthroscopic ACI this is said to be £6,384, and for open knee ACI it was £8,646 (due to the increased recovery time in hospital). Although not completely clear in the NHSC briefing, it seems that the ChondroCelect procedure would use <i>open knee</i> surgery to implant the cultured cells, rather than an arthroscopic procedure which only uses a small incision<sup>23</sup>. The NHSC briefing indicates that ChondroCelect “may be a cheaper alternative”, but gives no indication of why this might be the case (this would have been especially useful information considering that ChondroCelect would be applied as an open knee ACI, which is the more costly version). Mosaicplasty costs £3,710.</p> <p>Taking a short time horizon, these differences in</p>
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<sup>23</sup> The NHSC briefing provides average costs of both open knee and arthroscopic ACI, but does not indicate where the ChondroCelect system fits into this picture. When describing the procedure, they say that the cultured cells are implanted via ‘Arthrotomy’, which refers to a process of creating an opening in the joint. Upon further investigation, I find that in the context of ACI this refers to open knee surgery, which is the traditional method of surgically opening the knee with long incisions.

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>intervention cost would have a great deal of influence on relative cost-effectiveness of the treatments.</p> <p>As the procedure for ChondroCelect looks to be the same as conventional ACI, service costs involved in the procedure itself are likely to be the same. Although it is proposed that ChondroCelect may be more effective, the assumptions required to quantify this improvement on longer term service costs are not provided.</p> <p style="text-align: right;"><b>(Total) ΔSC=</b> <b>(Av. Per person) ΔSC=</b></p> <p style="text-align: right;"><b>P<sub>1</sub>= £3,710</b></p> <p><i>Although of limited relevance to the NICE reference case, Lindahl et al present the estimated impact of ACI on productivity (Lindahl, Brittberg, &amp; Peterson 2001). They find that for the 10 years pre-ACI procedure, absenteeism costs reach £74,352 per person. For the 10 years following an ACI procedure, this dropped to an average of £15,683.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>Given the long term impact of knee problems, we would ideally have estimates of health status following intervention spanning many years. However, quality of life valuations in the literature using generic instruments such as SF-36 or EQ-5D are limited to just two years (Clar et al. 2005).</p> <p>The HTA performed by Clar et al. presents a simple short-term model which shows that the required QoL gain from switching from microfracture to ACI must be between 70 and 100% over two years in order to be cost-effective ( the evidence so far does not indicate gains of this magnitude) (Clar et al. 2005). If, however, this QoL gain could be maintained for a decade, ACI would need to provide a QoL increment of just 10-20% over microfracture in order to justify its higher cost. <b>However, this has been calculated for arthroscopic ACI.</b> Clar et al. assume open knee and arthroscopic ACI to be of equivalent effectiveness, meaning that (more expensive) open-knee ACI is dominated by arthroscopic ACI in all scenarios. They present the incremental cost-effectiveness ratio of open knee ACI versus microfracture (assuming a QoL gain of 0.1 for microfracture and 0.2 for ACI) which at year 1 is £62,980 but only £7,317 at year 10.</p>
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	<p>However, the same calculations for arthroscopic ACI render an ICER of £40,360 at year 1 and just £4,689 at 10 years.</p> <p>In the long-term model, Clar et al. consider the base-case to be where ACI (successful cases) offers a QoL increment of 0.1 compared with microfracture, and once considering the relative impact on future health and service costs (including knee replacement), find the cost-effectiveness of switching from microfracture to ACI to be between £3,500 and £5,500 per QALY (very favourable). Again, however, they assume arthroscopic ACI, which the ChondroCelect isn't: "since open-knee ACI is more expensive than arthroscopic ACI, in the absence of any data suggesting it to be more cost-effective than arthroscopic ACI, open-knee ACI is dominated in terms of cost-effectiveness and has been largely disregarded in this section" (p.36, (Clar et al. 2005)).</p> <p>It seems now that the most pertinent comparator from a development decision perspective is arthroscopic ACI, even though this is not yet current practice. In order to present an attractive case for NHS purchase, the benefits arising from ACI with ChondroCelect would need to be greater than those incremental benefits needed for arthroscopic ACI to be cost-effective, that were estimated in the HTA.</p> <p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p>	<ul style="list-style-type: none"> <li>• [RED] ACI has been reviewed by NICE, who issued a recommendation that ACI should not be used in the clinical treatment of knee cartilage defects.</li> <li>• [RED] This non-recommendation was based on the fact that short-term data showed ACI to be dominated by alternative treatments, and that long-term data on which to base effectiveness estimates did not exist. Data of this nature will take at least 20 years to collect. Until then, unless the current clinical landscape changes, it is likely only to be used as part of clinical trials in the UK.</li> <li>• [AMBER] There are a number of device manufacturers named on the 'Consultees' list for NICE's ACI technology appraisal (TiGenix is not one of these). This suggests that there are many</li> </ul>
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<p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<p>companies with an interest in producing products for ACI, so competition may be fierce.</p> <ul style="list-style-type: none"> <li><b>[RED]</b> Clar et al. showed that open knee ACI was dominated by arthroscopic ACI given its more expensive intervention cost, and the fact it has not been proven to be more effective. <b>[AMBER]</b> ChondroCelect would need to prove to be more effective than arthroscopic ACI.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>Would ACI using ChondroCelect generate <i>more than</i> a 100% utility benefit in the two years following intervention, as compared with microfracture (and is this impact greater than other versions of ACI)? This would be necessary to ensure short-term cost-effectiveness, unless the ChondroCelect procedure could be cheaper than current ACI.</li> <li>Would the use of ChondroCelect lead to better outcomes in the long term compared to available methods of arthroscopic ACI? This would be necessary to ensure its long-term health economic case.</li> <li>Significant barriers have been identified. In order for NICE to recommend ACI it would first need long term evidence of effectiveness as compared with microfracture. If this could be achieved, then ChondroCelect would need to prove to be more effective than arthroscopic ACI, as procedure costs are likely to be greater (longer hospital stay).</li> <li>Can the company afford to develop a product which is likely to be launched into a market where (at least initially) ACI products are only being used as part of clinical trials?</li> <li>Could the ChondroCelect procedure be undertaken using arthroscopic means of implanting the cultured cells rather than an Arthrotomy, as currently indicated? This would reduce the service costs involved in undertaking the procedure, and put it on an even keel with other arthroscopic ACI systems.</li> </ul>
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## Headroom Notes (ChondroCelect)

No MRP has been calculated, but as an HTA relating to ACIs has already been published within the relevant timeframe (the ChondroCelect represents an 'incremental development' to other ACI procedures), some quite precise qualifications for the reimbursement opportunity have been identified.

If the ChondroCelect procedure could be undertaken by the NHS for the *same cost* as arthroscopic ACI, then the required effectiveness and QoL impact to make it cost-effective would be the same as that identified in HTA by Clar et al (Clar et al. 2005) (see pro forma). Although open-knee ACI (which is supposedly the method of implantation for ChondroCelect) is a more costly procedure due to longer lengths of hospital stay, the NHSC briefing indicates that the procedure could be cheaper (though it does not indicate how this would be the case, and compared to what). If the ChondroCelect procedure were to be more expensive than arthroscopic ACI, it would need to prove itself to be more effective (by some margin depending on how much more expensive it is).

As no MRP is delivered, the headroom analysis and what it has to offer to a development decision is most concretely presented in the 'Research Questions' section. The output of this section is summarised below:

- If purchasers were to take a short-term perspective, *arthroscopic* ACI would need to prove with two year data to have at least 70% better outcomes than microfracture (at the moment the literature does not show this to be the case). If ChondroCelect is more expensive, it would need data to show it is even more effective than that.
- If this is seen by the developer as feasible, then there is a reasonable case for development. However, this should be with the knowledge that the lack of long-term data at the moment means that NICE aren't willing to recommend the procedure unless in the short term ACI is proven to be more effective than the current literature suggests. It should also be kept in mind that it will probably be 20 years or so until that long term data might become available, until which time ACI is only recommended as part of clinical trials.

## Follow-up (ChondroCelect)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

No MRP as such was delivered by this analysis. What it did identify was the price and total cost of current ACI procedures, and the increased effectiveness over microfracture that would need to be achieved (or more pertinently, shown by clinical trial data) for ACI to be the more cost-effective treatment, and thus reimbursable by the NHS.

The purpose of a headroom analysis is to get a better idea of the reimbursement opportunity for a specific product which is to be developed in the context of a specific market. ChondroCelect is an

incremental development of established ACI procedures; in this case a lot of work had already been done to collect and summarise the relevant clinical and economic data for the procedure versus current practice. There was even a NICE decision on ACI (which was unfavourable), and a full HTA regarding its actual and potential cost-effectiveness. The main lessons and questions generated by the headroom pro forma to inform a development decision were those presented in the 'research questions' section.

It is difficult to know whether or not the developer would have considered that the criteria given for a positive reimbursement case (from a NICE perspective) would have been feasible. One could suppose that as the information used to generate these criteria came from a published HTA and NICE guidance, then the developer would have considered this information, and decided to develop in light of these potential barriers.

As indicated by the analysis: if the ChondroCelect procedure were to cost the same as arthroscopic ACI, then in the short term it would have to show benefits over microfracture of over 70% (the fact that consideration of the procedure alone (open-knee) would cost more than arthroscopic ACI suggested that ChondroCelect would probably be more expensive). As for the long-term, NICE will not recommend the procedure for widespread clinical use until long term data is available.

I cannot guess the thoughts of the developer at the beginning of the development process on the potential *effectiveness* of ChondroCelect over microfracture and other ACI procedures. However, the product does not seem to present a cost-saving case in the short term. A cost-utility analysis performed in 2010 by Gerlier et al. presents the costs of microfracture versus ACI using ChondroCelect (Gerlier et al. 2010). According to this recent cost-utility analysis, Microfracture costs (the Belgian health service) a total of €1,035, compared to ACI using ChondroCelect which costs €24,879 (including the whole three step procedure, hospital stay, and cell culture).

It seems that the use of ChondroCelect poses much higher costs than arthroscopic ACI. With this information, and according to this analysis, the outcomes from the procedure would have to have been predicted as *much* better than microfracture and arthroscopic ACI to warrant investment in the current landscape.

**Not able to predict headroom decision with any certainty, but based on its headroom value, and realistically what ChondroCelect might achieve, potential for reimbursement seems unlikely.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

NICE have not developed new guidance or revisited the guidance on ACI since it published its review on the procedure in 2005 (NICE 2005b). It was due to be considered for review in May 2008, but no changes have been made.



### Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?

TiGenix headquarters are in Belgium, but other offices are in Madrid (Spain), Sittard-Geleen (the Netherlands) and Cambridge (UK)<sup>24</sup>.

ChondroCelect received EU market authorisation in October 2009 (EU/1/09/563/001). The therapy has been classified as a tissue-engineered product: 'a type of *medicine* containing cells or tissues that have been manipulated so that they can be used to repair, regenerate or replace tissue' (EMEA (European Medicines Agency) 2009)<sup>25</sup>. ChondroCelect represented the first Advanced Therapy Medicinal Product (ATMP) to be approved and receive European marketing authorisation (ATMP is defined as any medicinal product prepared industrially or manufactured by a method involving an industrial process (Gerlier et al. 2010)). On their website TiGenix reveal that ChondroCelect is reimbursed in Belgium, Germany and the UK (on a *case by case* basis in the case of Germany and the UK) (TiGenix.Living Medicines 2011). A news article from October 2011 reveals that TiGenix have also signed an agreement for ChondroCelect distribution in Finland (4-traders 2011).

In a presentation for the UK National Stem Cell Network in Nottingham, Francois Meurgey presented some slides on the difficulty of achieving reimbursement for regenerative medicine products in general, and ChondroCelect specifically (Meurgey 2010). In this presentation he says that "in some countries the procedure is reimbursed (often as part of DRG<sup>26</sup>), in most it is not". Going into more detail about the situation in some European countries, Meurgey revealed that negotiations and national evaluations were underway, often being proposed to be on the 'expensive drugs list' (Netherlands), or to obtain 'innovative status' (Belgium). In the UK, he confirms that NICE did not recommend ACI and that TiGenix would need to request an STA (single technology appraisal) to be reviewed independently by NICE. In the meantime, however, the company are "working with orthopaedic surgeons to obtain Pass-Through Payment<sup>27</sup> from individual PCTs, and also working with private insurance: very positive initial reception from BUPA" (Meurgey 2010).

ChondroCelect is on the MHRA's 'Black Triangle List', which consists of UK marketed drugs for which there is limited clinical trial evidence, and so which are under intensive surveillance by the MHRA (MHRA 2011). It first came onto this list in August 2010.

### Have there been investigations into its clinical / cost effectiveness?

What was unclear in the NHSC briefing was the way in which ChondroCelect improved the cell culture process that is used for conventional ACI. Rather than simply expanding the cells that are

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<sup>24</sup> Email enquiry sent to the company regarding use of ChondroCelect here in the UK. Response pending.

<sup>25</sup> Having considered initially that this product might be classified as a medicine, I decided to review this anyway as: a) the NHSC had considered it a device, and b) the procedure contains elements of medicine, surgery and medical device implantation, so is representative of complex procedures that involve many elements.

<sup>26</sup> DRG: Diagnosis-Related Group. This looks similar to the UK version- HRG (Healthcare Resource Groups). They are used as a classification system to aid reimbursement.

<sup>27</sup> Pass-Through Payments are *additional* payments that can be sued to support (reimburse) a particular device over and above the relevant tariff. These are sometimes used to support the use of new products (Pate 2009).

harvested, this autologous *characterised* therapy uses characterised viable autologous cartilage cells which are expanded, and which express *specific marker proteins* that reflect their capacity to form hyaline-like cartilage (hyaline is the most robust and natural form of cartilage, as opposed to fibrocartilage which has poor histological outcome) (Gerlier et al. 2010). It is thought that microfracture produces a fibrocartilage repair, which can jeopardise longer term outcomes.

Saris et al. report on the one RCT that has been performed for ChondroCelect, which is compared to microfracture (Saris et al. 2008). Follow-up at 12 and 18 months show no significant difference in outcome scores between the two treatments, though use of ChondroCelect was said to be associated with superior tissue regeneration, which they hypothesise could lead to improved long-term clinical benefits. Indeed, a follow-up at 36 months was published in 2009 which showed that improvement in clinical outcomes was greater in the ChondroCelect group compared to microfracture (Saris DB et al. 2009). Van Assche et al. find that two years after surgery, patients' activity levels were similar between the ChondroCelect and microfracture group (Van Assche et al. 2009).

A Cochrane review from 2010 considers the evidence for ACI versus other procedures (Vasiliadis & Wasiak 2010). Whilst highlighting the positive outcomes of ChondroCelect at 36 months, they also present results from a trial comparing MACI (matrix-guided ACI) to microfracture, which reports more favourable outcomes and within a shorter time period (in the ChondroCelect trial improvement in functional outcomes was only detected at 36 months). When referring to the Saris report, they highlight potential risks of bias because of incomplete outcome data, selective reporting and conflict of interest (trial was sponsored by TiGenix and eight of the authors declared a conflict of interest). They conclude that there is still insufficient evidence to draw conclusions on the use of ACI, with further good quality RCTs with long-term functional outcomes needed (Vasiliadis & Wasiak 2010). One discussion paper emphasises the potential adverse effects of the ChondroCelect procedure (and ACI in general), and also stress the need for more data ([No authors listed] 2011).

One cost-utility analysis has been produced for ChondroCelect, using effectiveness data from the Saris trial (Gerlier et al. 2010). The perspective taken is that of the Belgian healthcare payer. Long term outcomes are projected, based on the hypothesis that success rates (and risk of long-term problems) will relate to presence of hyaline or hyaline-like cartilage (which was found in 44.9% of patients at 12 months in the ChondroCelect group and 23.2% in the microfracture group). They derive a utility score from SF-36 questionnaires which were sent to those who participated in the RCT two years after randomization. Using their base-case assumptions, the forty year ICER (€ per QALY) was €16,229. Taking a shorter-term horizon (5 years) this ICER increases to €394,812. They conclude that the relatively high cost of the ChondroCelect procedure should be considered against the longer-term benefits.

## Has the landscape described changed significantly?

### **What is current gold standard clinical practice now? Has this changed?**

Given the fact that the longer-term data (or indeed any short term data that shows ACI to be considerably better than other techniques) do not exist, 'gold standard clinical practice' has not changed. Although ChondroCelect and ACI in general have been found to have the potential for improved outcome, no study or review has provided the evidence to *confirm* the potential benefits of ACI that would make the intervention attractive from a health service perspective.

In this clinical setting there is still no one intervention that is considered to outperform all others, and as such various options exist, both non-surgical and surgical (NHS Choices 2011a). The fact that ChondroCelect is on the MHRA's surveillance list shows that the product has UK market authorisation, and is being utilised in some settings (though perhaps not outside of clinical trial given NICE's recommendations).

### **Are there now many direct competitors?**

There are still many companies that provide the cell culture service for an ACI procedure, but the only product I have found in the context of characterised chondrocyte implantation is ChondroCelect.

## Conclusions: How useful might the headroom exercise have been?

In this example, a health technology assessment produced just one year before the time-perspective taken for the headroom analysis meant that much of the work relating to the feasibility of ACI being a cost-effective alternative to microfracture had been done. The usefulness of the exercise then rests on whether this information would have been picked up by the company anyway (very likely).

From purely a reimbursement perspective, I believe that the product **would not have appeared viable** (at least if reimbursement was required within the next 20 years or so). This was based on the (unrealistically) high comparative benefit that it would have needed to have over microfracture in the short term (especially as it is much more expensive even than other ACI procedures), and the unwillingness of NICE to recommend the procedure without long term effectiveness data. The subsequent evidence has not altered this situation.

However, this conclusion is based on the supposition that if NICE do not consider it to be cost-effective, then no UK healthcare provider will provide it. This seems not to be the case. As mentioned, TiGenix are working with orthopaedic surgeons in the UK to obtain Pass-Through Payment from individual PCTs, and also with private insurance companies. This demonstrates that there are alternative methods of reimbursement; these are difficult to grasp in the context of a headroom analysis.

The difficulty of pricing and reimbursement for medical products and the uncertainty of these issues, especially for a product like ChondroCelect, is an issue for the developer as well as the headroom method. Meurgey (V-P commercial development of TiGenix) emphasised this in his talk to the UK

National Stem Cell Network (Meurgey 2010). He said that gaining regulatory approval was the 'easy part', and that the so-called '4<sup>th</sup> hurdle' that is Pricing & Reimbursement is possibly the most difficult, especially considering the diverse healthcare systems (and languages!) across Europe. As indicated in the above section, there are some special allowances and reimbursement support for novel / expensive products, but these of course vary from country to country. This makes negotiating the system very difficult for companies.

This reimbursement landscape is especially challenging for products such as ChondroCelect, which makes use of regenerative medicine. From an 'evidence required for reimbursement' perspective, this product has been regarded in the same light as medicines. However, the time horizon needed to demonstrate its full benefit may be many years. This makes the health-economics very difficult. Meurgey closed his presentation with the following words: "Unless national authorities demonstrate willingness to experiment with conditional reimbursement, there is a real risk that regenerative medicine will remain a nice idea without any routine clinical use (or a luxury reserved for the rich" (Meurgey 2010).

## 10. KRYPTOR compact. *Brahms AG*

<p><b>1. Description</b></p> <p><i>Diagnostic;</i></p> <p><i>Incremental development/New indication;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: April 2007</i></p> <p><i>Time perspective of this report: 2005</i></p>	<p>A lower respiratory tract infection (LRTI) can cause symptoms such as shortness of breath, fever, weakness, cough and fatigue. An LRTI is principally associated with acute bronchitis, chronic obstructive pulmonary disease (COPD) exacerbation, and community-acquired pneumonia.</p> <p>Using a clinical examination only, it is very difficult to distinguish between bacterial and non-bacterial (viral) LRTI. Levels of the biological marker procalcitonin (PCT), which can be detected from blood samples, can indicate whether an infection is bacterial, and so whether antibiotics are appropriate. The Brahms Kryptor assay (classic version), which has been available since 1997, is a sensitive assay to measure levels of PCT; it can produce quantitative results in 19 minutes. Antibiotics can then be prescribed or withheld on this basis.</p> <p>The Kryptor compact is based on exactly the same reagent system, but is smaller, less costly, and easier to maintain than the classic version.</p> <p>The Kryptor assay is already used for other diagnostic purposes, especially prenatal screening.</p>
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<p><b>2. Comparator</b></p>	<p>There are no reliable clinical tools to distinguish between bacterial and non-bacterial LRTI. Current means of diagnosis (which are not routinely indicated) are: sputum culture, viral or atypical organisms' serology, chest x-ray, and C-reactive protein (another biomarker).</p> <p>The Kryptor compact looks as though it would have the same expected effectiveness as the classic version, which <i>isn't</i> currently used systematically for this indication. This is why the technology represents both a new indication (no prognostic tool is currently used: clinical examination is the only widely used method of distinction, which is often unreliable), <i>and</i> an incremental development (of Brahms' original version of the Kryptor assay). Therefore, it is possible to use trial results for the assay, to try to identify the maximum reimbursable price (for this particular clinical indication), and consider whether the new system could possibly fit into this space.</p> <p>The main hypothesis, upon which the usefulness of such a test is based, is that currently antibiotics are not being prescribed appropriately to patients who present with an LRTI. In other words, antibiotics are not being given to those who would benefit from them (when their LRTI is caused by a bacterial infection) and/or patients who would <i>not</i> benefit from antibiotics (as the cause of the infection is viral) are being prescribed antibiotics. The large body of literature on this matter paints a picture of the latter being the main problem in this area (over-prescription of antibiotics) (Gonzales, Steiner, &amp; Sande 1997; SIGN (Scottish Intercollegiate Guidelines Network) 2002). Antibiotics are in too many</p>
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	<p>cases used as first-line therapy with no justification. The problem with this is three-fold:</p> <ol style="list-style-type: none"><li>1. Over-prescription means unnecessary costs for the NHS</li><li>2. Unnecessary use increases the risk of patients developing bacterial infections in the future that are <i>resistant</i> to antibiotics.</li><li>3. Side-effects associated with antibiotics include nausea, vomiting and diarrhoea, so should be avoided unless necessary. These side-effects also commonly cause repeat visits to the GP (SIGN (Scottish Intercollegiate Guidelines Network) 2002).</li></ol> <p>It is thought that as much as 75% of all antibiotic doses are prescribed for respiratory tract infection, even though they are mainly viral in cause (Christ-Crain et al. 2004). The World Health Organization (WHO) estimate that only 20% of respiratory infections are of bacterial cause (and thus warrant antibiotics) (Brundtland 2000).</p> <p>A prospective, cluster-randomised, RCT that tested the use of the Kryptor assay to guide antibiotic treatment for patients presenting with LRTI in the University Hospital of Basel, Switzerland, found that antibiotic prescription was reduced by about 40% in the procalcitonin guided group compared with routine clinical practice (44% versus 83%). It was also found <i>not</i> to compromise clinical and laboratory outcome (Christ-Crain et al. 2004).</p> <p>Two caveats to using this 40% estimate as our assumption for Kryptor compact effect on antibiotic use are that:</p> <ol style="list-style-type: none"><li>1) Clinical practice in LRTI treatment varies from country to country (Halls 1993).</li><li>2) The estimate from this trial is derived from an acute hospital setting. It may be that antibiotic use is lower or higher in a primary care setting, so the impact may be different (though from the studies that I have come across, this initial 83% estimate does not seem too far off the situation in primary care also).</li></ol> <p>However, it makes sense to use this as an <i>estimate</i> of value for this headroom analysis.</p> <p>Although it has been mentioned that the side-effects associated with antibiotics can be a major cause for repeat visits to the doctor, the data I have found for this effect in the literature seem to indicate that this may not have a big impact. One study finds the 30% repeat consultation rate that was found for patients with LRTI was not related to whether or not they were initially prescribed antibiotics (Holmes, Macfarlane, Macfarlane, &amp; Lewis 1997), and another finds that only 9 of the 160 repeat consultations were due to the adverse effects of antibiotics (Davey et al. 1994). Therefore, I will omit this potential effect from the analysis. I will also ignore sensitivity and specificity issues, and base the estimates directly on the findings of the trial where a 40% reduction in antibiotic prescription was achieved with no effect on outcome.</p>
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<p><b>3. Market size</b></p>	<p>As LRTIs are so broad in definition, it is very difficult to estimate the number of episodes per year. One UK study estimated (by extrapolating data from one general practice) that there are around 1,700,000 LTRI cases in England &amp; Wales between the ages of 16 and 79 (Macfarlane et al. 1993).</p> <p style="text-align: right;"><b>Market size per year (NHS England &amp; Wales: Adults) : 1.7 million</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>One cost-of-illness study estimated that LRTIs cost the NHS £1,364 million a year: 0.5% of the NHS budget (Guest JF &amp; Morris A 1996).</p> <p>Antibiotic cost per patient is likely to vary greatly according to type and severity of LRTI; the antibiotic cost of a patient admitted to hospital for community-acquired pneumonia was on average £155 in 1997 (Guest &amp; Morris 1997); whereas the cost of one course of Amoxicillin (first-line treatment of a chest infection) is only £1.85 (Prodigy 2005a).</p> <p>As indicated above from the RCT reported by Christ-Crain et al., antibiotic prescription was reduced by about 40% (Christ-Crain et al. 2004). For those in the procalcitonin-guided group who <i>were</i> prescribed antibiotics, treatment duration was also shorter (10.9 days versus 12.8) than the standard treatment group. This all led to total mean antibiotic cost <i>per LRTI patient</i> of \$96.3 (£50) for the procalcitonin-guided group versus \$202.5 (£106)<sup>28</sup> for the control group (a 52% reduction).</p> <p>Another study finds an average cost per treatment across the various antibiotics treatment options of £19.37 (Lavoie et al. 2005)<sup>29</sup>.</p> <p>Estimates of antibiotic treatment cost seem to vary greatly according to source of information (probably due to the different settings in which they were acquired). I will use the 52% reduction in antibiotic cost found per LRTI patient (as shown by the Kryptor assay RCT (Christ-Crain et al. 2004)) to assess the value of this prognostic test given varying assumptions of antibiotics cost. As this cost reduction was found for the average LRTI patient (rather than the average per patient treated with antibiotics), I will multiply the assumed antibiotic costs by 0.8 to estimate the initial 'average cost of antibiotics per LRTI patient' (assuming that about</p>
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<sup>28</sup> Converted to pounds sterling at the exchange rate in Jan 2005: \$1.9129

<sup>29</sup> \$37.06 converted to pounds sterling at the exchange rate in Jan 2005: \$1.9129

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>80% of patients are initially prescribed antibiotics, as per trial data), and multiply this by 0.52 in order to estimate the costs saved <i>per LRTI patient</i>.</p> <p>Cost per antibiotic course (in bold):</p> <ul style="list-style-type: none"> <li>- <b>£2:</b> <math>(£2 * 0.8) * 0.52 = £0.83</math> saved per patient</li> <li>- <b>£10:</b> <math>(£10 * 0.8) * 0.52 = £4.16</math> saved per patient</li> <li>- <b>£20:</b> <math>(£20 * 0.8) * 0.52 = £8.32</math> saved per patient</li> <li>- <b>£50:</b> <math>(£50 * 0.8) * 0.52 = £20.80</math> saved per patient</li> <li>- <b>£100:</b> <math>(£100 * 0.8) * 0.52 = £41.60</math> saved per patient</li> <li>- <b>£150:</b> <math>(£150 * 0.8) * 0.52 = £62.40</math> saved per patient</li> </ul> <p>The 'saved per patient' figures above thus represent the NHS resource savings in antibiotic costs, resulting from reduced antibiotics prescriptions (and according to the initial cost of those antibiotics). To estimate the yearly total resource saving, the appropriate figure would be multiplied by the total number of LRTI patients seen by clinicians in a given year. This is likely to be in-between the extremes presented.</p> <p><b>Cost of average antibiotic course for LRTIs: £2</b>  <b>(Total) ΔSC= £1,411,000</b>  <b>(Av. Per person) ΔSC= £0.83</b></p> <p style="text-align: right;"><b>P<sub>1</sub>= 0</b></p> <p><b>Cost of average antibiotic course for LRTIs: £150</b>  <b>(Total) ΔSC= £106,080,000</b>  <b>(Av. Per person) ΔSC= £62.40</b></p> <p style="text-align: right;"><b>P<sub>1</sub>= 0</b></p> <p>These represent the total and per patient savings considering the number of (adult) LRTI episodes in England &amp; Wales per year.</p> <p><i>Another important benefit of reducing antibiotic prescriptions, aside from the direct cost savings estimated above, is the antibiotics resistance problem. Where antibiotics are prescribed unnecessarily, the body can be at further risk of later developing bacterial infections that are resistant to antibiotics. This causes problems when trying to treat subsequent infections, but the precise cost of this in terms of increased medication and treatment costs would be very difficult to define. The fact that antibiotic costs should include consideration of side-effects of treatment and long term costs resulting</i></p>
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	<p><i>from bacteria resistance to antibiotics is emphasised in a pharmaco-economic paper by Delporte (Delporte 1998).</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>The hypothesis upon which this analysis is based, is that by making sure antibiotics are prescribed appropriately, antibiotics use will go down but with no impact on outcome (i.e. those patients that would previously have received antibiotics but whose infection is of a viral nature, will not experience any reduced therapeutic benefit by not receiving the medicine). This was confirmed in the trial which used the Kryptor assay to guide antibiotic prescriptions. It has also been argued though that outcomes could actually be improved, given the side-effects that can be caused by antibiotics which could be avoided where unnecessary, as determined by the Kryptor assay. As described in section 2, I have decided to omit these from this analysis on both the cost and patient benefit fronts, as the literature seems to indicate that this does not have an obvious impact on the health service. The effect of procalcitonin-guided therapy from a patient's perspective was investigated in the RCT reported by Christ-Crain. As part of the study they had all patients fill in a QoL questionnaire and visual analogue scale (marking how they felt between 0% [feeling very ill] and 100% [feeling completely healthy]) on admission and at follow-up. The HRQoL estimated, and changes in this from before and after treatment, were not significantly different between the two treatment groups. Adding to this the fact that potential side-effects are very diverse in nature and impact, it does not seem appropriate or feasible to turn this into a QALY estimate.</p> <p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p> <p><i>The potential for reduced morbidity from limiting antibiotics side-effects (although not identified in the RCT), have been ignored here, as has the reduced risk of patients being faced with future infections that are resistant to treatment.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p>	<ul style="list-style-type: none"> <li>• [GREEN] LRTI accounts for a greater number of GP consultations each year than any other illness. Many of these cases are self-limiting and can be</li> </ul>
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<p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<p>managed at home, but antibiotics are often prescribed for clinical reasons that have no evidence-base, or non-clinical reasons such as patient expectation, or to reduce re-attendance (SIGN (Scottish Intercollegiate Guidelines Network) 2002).</p> <ul style="list-style-type: none"> <li>• <b>[GREEN]</b> The overuse of antibiotics, leading to antimicrobial resistance, is now a world-wide phenomenon which must be controlled. A message from the director-general of the World Health Organization in 2000 emphasised the need for a global effort to tackle this issue (Brundtland 2000).</li> <li>• <b>[AMBER]</b> Some experts propose that antibiotics are not even always necessary for patients with <i>bacterial</i> infections (Hopstaken, Coenen, &amp; Butler 2005).</li> <li>• <b>[AMBER]</b> One retrospective analysis conducted in 2004 showed that winter antibiotic prescribing for LRTIs in England and Wales had shown a 30% decline since 1995/6. They found that this reduction had a small but significant association with the increase in pneumonia mortality (Price et al. 2004). This puts into question the assumption that a reduction in antibiotics prescriptions will have no effect on outcome, though it could be argued that this change was made in the absence of effective guidance, which the Kryptor compact could provide. The general decline in antibiotic use described in the report, if found to be generalisable, could reduce the impact of the Kryptor assay.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or</p>	<ul style="list-style-type: none"> <li>• This analysis has been based on the efficacy results from a trial on the Kryptor assay, Brahm's original model. It has been assumed that the new model (Kryptor compact) has the same impact as the original model. Is this an appropriate assumption?</li> <li>• The reason that the MRP has not been taken as simply the price of the original Kryptor assay, is that it is not used as part of widespread clinical practice, and so is not the appropriate comparator in terms of its value proposition to the NHS. Why is the original Kryptor assay <i>not</i></li> </ul>
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<p>assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<p>used in routine clinical practice? Is it anything to do with issues that the new model (supposedly cheaper, smaller, and easier to maintain) would address / change?</p> <ul style="list-style-type: none"> <li>• Is the proposition of this new development to the company more an issue of simple product evolution, and changes that the company must make to keep their products up to date or dominant in the market place? It its consideration in terms of clinical value inappropriate?</li> <li>• Does the estimated reduction in antibiotic prescription as a result of the Kryptor assay, that was found from a trial based in Switzerland, seem appropriate and relatable to the situation in the UK?</li> <li>• To what extent might these parameters (cost and rate of antibiotic prescription) change according to setting? (primary/secondary care?)</li> <li>• The estimated patient population includes adults aged between 16 and 79. What about patients outside of this age bracket? This could widen the market.</li> <li>• Is the introduction of such a diagnostic test feasible in a primary care setting? To what extent would the service need be centralised?</li> <li>• How many devices would be required to service all LRTI episodes, and how long would the piece of equipment last? Estimates of these would be required in order to calculate a maximum reimbursable price (MRP) per device.</li> <li>• Could the cost and patient value of antibiotics side-effects, and later treatment resistance, be quantified? If it could, then this may well add to the headroom for the Kryptor compact.</li> <li>• Is standard practice likely to change? All relevant LRTI guidance proposes the careful use of antibiotics for LRTI patients. Is this changing the landscape for antibiotics prescription of the future? This may affect the impact of the Kryptor compact.</li> <li>• Although in most cases the LRTI is self-limiting, it is indicated in the literature that a big reason for over prescription of antibiotics is patient expectations (patients want to feel like they are being treated). Clinicians are bound to respond to this expectation and also feel like they should be actively treating the patient's symptoms. Is this phenomenon likely to change, and to what</li> </ul>
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	<p>extent might the initiation of the serum test (Kryptor compact assay) be likely to overcome this?</p> <ul style="list-style-type: none"> <li>This analysis looks only at the value of the Kryptor compact in this specific market (LRTIs). The company are already aware that the technology is in demand in this context of other disease areas, so the value to the NHS of this device is by no means limited to this market.</li> </ul>
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### Headroom Notes (KRYPTOR compact)

The headroom analysis allowed me to estimate the value to the health service per patient of the more appropriate prescription of antibiotics using the Kryptor compact assay. As the average cost of antibiotics per LRTI treatment to the NHS was uncertain, the value across a range of estimates was calculated. These are three of these estimates:

Cost per antibiotic course	Headroom per LRTI patient (i.e. value to NHS of the Kryptor compact, on a per patient basis)	Total headroom (value to the NHS of using the Kryptor compact to guide antibiotic treatment, based on an adult LRTI incidence of 1.7 million per year)
£2	£0.83	£1,411,000
£20	£8.32	£14,144,000
£150	£62.40	£106,080,000

The basis of this value is the reduced spending on antibiotics. Considering this information in the context of a development decision would require the developer to have an understanding of the average cost of antibiotics, and what the best estimate might be across the whole LRTI population (assuming that the device is to be marketed across all NHS services). The value described by the numbers presented must cover the cost to the health service of consumables such as materials, technician time etc. per test.

In order to calculate an MRP *per device*, we would need an understanding of how many of the devices would be needed to service all LRTI patient serum samples, the consumables cost per test, and the number of years that one Kryptor compact system is likely to last.

In terms of a development decision, even if we were able to estimate an MRP per device, and the cost of consumables, it would not be considered in the same way as other examples. The baseline in terms of NHS value is 'no useful test', but for Brahms the baseline in terms of development is their previous model of the Kryptor assay. This means that development costs are likely to be relatively minimal, and such an evolution may in any case be natural (not requiring a value analysis of this sort).

As indicated by the wide-ranging estimates of headroom above, the value of such a device would probably vary greatly according to treatment setting. If, as indicated by the literature, cost of antibiotic treatment is greater in a hospital setting, then the value created by the Kryptor compact is going to be greater in this setting. This may be of consideration in development/distribution decisions.

## Follow-up (KRYPTOR compact)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The headroom analysis could not deliver an MRP per device, due to the lack of information regarding the likely / feasible distribution strategy for the Kryptor compact (i.e. how many samples would each device process per year?), and also how long it is likely to last. However, by using estimates of antibiotics prescription impact from an RCT of the Kryptor compact's predecessor (the classic Kryptor assay), the value per patient was calculated. A range of values was presented, assuming different antibiotics cost. This ranged from a value per patient of 83 pence up to £62.40. The lower of these values was based on an antibiotic treatment course cost of £2 (supposedly the first-line treatment for LRTI), whereas the higher estimate was based on an antibiotic cost of £150, which is close to that estimated for hospitalised pneumonia patients.

The "average" antibiotics cost per patient is likely to fall somewhere in-between these two extremes, but will certainly vary in relation to clinical setting. The cost of antibiotics for patients who are more severely ill from their respiratory infection will on average be higher than those who go to their GP with mild symptoms. It is probable, therefore, that the Kryptor compact could fetch a higher price if aimed at a secondary care setting. Although I cannot anticipate the likely cost per patient for diagnosing patients with the Kryptor assay (especially given my lack of understanding of the number of samples processed by each device), 83 pence seems like a small reimbursement opportunity, especially as this would have to cover the service costs involved in the process e.g. lab costs, transport if required, time, etc. Therefore, the reimbursement opportunity seems much greater / more likely in situations where the cost of antibiotics is relatively high.

In terms of the 'yes or no to development' aspect of this headroom analysis, this represents a bit of a special case. The baseline in terms of clinical value was 'nothing' (i.e. no other useful diagnostic test is used to determine bacterial/viral cause of infections), and that's why the Kryptor compact represented a 'new indication' in this respect. However for the company, the Kryptor compact is an incremental development of their previous model. Therefore, the development costs are likely to be minimal. Also, the Kryptor can be / is already used for several diagnostic purposes, such as in prenatal setting; this will at least increase the market for the Kryptor compact, but it could also scale-up the value of the device dramatically if one unit can serve several different indications.

The actual cost per procalcitonin measurement using the Brahms Kryptor is about £15 according to the company, as reported by a PASA economic report (CEP 2010) (this includes assay material, reagents, technician time, and purchase / maintenance of bench-top analyser). However, the use of procalcitonin testing usually requires repeat testing within 6 to 24 hours, and Brahms indicates that two tests are likely to be sufficient. This means an actual cost of about £30 per patient tested. This indicates that at the lower estimate of antibiotics cost, the reimbursement opportunity per test as

indicated by the headroom analysis would have fallen far short of what would be required to support the test in clinical practice. The upper range of these estimates, however (i.e. where the cost of antibiotic treatment is about £70 and above) seems likely to present an adequate reimbursement opportunity.

**Headroom unfavourable for situations where antibiotics are likely to cost under £70 per course (assuming negligible development costs being needed to be made back). Headroom seems favourable for cases where antibiotics costs are high. This may indicate that the secondary care setting might provide a viable setting for the Kryptor compact.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

No NICE guidance has been issued for this technology specifically. In 2008, NICE produced a clinical guideline on 'Prescribing antibiotics for self-limiting respiratory tract infections in adults and children in primary care' (NICE 2008a). In this guideline they emphasise that whilst prompt antibiotic treatment may have been relevant in the past, in modern times rates of complication are low; the fact that most people presenting in primary care with an acute uncomplicated RTI receive antibiotics, is no longer appropriate. They recommend a strategy of no antibiotic / delayed antibiotic prescribing in all cases except for: bilateral acute otitis media in children under 2 years of age or in children with otorrhoeia, or acute sore throat/pharyngitis/tonsillitis when three or more Centor criteria are present. In these cases, antibiotics should be prescribed immediately. In a costing report that was issued as part of this guideline, it was estimated that, if implemented, £3,678,000 of savings could be realised due to the reduced antibiotics costs.

In May 2007 NICE issued a clinical guideline for 'Feverish illness in children' (NICE 2007a). A research recommendation was that the performance and cost-effectiveness of procalcitonin versus C-reactive protein (another inflammatory marker) for identifying serious bacterial infection in children with fever *without apparent source* should be investigated.

In July 2007 the topic of serum procalcitonin as a marker for respiratory LRTI was considered by the NICE TA committee but was referred to the national coordinating centre for HTA (NCCHTA).

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

When looking up the Brahms product range it is clear that the Kryptor assay has been developed for many indications, the list of which includes Intensive care and emergency medicine, Thyroid diseases, Tumour markers and Prenatal screening (categories which comprise 5 to 14 individual tests). In fact, the procalcitonin test is only listed as one of the three products in 'Other Parameters' (BRAHMS 2011b). On their own website, they describe the Kryptor compact as 'a fully automated random-access immunoassay system, offering optimal analytical precision as well as maximum economic efficiency' which was developed 'to meet the needs of today's laboratories' (BRAHMS 2011a). The company has distribution partners across the world. As well as Brahms PCT assay for the Kryptor system, the company also have agreements with other companies (DiaSorin S.p.A, bioMerieux A.A., Siemens Medical Solutions Diagnostics and Roche Diagnostics GmbH) to provide / distribute the PCT assay compatible with these various other systems (BRAHMS 2008; Thermo Scientific 2011).

### Have there been investigations into its clinical / cost effectiveness?

A news article published on several biomedical websites in July 2009 reported that the Kryptor Compact had been successfully proven in the context of risk assessment for Down's syndrome in first trimester screening; the King George hospital in Essex conducted an evaluation of the Kryptor Compact and found the results to be interchangeable with the classic system, with performance "equally as good", being the instrument of choice for 1<sup>st</sup> and 2<sup>nd</sup> trimester screening (Buchholzer 2009). Apart from this article, I have not found the Kryptor *compact* mentioned specifically (the system is simply referred to as the Brahms Kryptor system). This is not surprising, but we are at least assured that the assumption of equivalent performance seems to be well founded.

### Clinical effectiveness

There have been five major RCTs which have tested the use of procalcitonin-guidance for antibiotic prescription versus standard care in a clinical setting, one of which was discussed in the headroom analysis (Christ-Crain, 2004). The other four RCTs were also all based in Switzerland, and all used the Brahms Kryptor assay for treatment guidance. The following is a summary of findings:

- Briel (2008, LRTIs, primary care) found an absolute reduction in antibiotic use of **72%** (Briel et al. 2008).
- Christ-Crain (2006, community-acquired pneumonia, emergency department) found an absolute reduction in antibiotic use of **14%** (Christ-Crain et al. 2006).
- Stolz (2007, COPD exacerbations, emergency department) found an absolute reduction in antibiotic use of **32%** (Stolz et al. 2007).
- Schuetz (2009, LRTI admissions, tertiary care hospitals) found an absolute reduction in antibiotic use of **13%** (Schuetz et al. 2009).

These show variable results, and the trial results that I used sit somewhere in between these estimates (I used results from the RCT reported by Christ-Crain in 2004 which found a 39% reduction in antibiotic use, which translated into a cost-saving for antibiotic spend of on average 52% per patient admitted). None report any changes in outcome.

### Cost-effectiveness

An economic report was produced by the NHS purchasing and supply agency (PASA) in March 2010 (CEP 2010) (presumably the result of the referral by NICE of the topic to the NCCHTA). Their analysis uses the following assumptions:

- Average cost of antibiotics: £16.63,
- 86% of patients are prescribed antibiotics in routine clinical practice,
- Cost per tested patient is £30 (based on estimate by Brahms),
- Sensitivity & specificity are 76%, and
- 20% of LRTIs have a bacterial cause.

They calculate that it costs an additional £51 to correctly treat (by either giving or withholding antibiotics) a patient using the procalcitonin test (as compared with standard care). Like the headroom analysis, the report does not quantify any outcome measures, but urges the reader to



consider this cost alongside potential benefits achieved, which include the reduction in side-effects of antibiotics and the reduced likelihood of further antibiotic-resistant strains of bacteria (CEP 2010).

A more recent cost-effectiveness analysis which uses published estimates of the impact of procalcitonin guidance on antibiotic usage, calculates that the point at which the cost of testing equals the cost of antibiotics saved is when daily antibiotics cost Can\$148.26 (about £80)<sup>30</sup> (Heyland, Johnson, Reynolds, & Muscedere 2011).

I found two UK based (non-randomised) studies. Bignardi et al. applied the Kryptor analyser for two months and found that savings in antibiotic use (£1,306) did not cover the cost of testing (£6,570) (Bignardi et al. 2006). The reason for this was that the antibiotics discontinued were mainly inexpensive oral antibiotics (e.g. doxycycline and amoxicillin). By contrast, Saeed et al. found that, by applying the PCT test to those admitted to the intensive care unit of The Royal Hampshire County Hospital in Winchester, there was a net saving of about 17% (Saeed et al. 2011).

The results of these clinical and cost-effectiveness analyses confirm the headroom analysis results; that the test would only be cost-effective where the antibiotics courses that are discontinued as a result of the test are expensive. The literature also supports the decision to leave aside outcome issues from the quantified analysis, leaving these for 'value judgement' only.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

In their clinical guideline on prescribing antibiotics for respiratory tract infections, NICE indicates that a no antibiotic / delayed antibiotic strategy should be applied where patients in primary care present with acute otitis media, acute sore throat/pharyngitis/tonsillitis, common cold, acute rhinosinusitis, or acute cough / acute bronchitis (NICE 2008a). If this were to be systematically undertaken across the health service, it is likely to reduce the overall prescription rates of antibiotics under 'standard clinical practice', and thus reduce the savings that could result from the Kryptor compact (or any PCT test).

Blood tests taken for procalcitonin analysis do not seem to be widely applied in clinical practice in the UK. NICE guidelines do not mention the use of serum tests, and advice to patients presented by 'NHS Choices' indicates that clinical diagnoses of chest infections still rely predominantly on symptom analysis (NHS Choices 2010a); blood tests ('to identify the germ that is causing your infection') is only mentioned among the list of 'further testing', which may be required only if chest infection symptoms are severe.

### **Are there now many direct competitors?**

Although all of the RCTs identified considered PCT testing using the Brahms Kryptor assay, the economic report by CEP identified other suppliers: Siemens, Roche and BioMerieux (though I found that Brahms appears to hold license agreements with these companies).

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<sup>30</sup> Cost results from this study were reported in Canadian dollars at 2009 prices. In December 2009 the exchange rate was 1.8573CAD to the pound.



C-reactive protein (CRP) is another biomarker that has been found to be associated with bacterial infection, and has also undergone trials. However, a meta-analysis conducted by Simon et al find procalcitonin to be more accurate (more sensitive and specific) than CRP in the diagnosis of bacterial infection (Simon L et al. 2004).

### **Conclusions: How useful might the headroom exercise have been?**

The headroom analysis considered the case for developing the Kryptor Compact, which was described in the NHSC briefing and became available in 2007. Although this model was an update of a previous version from the same company, from a health economic perspective the base-line comparator was standard clinical practice, which did not appropriately discriminate between bacterial and viral infections, and thus led to a situation of over-prescription of antibiotics.

As the classic Kryptor assay had already been tested in a clinical trial, I was able to use the results of this directly to estimate the headroom per LRTI patient for the Kryptor Compact. Relating this to the actual cost per patient tested with the Kryptor of £30 (though it is unclear which model this is based on), the result of the headroom would have been that the device only looked cost-effective to the NHS if antibiotic costs were over £70 (development costs may be minimal, as the Kryptor compact represents an incremental change to a previous model). This would have indicated to the company that the test may be appropriate for high-risk infections where antibiotic prescription costs are large, but not as part of general routine clinical practice.

Indeed, blood tests are not recommended in current clinical guidelines for the routine management of LRTI patients in the community (NICE 2008a).

Although the headroom analysis reflected reasonably well the clinical and economic studies that have since been published on the Kryptor system, taking the entire follow-up into consideration, it may be that the headroom method was not relevant / well suited to this case, for the following reasons:

1. The Kryptor compact has a wide spectrum of clinical applications. The headroom analysis considered its clinical and economic value in relation to this specific market which, although perhaps useful for the company in understanding reimbursement opportunity for this particular indication, is not useful as the sole determinant of a Go/No-Go development decision.
2. The decision to develop the Kryptor Compact probably represented a natural evolution of the company's product portfolio, and the desire to keep their technologies up-to-date and competitive. A headroom analysis may have seemed redundant if this is the case.
3. The business and implementation context of this diagnostic test is clearly much more complicated than a headroom analysis can fathom/reflect. Not only is the question of number-needed (to serve whole population) a problem, but the follow-up has brought to light that the company have licence agreements with other companies and providers, and that distribution is not straightforward.

## 11. Aquadex FlexFlow. CHF Solutions

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Incremental Development / Addition;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: Dec 2006</i></p> <p><i>Time perspective of this analysis: 2004</i></p>	<p>Acute decompensated heart failure (ADHF) is a common cause of acute respiratory distress, and is often associated with an accumulation of fluid ('volume overloaded state'). A sufferer of congestive heart failure (CHF) may easily decompensate (where the heart fails to maintain adequate blood circulation). It is thought that approximately 1-2% of healthcare budgets in developed countries are spent on heart failure, and that in the UK, 66% of this spend is accounted for by hospitalisations (Varney 2001).</p> <p>Ultrafiltration using the Aquadex FlexFlow aquapheresis system (by CHF solutions) is for patients with ADHF who are unresponsive to 'conventional therapies', or those with very severe peripheral oedema and fluid overload.</p> <p>It is a portable, trolley based device which removes excess water and salt from a patient's circulation (much like the set-up of a dialysis system), and can be performed in a hospital ward or outpatient department. Each treatment lasts approximately 24 hours (multiple treatments may be required per patient).</p> <p>Being able to reduce the fluid overload associated with ADHF will help the heart to work more efficiently, and thus maintain perfusion to vital organs (Southworth 2003).</p>
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<p><b>2. Comparator</b></p>	<p>Diuretics are the first-line management for patients with ADHF; they are the cornerstone therapy for these patients as they help to manage fluid overload. Two types of drugs, IV vasodilators and IV inotropes, are used as adjunct therapy for patients hospitalised with ADHF. Treatment of the precipitating cause is also important.</p> <p>When patients do not respond to diuretics therapy, management can also include conventional ultrafiltration which, unlike the Aquadex FlexFlow, requires high blood flow rates and is used mainly in intensive care units.</p> <p>Although diuretics are usually effective in controlling fluid overload, the management of patients who do not respond to conventional drug treatment is presenting an increasing problem for clinicians (Lécluse et al. 1999). It is thought that as many as a third of CHF patients become resistant to diuretics; what's more, resistance occurs most frequently in moderate and severe CHF patients, making this a serious problem (Ravnan, Ravnan, &amp; Deedwania 2002). Although trying different combinations of drug therapies can help to overcome this resistance, including inotropic support (though the effectiveness of this drug in diuretic resistance is not well established), the issue makes the need for an alternative ever more important.</p> <p>It is difficult to know in this case whether to consider the standard pharmacological therapy (diuretics, with vasodilators or inotropes added</p>
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	<p>in hospital care) as the gold standard of clinical practice, and thus the appropriate comparator for this analysis, or whether to take as a baseline conventional ultrafiltration (which must be carried out in an intensive care unit). On the one hand, ultrafiltration/aquapheresis is not included in the “treatment options” of a review by Southworth (Southworth 2003) and other recent summaries of treatment for refractory patients (Ravnan, Ravnan, &amp; Deedwania 2002), is not mentioned in the NICE clinical guideline for heart failure produced in 2003 (NICE 2003a), nor is it included in the guidelines produced by the American College of Cardiology for the Evaluation and Management of heart failure (Williams, Bristow, Fowler, &amp; et.al. 1995).</p> <p>On the other hand, in 2007 this technology was submitted to the technology appraisal team within NICE but rejected, and Ultrafiltration seems additionally to have been submitted to the Interventional Procedures team, but was rejected as it was ‘not in remit’; the reason for this was that ultrafiltration / aquapheresis was regarded as a “minor modification of an existing procedure which is considered established clinical practice with risks and benefits that are sufficiently well known”(NICE 2010f). They do not, however, explain the context of this statement, and whether they refer to its use in ADHF patients.</p> <p>The NHSC document refers to the Aquadex in relation to both of these potential comparators:</p> <ul style="list-style-type: none"> <li>• Conventional ultrafiltration requires high blood-flow rates and large bore vascular access, and is therefore mainly used in intensive care or renal departments. Aquadex can be used in a normal ward environment, or outpatient department.</li> <li>• Compared with standard care, it is thought that the Aquadex could reduce length of stay in hospital and reduce readmission rates.</li> </ul> <p>Small clinical studies of ultrafiltration (sometimes referred to as haemofiltration or peritoneal dialysis [though this is slightly different]) date back many years to at least the 1960s (Cairns et al. 1968), but the principles of ultrafiltration were described even earlier in the 1940s. There were many publications through the 1970s, 80s and early 90s of individual patient cases (Morgan, Mansell, &amp; Thompson 1985) and very small clinical studies (Asaba et al. 1978;Kramer et al. 1980;Sagliaschi et al. 1992;Simpson et al. 1987;Simpson &amp; Hutton 1987), which showed the usefulness of ultrafiltration in refractory ADHF patients (diuretic-resistant). In 2001 Ellison (Ellison 2001) mentions mechanical ultrafiltration for the treatment of diuretic resistant CHF patients, but more recent literature on this has been limited. In the literature that relates to ADHF treatments more widely, ultrafiltration is either not mentioned, or mentioned in passing and without great detail relating to the extent to which it is actually used in clinical practice.</p> <p>So, whilst it has been around a long time, conventional ultrafiltration still does not seem to be part of mainstay clinical practice. I found one paper from 1989 that related to the cost-effectiveness of ultrafiltration (said to</p>
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	<p>be “highly cost-effective), but could only access the abstract, and got no indication of what this statement was based on (L'Abbate et al. 1989). One paper considers why ultrafiltration has tended to be overlooked, and why official clinical guidelines have tended to ignore the management of <i>refractory</i> patients. Sackner-Bernstein and Obeleniene (Sackner-Bernstein &amp; Obeleniene 2003) propose three reasons: firstly, the requirement of central access has meant that ultrafiltration has needed to be delivered in an intensive care unit (putting a strain on resources); secondly, this type of intervention has tended to be focused toward nephrology (kidneys) rather than used by cardiologists (so might be met with some resistance), and; thirdly, clinical cardiologists are used to considering pharmacological rather than mechanical treatments for their patients. The Aquadex FlexFlow could overcome the first barrier by allowing ultrafiltration to be offered in more a accessible and less expensive setting (the ward or outpatient department), and if it can be proven to be both effective and cost-effective, then clinicians may embrace such a procedure, as a way to treat their refractory patients for whom currently there are few options.</p> <p>The Aquadex FlexFlow is intended as a treatment option for those who do not respond to diuretics, rather than a complete replacement of diuretic therapy, which is relatively cheap and well supported by evidence. Therefore, it would be appropriate to conceptually place the Aquadex in the context of diuretic resistance, and the outcome of those patients who are not well managed by current therapy. However, I have found no assessment of the impact of diuretic resistance on outcomes.</p>
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<p><b>3. Market size</b></p>	<p>It is estimated that as many as one third of patients develop resistance to diuretic therapy. Lloyd et al. estimate that there are about 181,000 hospitalised CHF events every year (Lloyd, Schmieder, &amp; Marchant 2003). This means that a potential 60,000 could be indicated for ultrafiltration using the Aquadex FlexFlow.</p> <p style="text-align: right;"><b>Market size (UK) per year: 60,000</b></p> <p><i>I have rounded this estimate down, as the NHS hospital cost of an acute CHF event that was reported alongside this incidence figure, was £1,337. This seems very low for ADHF events compared with estimates I have found in the literature. Therefore, it may include a wider range of CHF events than those that could be relevant for the Aquadex. This may still be a very optimistic estimate considering the low current uptake of ultrafiltration in clinical practice.</i></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in</p>	<p>Although the literature does not facilitate a precise estimate of potential costs that may be saved by treating patients with a new intervention like the Aquadex, either compared to conventional ultrafiltration <i>or</i> to conventional pharmacotherapy, one study indicates that the effect of Aquadex</p>
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<p>previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>treatment might be comparable for both of these baseline comparators (in terms of the incremental effect on hospital resources, not taking into account the costs of the interventions themselves).</p> <p>As indicated in the NHSC briefing, the Aquadex would allow for treatment in the ward environment rather than in an intensive care setting; hospital costs could be saved by the relocation of treatment. A cost-effectiveness study of a new drug (nesiritide) for ADHF patients showed that, when compared to standard (milrinone) treatment, length of stay in the intensive care unit was reduced by 2 days, though overall length of stay was not statistically different (Lewis, Gurram, Abraham, &amp; Akers 2003).</p> <p>So, to roughly estimate the impact of: a) moving ultrafiltration from an ICU setting to a ward, or b) simply providing more appropriate therapy to refractory patients than that offered by current management: I will assume a reduction in ICU length of stay by two days<sup>31</sup>.</p> <p>The PSSRU's 'Unit Costs of Health and Social Care 2004' (which draws its data from DH reference costs) indicates that the national average cost per bed day in an Intensive Therapy Unit / Intensive Care Unit is £1,330; a bed day in a Coronary Care Unit (ward) is £437 (PSSRU 2004). Treating a patient in the ward rather than an ICU would save the service approximately £893 per day.</p> <p>I could find no cost estimates of conventional ultrafiltration, nor could I identify the cost of hospitalisation attributable to the medication that would be replaced by Aquadex (although one study found diuretic cost to represent just 2% of total drug expenditure for HF hospital admissions, less than 0.001% of the total admission cost (McGowan, Heerey, Ryan, &amp; Barry 2000)). Therefore, the peripheral service cost implications must be considered alongside the headroom estimated.</p> <p><b>Service costs saved by reduction of LOS in ICU:</b>  <b>(Total) ΔSC= 107 million</b>  <b>(Av. Per person) ΔSC= £1,786</b></p>
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<sup>31</sup> The NHSC briefing indicates that for severe cases of fluid overload, 'multiple' treatments may be required, each typically lasting 24 hours.

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p style="text-align: right;">P<sub>Diuretics</sub> = ? P<sub>Conventional Ultrafiltration</sub> = ?</p> <p><i>Intuitively, this seems like it could be an overestimation of the hospital costs. This may be because the costs per bed day of ICU and Coronary Care unit were derived from an NHS reference cost database, and did not represent 'cost per excess bed day' (as they are too generic to have an HRG), but were the national average unit cost, presumably encompassing the total cost of treating those patients admitted to that unit. This is not ideal, as the high cost for an ICU day will probably cover the cost of those expensive treatments used in ICU, which I do not want to capture when looking simply at the effect of changing location of a treatment.</i></p> <p><i>The 'total' service cost impact is speculative, given the uncertain number of refractory ADHF patients.</i></p> <hr/> <p>Something not incorporated above is the potential reduction of hospital readmission rates (I have included this separately as the sources indicate quite different hospitalisation costs, so aggregating them seems inappropriate). An Irish study which estimated the cost of hospital treatment arrived at an average cost per heart failure patient of £2,774 (i) (this might be quite low because the sample of 30 patients may not have included those patients serious enough to warrant ultrafiltration). Another study based in the U.S. finds an overall cost of £3,085 (ii) (also an estimate that is not based specifically on patients resistant to diuretics).</p> <p>The average of the above estimates is £2,930 (cost per hospital admission). If half (speculative assumption) of current readmissions could be avoided per Aquadex use, then on average this could lead to a £1,465 reduction in health service cost per patient (of the 'readmitted' population: I don't know how big this population is), additional to any cost saving in the initial visit.</p> <p><b>Service costs saved by reducing readmission rate by half:</b>  <b>(Av. Per person of the 'readmitted' population)</b>  <b>ΔSC= £1,465</b></p>
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<p>Describe any potential costs/savings that you haven't quantified.</p>	<p><i>This is all speculative, but was included as the briefing indicated that readmission rates could be reduced. Adding these two effects together, if deemed appropriate, would lead to an average service cost saved for some patients of up to <b>£3,251</b>. (This assumes that they would only be readmitted once!)</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>I could not identify any HRQoL studies using an accepted method such as the EQ-5D.</p> <p>One cost-utility analysis of CHF patients delivered by Capomolla et al. used the time trade-off method to compare the costs and utilities of patients managed according to 'usual care' or 'day hospital' (Capomolla et al. 2002). Usual care was a management strategy whereby care was driven by the patients' needs, encompassing emergency room management, hospital admission, and outpatient access. Although the method and results for utility elicitation are not well documented, the utility weighting estimated for the usual care group could be used as a proxy for baseline utility of heart failure patients: this was 0.63. Other estimates using time trade-off to estimate the mean utility of heart failure patients are 0.76 (Havranek et al. 2004) and 0.77 (Havranek et al. 1999).</p> <p>What would be useful to identify is the impact of an acute exacerbation of CHF (resulting in hospitalisation) on HRQoL. One study elicited the HRQoL of heart failure patients using the Cantril Self-Anchoring Scale (Welsh et al. 2002), and on a scale of 1 to 10 found an average QoL of 5.1 at time of visit to the emergency department. However, the 8.0 found at 'baseline' was derived from patients being asked about their QoL before heart failure diagnosis.</p> <p>A study by Jaagosild et al. used the time trade-off method to measure the utility of severe CHF patients at hospital admission (0.84), at 60 days (0.93), and at 180 days (0.94) (Jaagosild et al. 1998). Although these utility weights are very high and probably reflect the method of elicitation, we could use the % change in utility found (an 11% reduction) or the absolute reduction (about 0.1) to estimate the impact of hospitalisation on HRQoL. Taking baseline to be about 0.7 (from the three estimates mentioned above), this would imply a utility at hospitalisation of about 0.6.</p> <p>However, in this analysis the only variable we are</p>
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<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>changing is the length of stay in ICU rather than overall length of stay. As such, it would seem too speculative to try and imagine an impact on HRQoL in that respect.</p> <p>The NHSC briefing indicates that the Aquadex FlexFlow may be able to reduce length of hospital stay, and readmission. If readmissions were to be reduced by half, and the average length of hospital stay is 8 days (Lewis, Gurram, Abraham, &amp; Akers 2003) (0.022 years), then a drop in utility of 0.1 for the hospitalisation itself (as outlined above) could be used to estimate the reduction in QALY loss:</p> <p>0.1*0.022 years = 0.0022 QALYS per patient that avoids a hospital readmission, which is half of those currently readmitted.</p> <p style="text-align: right;"><b>ΔQALY= ?</b> <b>(Av. per person who would currently be readmitted)</b> <b>ΔQALY= 0.0011</b></p> <p><i>(This also presumes a single readmission). I've not considered issues of survival and impact on mortality. One paper suggests that prognosis remains negative for those treated with ultrafiltration, but it may allow those waiting for heart transplant to survive, and improve their chances of surviving heart surgery as well (Sagliaschi et al. 1992). I have also not considered that length of stay of subsequent visits might be reduced.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This</p>	<ul style="list-style-type: none"> <li>• [GREEN] Congestive heart failure is the most common reason for fluid overload, but is by no means the only cause (liver cirrhosis, kidney disease, hypertension, certain surgical procedures, etc). This may mean that the potential market for Aquadex FlexFlow is large, and that that if a hospital were to invest in the unit (trolley-based and portable), it could provide value to patients and the NHS through its use in other areas as well.</li> <li>• [GREEN] The small studies that have tested ultrafiltration as a way to treat diuretic-resistant ADHF patients have all been positive, indicating that the therapy is effective.</li> </ul>
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<p>could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [AMBER] Even though ultrafiltration has been around for many years, it is still not part of mainstay clinical practice, and is omitted from various national guidelines. Although the Aquadex may help to overcome the logistical / financial barrier to the use of ultrafiltration in clinical practice, whatever else has inhibited the therapy's use until now (e.g. clinician reluctance) may remain.</li> <li>• [AMBER] As the use of ultrafiltration has existed in the context of CHF since the 1970s, it seems feasible to assume other companies will easily fill the market if it becomes a viable product.</li> <li>• [AMBER] Combining classes of diuretics is the normal strategy adopted to combat diuretic resistance (De Bruyne 2003;Paul 2003). Many recent reviews do not indicate that any other strategy is necessary.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• As described, diuretic resistance is usually tackled by using a variety of available drug therapies. For what proportion of patients does this still not offer adequate control of symptoms?</li> <li>• What proportion of patients are currently readmitted?</li> <li>• If possible, find the cost associated with conventional ultrafiltration, and diuretic therapy.</li> <li>• What is the likely impact of the Aquadex on overall length of stay? Does it have the potential to reduce more than just ICU stay?</li> <li>• How many courses of treatment are typically required?</li> <li>• How many machines would be required to equip a cardiac ward so that all relevant patients could receive the therapy when needed?</li> <li>• Are other products (haemodialysis products?) able to perform the same function as the Aquadex FlexFlow? If so, how is the Aquadex better?</li> <li>• The main difficulties in eliciting the 'headroom' for this product, were:             <ul style="list-style-type: none"> <li>○ Not understanding the most appropriate comparator</li> <li>○ Having no estimates of the extent of potential impact (an idea of this is likely to have been present if this were to be</li> </ul> </li> </ul>
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	<p>filled in by the developer themselves)</p> <ul style="list-style-type: none"> <li>○ In the absence of this, inadequate information in the literature upon which to base these assumptions.</li> </ul> <p>As such, the analysis should be updated once more is known or a greater understanding has been developed of the potential impact of Aquadex on outcome and cost parameters.</p>
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### Notes by AC

- (i) The cost reported in the Irish study for a heart failure admission was IR£2,146, for which the data was collected in 1999/2000 (McGowan, Heerey, Ryan, & Barry 2000). Converting this to pound sterling gives a cost of £2,331. To convert to today's (2004) prices, I inflated this according to the HCHS 'Pay and Prices' Index:  
HCHS P&P Index 1999/00: 188.5  
HCHS P&P Index 2003/4: 225.6  
Inflation rate: 1.119  
 $£2,331 * 1.19 = \mathbf{£2,774}$
- (ii) The cost reported for the control arm of this trial (overall cost of ADHF admission per patient) was \$4553, and the paper was published in 2003. The exchange rate at this time was \$1.5495 to the £, resulting in a pound value of £2,938. To convert to today's (2004) prices, I inflated this according to the HCHS 'Pay and Prices' Index:  
HCHS P&P Index 2002/3: 213.7  
HCHS P&P Index 2003/4: 224.8  
Inflation rate: 1.05  
 $£2,938 * 1.05 = \mathbf{£3,085}$

### Headroom Notes (Aquadex FlexFlow)

The only numbers to be estimated from this analysis were:

- 1) The saved service costs that could result if the Aquadex FlexFlow were to reduce length of stay in ICU by 2 days compared with conventional ultrafiltration or conventional pharmacologic treatment. This saving was £1,786.
- 2) An estimate of the service costs saved by halving readmission rates. This saving was £1,465

Together, these would lead to a headroom in service costs of £3,251, but only in patients who would currently experience a re-admission; as these are quite speculative it would be down to the developer to decide if either or both of these estimates would be appropriate. The QALY impact of reducing readmissions was not included in the headroom calculation, as it is not known for what proportion of patients this would apply, so it is impossible to know the average per patient. However, the QALYs generated for those patients who are no longer readmitted to hospital would be 0.0022, for which the NHS should be willing to pay £44 to £66 per patient (but this cannot be aggregated across the whole ADHF population without knowing more about the total incidence of readmission).

What must be considered alongside these savings is the cost of provision of this service. As well as estimating the cost saved from disinvesting in current practice, the extra cost implications must also be accounted for. Nurse time will be required in order to empty the ultrafiltration bag (every three hours), and to attend if an alarm is raised.

An MRP can only be delivered with an understanding of how many patients one unit could serve, and the likely cost of consumables per course.

## Follow-up (Aquadex FlexFlow)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The difficulty that arose from trying to estimate a headroom for development for the Aquadex FlexFlow by CHF Technologies was that the potential benefits projected in the NHSC briefing document were not specific enough and, in the absence of these estimates, the literature on ADHF and ultrafiltration (at least that which I was able to access within a reasonably short time frame), did not offer much help in informing these estimations.

What I did find was that in one drug study, improved therapeutic benefit resulted in a reduced ICU stay (by two days). So, I hypothesised that if ultrafiltration could improve outcome for those who do not respond to drug therapy, then a similar benefit could be achieved. Also, I knew that the benefit over conventional ultrafiltration was that it could be carried out in a ward rather than ICU setting, so this also fit into that comparison. This would lead to a reduced hospital cost (from the marginal difference in the cost of a bed day) of **£1,786** per patient. I also presented the effect of reducing readmissions by half, both in terms of costs (£2,930 per readmission avoided; **£1,465** on average for the cohort of patients who would otherwise be readmitted), and in terms of QALYs (which would generate a reimbursement of £44-£66 per readmission avoided; **£22-£33** on average for the cohort of patients who would otherwise be readmitted). However, I could not aggregate these effects as: a) the costs used for the two seemed quite different in magnitude, and b) I could not find an estimate of % readmission, meaning I could not find the average costs or QALYs saved across the whole ADHF population.

The actual cost of the Aquadex FlexFlow system is approximately £12,000 (though it can be loaned or leased to hospitals). For each ultrafiltration course, a new filter and blood circuit is required; these cost about £600 (leasing costs are £500 a month, and leasing reduces circuit costs from £600 to £450). Multiple treatments may be required per patient for severe cases. Depending on how many courses each patient would require, this may or may not exceed the estimated headroom.

Of the economic analyses that I have found, one implies the use of only one filter system per treated patient (CEP 2007b), and one (that uses unpublished findings from the UNLOAD trial (Costanzo et al. 2007)) indicates that the average patient treated with ultrafiltration (using Aquadex) underwent two

treatments with an average of 1.2 filters per treatment (Bradley, Levy, & Veenstra 2009). If patients did only undergo one session of ultrafiltration (with £600 consumables cost and the amortised cost of equipment presumably relatively small), then the reimbursement opportunity presented by the headroom may well have seemed attractive. Using the estimate of 2.4 filters (at a cost of £1,440 per patient) would mean that the prospect for profit would be reduced, but may still seem viable given the potential opportunity of reimbursement estimated. However, this would have depended on the developer's estimates of effect, which I found difficult to guess when undertaking the headroom analysis.

**Given the exploratory estimates of potential reimbursement opportunity (and comparing this to the actual cost of the device), the headroom analysis may have indicated a positive development decision. However, the analysis undertaken and assumptions made were highly speculative; the developer's input of early estimates of potential effectiveness would have been useful.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

As described in the pro forma, this technology was put forward for evaluation by the Interventional Procedures team, but rejected on the basis of being a 'minor modification' of established clinical practice. It was also submitted for technology appraisal but rejected by the panel ("to be considered for inclusion in future update of Heart Failure clinical guideline) (NICE 2009b). Ultrafiltration is not mentioned at all in the NICE Clinical Guideline, either in its original publication (NICE 2003a) or the updated version published in August 2010 (NICE 2011a).

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

The Aquadex FlexFlow System (CHF Solutions) received FDA approval in September 2006 (FDA 2006a). The device is distributed in the UK by Kimal Plc. (Gambro is another supplier). A 'case study' on the Aquadex ultrafiltration system, presented by the ABHI, indicated that the system was being evaluated in three UK hospitals (the date of issue is not detailed, but appears to be post-2008) (ABHI 2011). It is not clear whether the treatment is widely used by the NHS, though an evaluation report for the Aquadex FlexFlow was produced for the NHS Purchasing and Supply Agency by CEP (Centre for Evidence based Purchasing) (CEP 2008). Early user experience from NHS consultants was favourable.

The CHF Solutions brochure for Aquadex FlexFlow 'How Are You Treating Fluid Overload?' (CHF Solutions 2011) indicates that the device is aimed not only toward the treatment of heart failure, but also fluid overload caused by problems with the kidneys, lungs, after surgical operations, burns, and trauma. Therefore, the market size and potential clinical utility derived from this ultrafiltration is wider than that estimated in the headroom analysis.

#### **Have there been investigations into its clinical / cost effectiveness?**

There are now many clinical investigations and publications for ultrafiltration, and many of them relate to the Aquadex system specifically. In 2007 CEP produced an evidence review for ultrafiltration, which included an economic evaluation of the Aquadex FlexFlow (CEP 2007b). They

used effectiveness results from the UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial (Costanzo et al. 2007), and NHS costs. They use the estimated difference between ultrafiltration and IV diuretics in the following parameters (all from the UNLOAD trial):

- Length of stay (LOS) (6.3 days vs. 5.8 days),
- Rate of rehospitalisation (18% vs. 32%),
- LOS for rehospitalisation (1.4 days vs. 3.8 days), and
- Rate of emergency hospital visits (21% vs. 44%),

The total cost per patient treated is found to be £1,379.39 for Aquadex and £771.39 for diuretics. However, they acknowledge that the effectiveness parameters did not relate specifically to diuretic resistant patients, whose baseline costs are likely to be much higher than the average (and thus stand far more to gain clinically and economically with ultrafiltration than the average ADHF patient). I found two problems with the analysis undertaken by CEP, the first relating to NHS unit costs used (the costs per bed day for the various settings described were much lower than those I found during my analysis, and since) and the second relating to Aquadex costs. The authors find bed day costs (for cardiac ward and ICU) from the *Unit costs of health and social care 2006* from the PSSRU (PSSRU 2006). A read of the document reveals that the £464 estimate used for an ICU bed day is actually for an ICU attendance associated with mental health services, and the £101 cardiac ward cost used by CEP is actually the cost per bed day of patient rehabilitation in cardiology—the costs that should have been used, from the NHS reference costs pertaining to the same year are £450 for the coronary care unit and £907 for the cardiac intensive care unit (Department of Health 2007). Secondly, the 'Aquadex equipment and consumables' costs used (per patient treated) was £621.97. Considering that just the filter costs £600 (and assuming that the rest is made up of the amortised cost of equipment), this assumes an average of just one filter required per patient treated. This does not seem likely, given trial results and manufacturer estimates.

Costanzo et al. published the results of the large clinical trial UNLOAD (Costanzo et al. 2007). They found that ultrafiltration (using the Aquadex system) was safe, produced greater weight and fluid loss than intravenous diuretics, and reduced 90-day resource utilisation. The same author published another study in 2010 (Costanzo et al. 2010), which found similar fluid removal results between ultrafiltration and diuretics, but fewer heart failure rehospitalisations were associated with ultrafiltration. Also, it more effectively reduced sodium levels in congested HF patients.

Bradley et al. presented a decision-analytic model in 2009 in a U.S. setting, finding that although rehospitalisation rates are reduced, ultrafiltration is unlikely to be cost saving (Bradley, Levy, & Veenstra 2009). They approached the model from various perspectives, and found that from a societal perspective, treatment with ultrafiltration had an 86% probability of being more expensive than IV diuretics (base case: \$13,469 versus \$11,610), from a Medicare payer perspective it had a greater than 99% chance of being cost *saving* (due to the set reimbursement model for CHF hospitalisation) (\$7,230 versus \$8,652), and from a hospital perspective there was a 97% probability that ultrafiltration was more expensive (ultrafiltration was associated with a \$6,157 shortfall between costs and revenues whereas IV diuretics were associated with a shortfall of \$2,820). The

model was based on the results of the UNLOAD trial (Costanzo et al. 2007), so related to the Aquadex system.

The Aquadex FlexFlow is indicated for those who have failed to respond to diuretic therapy (CHF Solutions 2011). I found just one study that looked at the use of ultrafiltration for *refractory* HF patients (non-responsive to diuretics and other management strategies), though the ultrafiltration was carried out by peritoneal ultrafiltration (from the abdomen rather than peripherally like the Aquadex), and used a haemodialysis device to do this (Sánchez et al. 2010). It was a Spanish single centre, prospective, non-randomized study of 17 patients, which tested the use of the intervention not just in an acute setting, but whenever symptoms required it (12 of the patients were still undergoing the treatment at the end of follow-up, which lasted between 6 and 35 months). Sánchez et al. report that for these refractory HF patients, use of ultrafiltration increased life expectancy by 82% after 12 months (56% after 24 months). They also provide the only estimate I have found of utility, as measured with the EQ-5D using the time trade-off method, which was 0.6727 for ultrafiltration versus 0.4035 for conservative therapy. This indicates that I may have underestimated impact on health (as I only considered the intervention in the context of an acute setting). They conclude that the intervention is highly cost-effective, both leading to improved quality of life *and* reduced health care costs (though as mentioned, they use a haemodialysis device to do this, which is likely to be much cheaper) (Sánchez et al. 2010).

There are many additional non-randomized, single centre studies, which tend to be positive about the treatment (though one found worsening renal function during ultrafiltration therapy (Liang et al. 2006). It can be concluded that ultrafiltration does have an impact on rehospitalisation (of nearly 50% according to one RCT (Costanzo et al. 2007), so very similar to the assumption used in the headroom analysis), but I have not seen any analysis of impact on ICU LOS. LOS for re-admissions seems to be reduced by ultrafiltration (not considered in the headroom analysis), and the rate of emergency hospital visits are also lower. I did not find any comparisons between conventional ultrafiltration and ultrafiltration with Aquadex.

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

In 2004 (time perspective of headroom analysis) there was little mention of ultrafiltration in any clinical guidelines that I came across. Although diuretics are still the clinical gold standard for the treatment of ADHF patients, there are many treatment guidelines that now support ultrafiltration for the management of refractory patients: Heart Failure Society of America 2010, American College of Cardiology / American Heart Association 2009, The Canadian Cardiovascular Society 2009, and the European Society of Cardiology (CHF Solutions 2011).

One review (Kazory & Ross 2008) describes the growing role of haemofiltration approaches in the management of heart failure.

### **Are there now many direct competitors?**

One issue brought up in the 'research questions' was whether the function of ultrafiltration could be achieved by machines currently used in other areas, like renal dialysis. Ross et al (Ross, Bellamy, Hawig, & Kazory 2011) describe the cost, reimbursement, and financial impacts of ultrafiltration for ADHF, and note that the costs associated with ultrafiltration are highly variable depending on brand and type of equipment used. They say that traditional haemodialysis machines and supplies can be used, and due to their mass production, are much less expensive than those devices designed specifically for ultrafiltration / aquapheresis only. They indicate that just the disposables can cost up to 50 times those used for haemodialysis equipment (Ross, Bellamy, Hawig, & Kazory 2011). However, these lower disposable costs should be balanced against the nurse and ICU expense of operating dialysis devices. The authors also indicate that re-calculating the results presented by Bradley et al (Bradley, Levy, & Veenstra 2009) (see above) swings further in favour of ultrafiltration when switching to lower-cost haemodialysis technology.

To my knowledge, this is the only commercial device marketed specifically for this indication.

### **Conclusions: How useful might the headroom exercise have been?**

In this case, the headroom analysis felt highly speculative, and would have benefited from a greater understanding of the developer's expectations around potential impact. The literature available in 2004 was not sufficiently detailed to inform very precise estimations. However, what the analysis did achieve was to identify some sources of cost and QALY estimations, which could have been used or manipulated according to the expectations of the developer.

The cost savings presented by the headroom analysis were reduced LOS in intensive care (which was derived from a study of an alternative drug therapy), and reduction in readmissions. Evidence has since emerged on the second of these but not the first. As for quality of life, there has only been one QALY estimate for ultrafiltration, which indicates that the potential for improvement in HRQoL may be substantial.

Overall, the headroom method (although not presenting a definitive MRP or 'headroom' value) painted a fairly positive picture for the reimbursement opportunity of Aquadex. The device has received much attention in the literature, and ultrafiltration seems to be increasingly utilised (though, in time this may generate a switch to cheaper available equipment, such as dialysis systems).

## 12. E-medICS. *QinetiQ*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Addition;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: July 2002</i></p> <p><i>Time perspective of this report: 1999</i></p>	<p>The Electronic Medical Integrated Care System (e-medICS) is a device intended for pre-hospital care; it is a touch screen panel PC (and wireless headset) with voice-enabled commands, which provides online decision support for paramedics at the scene of emergencies.</p> <p>The paramedics at the scene of an incident can feed information into the system (through touch screen or voice activation). The e-medICS then provides information on diagnostic aids and treatment protocols across the spectrum of acute medical emergencies and trauma (a decision support that incorporates 'Joint Royal College Ambulance Liaison Committee [JRALC] National Treatment Guidelines). This intuitive icon driven interface is from the Unified Emergency Care System (Morgan-Jones &amp; Hodgetts 1999a;Morgan-Jones &amp; Hodgetts 1999b). It also acts as an electronic patient report form, so a patient's vital signs and digital images can be relayed to A&amp;E before a patient's arrival. The two way communication system can also allow specialists to give detailed advice to paramedics on the scene.</p> <p>According to the Department of Health Statistical bulletin (Department of Health 1999), in 1998-99 the number of emergency calls to NHS ambulance services in England was 3.8 million (rising from 3.6 million for last year 1997-98, an 8% increase). The number of emergency patient journeys rose by 2% from last year, representing 2.7 million emergency journeys (total patient journeys were 18.6 million, with 1.1 million 'urgent' journeys and 14.8 million 'special/planned').</p>
<p><b>2. Comparator</b></p>	<p>There are a number of electronic patient report forms (ePRF) being developed to meet the needs of the NHS in this context. In their report '<i>Information for Health: An Information strategy for the Modern NHS 1998-2005</i>'(NHS Executive 1998), the Government set out specific objectives to be achieved over the period 1998 to 2005. The thrust of this strategy is the movement towards developing and maintaining a system of electronic patient records. The e-medICS system could support this strategy. Other ePRF forms are being developed; these are commonly referred to as pen-tablet computers, and have been shown in Germany and the US to improve data recording in medical emergency files (Balaban 1998;Ellinger, Luiz, &amp; Obenauer 1997). However, unlike the e-medICS device, these do not improve patient care at the road-side by providing electronic operational support and guidance at the scene of a major incident. This is the first system to offer this comprehensive support to paramedic teams.</p> <p>Rather than <i>changing</i> pre-hospital care, the e-medICS system would serve as an addition to current clinical practice, providing the tools to ensure that gold standard clinical guidelines are adhered to.</p>



	<p>In order to understand the health economic case for e-medICS, we need to understand the deficiencies in current clinical practice. One study of the warning times for A&amp;E departments by ambulance services, carried out in the West Midlands, found that in many cases A&amp;E departments should be alerted much earlier by the ambulance service (Harrison &amp; Cooke 1999). It can take some time to for the A&amp;E department to prepare and assemble the appropriate facilities, equipment, and personnel required to attend to a major casualty. An earlier and more informed warning (which could be facilitated by e-medICS) could improve the speed and effectiveness of treatment on arrival at the hospital.</p>
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<p><b>3. Market size</b></p>	<p>The NHSC briefing indicates that, if the e-medICS is widely accepted, it could be incorporated into 2,900 emergency ambulances across England and Wales, with the potential to benefit up to one million patients a year (there was no source given for this estimate, so it is assumed to come from the expectations of the manufacturer).</p> <p style="text-align: right;"><b>Market size per year (NHS England and Wales): 2,900 ambulances 1 million patients</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>As outlined above, advantages to the health service of the e-medICS system in ambulances would be:</p> <ol style="list-style-type: none"> <li>1. To make sure that paramedics are able to access decision-support enabling them to offer the appropriate treatment to patients, adhering to current guidelines and protocol. If patients receive the most appropriate treatment initially, then their outcomes should be improved and cost of subsequent treatment in hospital reduced.</li> <li>2. Better warning system to the hospitals. If the paramedics input the patient's vital signs (and even digital images of the patient), then the hospital is likely to be better prepared for the patient on arrival. This could mean more effective and efficient treatment in hospital.</li> <li>3. E-medICS could facilitate better record keeping, which not only plays towards the national movement to electronic records, but also allows for improved evaluation of the service.</li> </ol> <p>Aside from the 'warning system' element, the principal benefit of the product is to empower medical staff to make treatment decisions that are in line with clinical guidelines (which presumably represent the most appropriate way to manage patients). In other words, it should mean that</p>
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	<p>ambulance staff are equipped with the tools to do their job more effectively. This would be very difficult to evaluate from a health service cost perspective, as the spectrum of patients and ailments treated by ambulance staff is very wide, and we do not know the extent to which protocols are not adhered to currently.</p> <p>However, probably the most appropriate type of evidence to draw upon is from investigations that have considered the impact of <i>extra staff training</i>. All of the studies I have found that examine this issue of extended training for ambulance staff, are within the context of specific conditions or types of calls attended.</p> <p>One study considered the effect of training ambulance staff to carry out endotracheal intubation, intravenous infusion, and ventricular defibrillation (for cardio-pulmonary arrest) (Wright 1985). Wright proposed that one fully equipped ambulance that was permanently available and manned by personnel with extended training would save 3 to 4 lives per year, with a cost per life year of about £2000 (1981 prices) (Wright 1985).</p> <p>Brazier et al. provide a brief review of all the RCTs that have considered and provided evidence for pre-hospital care, but this was not restricted to ambulance care (Brazier, Murphy, Lynch, &amp; Bury 1999).</p> <p>One comprehensive HTA based on a large UK study (2,076 patients in all), presented by Nicholl et al., has been presented from an NHS perspective for pre-hospital care of serious <i>trauma</i> patients (Nicholl et al. 1998). They compared the outcomes and costs of trauma patients who received pre-hospital care by either emergency medical technicians (EMTs) or crews with at least one paramedic (who receive further training than EMTs, called 'advanced life support' training). The results in terms of parameters that might affect health service costs were the following:</p> <ul style="list-style-type: none"> <li>• Mean length of stay in hospital (15.2 nights) and percentage admitted to intensive care (5.9%) <i>were not significantly different</i> between the paramedic and EMT groups. Readmissions, outpatient attendances, and GP contacts were also similar between the groups.</li> <li>• Paramedics spent two minutes longer on scene than EMTs (even after case-mix adjustment).</li> </ul>
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	<p>Overall, the paramedic group cost £22 more per patient (£2231 versus £2209 per patient), but this difference was not statistically significant (<math>p=0.814</math>).</p> <p>It may be reasonable to assume that if patients are treated with the most appropriate care initially (facilitated by E-medICS), subsequent treatment costs would be reduced. Although one would presume that paramedics (as opposed to EMTs) would have a stronger basis to implement the most appropriate care for patients, the UK HTA found no difference between the two groups in this respect (cost of care upon arrival at hospital and subsequently). However, it would be inappropriate to generalise these findings, as they relate to a specific cohort of patients that receive pre-hospital care by the ambulance service (trauma patients), and the results may not be replicated elsewhere. Indeed, one review of the literature for 'The efficacy of advanced life support (ALS)' (Bissell, Eslinger, &amp; Zimmerman 1998) concludes that of the 51 articles reviewed, 8 had concluded that ALS care is no more effective than basic life support, 7 concluded that it is effective in some applications but not others, and the rest found evidence of improved effectiveness. They found that the strongest support for ALS was in cardiac arrest victims, whereas trauma studies and non condition-specific studies had more divergent results (Bissell, Eslinger, &amp; Zimmerman 1998).</p> <p>It would be very difficult to try and estimate the impact of e-medICS on health service costs. One NHS-specific study found that for trauma patients, subsequent hospital costs were not affected, but this result cannot be generalised across the whole ambulance service. In the absence of specific monetary estimates, the economic case should be made with careful consideration of points 1 to 3 above.</p> <p>The extra costs associated with E-medICS include installation into emergency vehicles, as well as staff training on the use of the system.</p> <p style="text-align: right;"><b>(Total) ΔSC=?</b> <b>(Av. Per person) ΔSC=?</b></p> <p style="text-align: right;"><b>P<sub>1</sub> ≈ £2230 per patient</b></p>
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<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p><i>The HTA presented by Nicholl et al (Nicholl et al. 1998) found significantly reduced indirect costs for the paramedic group, in relation to productivity loss from time off work. This probably relates to the improved outcome of survivors (see below); it could be proposed that the e-medICS might have the same effect.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>In terms of patient health, the e-medICS system aims to improve patient outcomes by:</p> <ol style="list-style-type: none"> <li>1. Improving the management of patients at the scene, by ensuring that medical staff have access to national treatment guidelines (and potential for two-way communication with specialists in the hospital).</li> <li>2. Allowing A&amp;E departments to have access to an incoming patient's vital signs, digital images, and summary reports, so that they are better prepared for the admission, thus improving the likelihood of quick and appropriate treatment in hospital.</li> <li>3. Providing a means by which to electronically manage patient records, which should improve the management of patients across the spectrum of health service interaction.</li> </ol> <p>The third of these points would be very difficult to assess in terms of health impact. The first two, however, should lead to a direct improvement of patient outcomes.</p> <p>Returning to the British HTA conducted by Nicholl et al. (for trauma patients), patient outcomes were measured and the following were the headline effects of paramedic treatment versus EMT attendance (Nicholl et al. 1998) (which I propose might represent the type of change that could be envisaged for e-medICS) :</p> <ul style="list-style-type: none"> <li>• Higher rate of mortality (6% for paramedic attendance versus 4.6% for EMTs), and, adjusting for case-mix, an increased risk of death from 4.5% (EMT) to 8.7% (paramedics).</li> <li>• An increase in avoidable deaths: 14.2% in deaths attended by paramedics, and 6.8% in those attended by EMTs.</li> <li>• Significantly improved outcomes for survivors. Treatment by paramedics was associated with</li> </ul>
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	<p>better scores on all of the SF-36 health dimensions<sup>32</sup> (5 of the 8 were significant once adjusting for case-mix). No aggregate score was provided.</p> <p>A trade-off between morbidity and mortality is apparent. For survivors, residual health was markedly improved in those receiving initial treatment from more highly trained staff. The noted mortality effect for paramedic-treated patients was observed in those patients with bleeding injuries, and could be related to the increased length of time at the scene that was associated with the paramedic group. The integration of the e-medICS could feasibly be associated with increased time at the incident before transportation to hospital (speculative), and so this effect might be worth considering.</p> <p>In her review of the literature of advanced training versus basic training, Bissell (Bissell, Eslinger, &amp; Zimmerman 1998) finds that, whilst not unanimous, research tends to indicate a positive effect of further staff training on clinical effectiveness, presumably indicating better patient outcomes.</p> <p>As there was no summary health value reported in this or any other HTA (and in any case it would be wrong to presume that this trauma-specific example would be indicative of the general service), we cannot use this to estimate QALYs. It would be impossible to try and estimate this effect with no data, as the breadth of patients that would need to be considered would make the problem very difficult to pin down.</p> <p>Like the question of health service cost impact, the rationale for e-medICS in terms of patient health should be viewed with points 1 to 3 (above) in mind, but with the awareness of the generally positive QoL results for patients treated by more informed healthcare staff, but also the potential for adverse mortality effects when treatment is delayed (at least for trauma patients).</p> <p style="text-align: right;"><b>ΔQALY=</b> <b>(Av. per person) ΔQALY=</b></p>
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<sup>32</sup> SF-36 health dimensions: Physical functioning, Social functioning, Role —physical, Role — emotional, Mental health, Energy/vitality, Pain, and General health perceptions.

<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [GREEN] Patient journeys in ambulances rose 2% from last year (Department of Health 1999). This upward trend in ambulance attendances enhances the need for more effective and efficient services. If e-medICS were to have the anticipated effect on patient treatment, it could help the service to cope with this rising demand.</li> <li>• [GREEN] The interface that will be utilised by e-medICS (the Unified Emergency Care System) was designed in the context of providing pre-hospital care to those injured on the battlefield; the interface developed utilises the experience of those medics who were required to provide a pre-hospital level of care comparable to that which a patient should expect to receive on the NHS (Morgan-Jones &amp; Hodgetts 1999b).</li> <li>• [GREEN] In the 'Information strategy for the modern NHS' issued by the NHS executive / Department of Health (NHS Executive 1998), it is asserted that telemedicine and telecare "will undoubtedly come to the fore as a way of providing services in the future" (p.8, (NHS Executive 1998)). They go on to explain that one of the greatest potential benefits of new technology in the NHS is improving quality of care by allowing better <b>access to information</b>, specialist advice, and support for both medical professionals and patients. It is in this way that e-medICS would facilitate improved patient care. In the same report, one of the stated objectives to be achieved before 2005 is "to provide every NHS professional with on-line access to the latest local guidance and national evidence on treatment..." (p.3, (NHS Executive 1998)). E-medICS could facilitate the provision of this resource in ambulances.</li> <li>• [GREEN] The NHS wish to create an Electronic Health record, which could allow for 24 hour access to clinical records. This should improve patient management, and the e-medICS would work toward this goal. The e-medICS thus complements various wider NHS goals: 1) electronic patient records, 2) incorporating JRCALC (ambulance treatment guidelines) strategies into practice, and 3) improving treatment equity.</li> </ul>
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	<ul style="list-style-type: none"> <li>• [GREEN] Technological advances in modern day life are such that many things that a few years ago seemed impossible are now facilitated by modern technology and gadgets. It seems appropriate that the NHS should make use of these advances to progress its own system of managing patients and improving care.</li> <li>• [AMBER] Having said that the NHS should move with the times in order to get the most out of advances in the technology sector, it must be kept in mind that this is not a consumer purchase. Buying a new gadget or mobile phone because it is clever and has improved capabilities might be a reason to make a consumer goods purchase, but in order to justify reimbursement from a publicly funded health service, it must prove to deliver value in terms of patient health and service costs.</li> <li>• [AMBER] As this device is based on technological rather than medical advances, it may attract competitors from the wider technology sector.</li> <li>• [AMBER] 1500 emergency ambulance journeys made over 2.5 years were investigated by P.S. London (London 1972) in 1972. He found that, whilst there were some respects in which equipment or performance by the ambulance service could be improved, there was no unnecessary life loss.</li> <li>• [GREEN] As in any public facing role, especially where the stakes are so high, paramedics are vulnerable to patient/family accusations and legal action when things go wrong. If the e-medICS system is employed, the actions of the medical team may be more defensible (if following the stated guidelines); the upload of patient data and images could also provide evidence of the medical team's handling of the situation.</li> <li>• [GREEN] One published letter regarding the collection of uniform cardiac arrest data by the UK ambulance service (Goodacre, Gray, &amp; McGowan 1997), notes that without uniformity of data collection for pre-hospital cardiac arrest,</li> </ul>
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	<p>the data is of little value when assessing the performance of the service. The e-medICS system could systematise that process.</p> <ul style="list-style-type: none"> <li>• [AMBER] The success of e-medICS would be reliant on its acceptance by the ambulance service community. It may be that some staff (especially experienced staff) might think it unnecessary or even a hindrance, if every decision should be run through the computer. Acceptance by the whole medical team is essential for the system to work, including: the medical staff in the hospital to which the patient will be admitted, specialists who might be called upon to give the paramedic advice at the scene, as well as the ambulance staff themselves. Additionally, in order to achieve its intended impact, uptake should not be isolated to individual ambulances, but e-medICS should be disseminated across the whole service. This means the case for e-medICS would need to prove to be very strong in order to warrant the huge investment that would be required to set the system up across all 2,900 ambulances in England and Wales.</li> <li>• [AMBER] Initial barriers to uptake that could be envisaged are that:             <ul style="list-style-type: none"> <li>○ Training of all ambulance as well as the relevant hospital staff would be required.</li> <li>○ The need for staff at the hospital to be responsive to incoming information and images may require some reorganisation of A&amp;E services.</li> <li>○ The NHS is generally a slow adopter of new technology, and it would take time for ambulance staff to get used to the new system. Benefits may therefore take some time to be realised.</li> <li>○ A large up-front cost would be required for installation of the equipment.</li> <li>○ It may be that over time the system would require systematic upgrading (in order to reflect changes in practice or advances in technology), so investment would not be one-off.</li> </ul> </li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>• The first proposition of this system is to improve patient care at the scene of emergencies, by ensuring that paramedics have access to clinical support and guidelines. Whether this would enhance current practice would hinge on the following questions:             <ul style="list-style-type: none"> <li>○ To what extent do ambulance staff <i>not</i> adhere to best practice guidelines, due to not knowing or not having access to what these are?</li> <li>○ Would paramedics be willing to adjust their actions even if they didn’t adhere to current guidelines?</li> </ul> <p>This would be difficult to investigate, and may not be fathomable until something like this system is tested, and outcomes do or do not change as a result.</p> </li> <li>• The second proposition is that the A&amp;E department has advanced and more detailed warning of the incoming patient.             <ul style="list-style-type: none"> <li>○ Would staff in the hospital be willing/able to receive and respond to this information?</li> <li>○ In the case of the two-way communication system, is it feasible that specialists at the hospital could respond to calls?</li> </ul> </li> <li>• Would the electronic patient record element of e-medICS be compatible with the NHS’s system for data collection?</li> <li>• The NHSC briefing does not indicate that the system could be used for the paramedics to access information and records of the patient’s medical history. Might this be feasible to incorporate in the future? Would this provide a useful and valuable function?</li> <li>• How much time (if any) would be added to pre-hospital treatment, by consulting with the e-medICS system before / during patient treatment? If more appropriate treatment is at the expense of more minutes at the incident scene, then these (even small) delays may have an impact on mortality rates.</li> <li>• <b>What is the reaction of the ambulance service community to this sort of device?</b> The response of the medical staff that would be involved in its operation, and their engagement in the process, would be absolutely key for the success, and indeed the uptake of the e-medICS. Therefore,</li> </ul>
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	<p>this must be gauged as soon as possible. Probably more so than any other medical technologies, its impact is completely reliant on the input by medical staff. If they are not on board, the investment might have been wasted. Additionally, this acceptance needs to be widespread in order to achieve maximum efficacy. Is this feasible?</p> <ul style="list-style-type: none"> <li>• The currently available evidence might indicate that improved medical skills / awareness of clinical guidelines may have a more positive impact in some clinical areas than others (e.g. cardiac arrest). Might it be feasible emphasise the use of e-medICS more urgently in those scenarios for which it would have the greatest impact?</li> <li>• The e-medICS system is a piece of technology that will likely have to compete in the highly dynamic and fast-moving technology sector. Does QinetiQ have the capacity and resources to keep the device up-to-date and competitive, so it is not overtaken by competitors? More so than many other devices, this will probably not be a question of a one-off development process.</li> <li>• Any clinical trial or investigations of the product must explicitly focus on the specific effect of e-medICS on subsequent hospital costs, and patient outcome in terms of mortality as well as morbidity.</li> </ul>
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### Headroom Notes (E-medICS)

No 'headroom' was delivered by this analysis. This was principally because of the very wide spectrum of patients, ailments, and costs, and the (unsurprising) lack of evidence upon which to base impact estimates. Instead, the bulk of the analysis is presented by section 6&7 of the pro forma, which provide some detailed factors/questions that the success of such a system as the e-medICS might rest upon. These should be considered, with the potential barriers weighed against the potential benefits. Especially important in this case would be the widespread acceptance by the ambulance community; this should be investigated carefully.

In terms of a development decision, as pointed out in the pro forma, it is probable that to stay competitive the process of development will need to be continuous.

## Follow-up (E-medICS)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The e-medICS innovation raises many interesting clinical, economic, and practical questions that should be considered when deciding whether the system might present an attractive offer to the NHS, and thus whether it will warrant a sufficient level of reimbursement. As the type of incidents and patients attended by the ambulatory service are so broad in nature, severity, and cost, estimating the service cost and health impact of the e-medICS system would be very difficult. The analysis therefore focused on presenting the important factors upon which the health economic case for the product would hinge, along with evidence or trends picked up in the literature that might help the developer to consider the likelihood of reimbursement prospects. As a result, parts 6 and 7 of the pro forma were extensive, as they outlined the current developments, trends, or issues in the market context which might work towards or against the case for adoption. These would have been important for a product such as this which would require the backing of staff and a major investment by the service. The 'research questions' section outlined the things that the developer would need to know in order to make an informed development decision, and begin to quantify the reimbursement opportunity. However, this topic is such that these questions are likely to remain largely unanswered until the system were to actually be put in place and used widely (e.g. to what extent do paramedics not follow guidelines, would their behaviour change, would it lead to longer time spent at the scene of the injury, would staff in the A&E department be receptive to incoming information, etc). Therefore, the developer would have to have considered these and the other research questions very carefully, and made a judgement call on likely reimbursement with all these factors (and evidence presented from specific emergency situations) in mind.

I am not able to guess what the result of that process would be, especially as a certain part of it related to the capacity of the company itself to manage the continual development of the system and the investment this would require, as well as the elicitation of user (paramedic) feedback.

#### **Headroom decision unknown**

#### **Has there been a decision made on it by NICE? What was the outcome?**

NICE has not issued any guidance on the (generic) topic of emergency care / ambulance services for the NHS. This is unsurprising given its very wide scope, and is reflective of why it also posed difficulties from a headroom perspective.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

In 2002, at the time the NHSC document was written, e-medICS was being trialled (a two year project) with the Surrey Ambulance Service NHS Trust. The project was funded by HM Treasury – Capital Modernisation Fund (Smith 2004). A brief report on this project (not a clinical trial as such)

was issued on the website of the 'Telecare Knowledge Network (TKN)'. They emphasise that there was much national and international enthusiasm for the project, and note that the UECS system (the interface used for e-medICS) has been shown in the military to improve treatment of patients, and has potential for mass use in the military environment (Smith 2004). As for its use by NHS ambulances, it is reported that "the volume of clinical evidence has not been generated to prove the clinical efficacy of the computerised UECS" (Smith 2004). However, much was learnt about implementation issues: "There are significant cultural and change management issues to be overcome before such a system becomes commonplace", but there is a big pressure on the NHS to realise the potential of modern technology to support decision making and flexible protocol delivery.

In 2003, QinetiQ joined forces with an Australian company called HAS Solutions (who are Australian IT providers in health care) to develop the e-medICS further (Worcester News Archive 2003).

I have not found any mention of e-medICS in the context of the NHS since the early 2000s in its trial with the Surrey Ambulance Service, and the product is not mentioned on QinetiQ's website.

### **Have there been investigations into its clinical / cost effectiveness?**

This specific device is not mentioned in any clinical or economic literature that I have found. Of those papers I have found, pre-hospital care is considered in the context of specific clinical problems (e.g. trauma and cardiac arrest) rather than effectiveness of practice in general.

One Australian study published in 2006 considered ambulance officers' use of online clinical evidence (Westbrook, Westbrook, & Gosling 2006). They found that over half of ambulance officers questioned had not heard of the Clinical Information Access Program (CIAP, an Australian online evidence system), and those who used the system was low. It was reported that lack of access in the work place deprives ambulance staff of the benefits of this system, and those that did use it (mainly at home) valued it highly. However, there was no link made in the study of CIAP use and performance / patient outcomes.

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

In response to the NHS white paper published in 2010, 'Equity and excellence: Liberating the NHS' (Department of Health 2010), the Department of Health developed clinical and quality indicators for urgent and emergency care, where response time guidelines are set, but it was emphasised that performance will be measured on quality and patient outcomes rather than times alone (Department of Health 2011e).

The value proposition for e-medICS was based on some guiding principles, which were that:

- 1) paramedic performance would benefit from access to a decision support device,
- 2) patient outcomes would be improved if their treatment was guided by national treatment guidelines, and if A&E departments could be better prepared for their arrival in hospital,

- 3) E-medICS could facilitate the movement toward an electronic health record system,
- 4) A resource such as e-medICS could make care more systematic and equitable.

As there is no evidence that e-medICS has been picked up by the NHS, do these factors still present an unmet need to the emergency care system? Points 1 and 2 above cannot be answered, and would not be answered until such a system is rolled out.

Some of the problems with clinical practice that probably inspired the development of e-medICS still exist, for example, there is still a great variation in the quality of ambulance care across the country (Department of Health 2011b). As for the general move toward an electronic health record system, progress was slow; a House of Commons health committee report published in 2007 revealed that just a few 'early adopter sites' were starting to trial the very basic form of electronic patient record (EPR), the 'Summary Care Record' (which includes information on things like allergies, adverse reactions and current medications) (House of Commons Health Committee 2007). Since this time, the whole NHS National Programme for IT (of which the electronic patient record plan was a major part) has been largely dismantled, the acceleration of which was announced by the government in September 2011 (Department of Health 2011d). It is said that some aspects of the programme have achieved a lot and that this will be maintained, such as the Summary Care Record. However, this goes no-where near what was envisaged back in 1998, toward which e-medICS could have played a role in the context of emergency ambulance care, and which formed a strong part of its case for adoption. The system of electronic patient records has been widely discussed and debated, with many claiming it to be less efficient than paper records or systems that are based locally (Quinn 2009), that the benefits are limited, that concerns of confidentiality and safety are an issue (Triggle 2010), and that clinicians may not even access them (Greenhalgh et al. 2010).

### **Are there now many direct competitors?**

The NHS is renowned for being a slow adopter of new technology. Despite the fact that e-medICS was first presented over a decade ago, when electronic patient record forms (e-PRFs) were being developed by many to fulfil the stated need by the NHS, such devices are still not in widespread clinical use. At the 2011 NHS Innovation Expo, a new device was presented as the 'Introduction of Electronic Patient Report Form (ePRF) to emergency care' using 'ToughBook' laptops (Healthcare Innovation 2011). This product also proposes the facilitation of patient recording, incident data transmission, and access to JRCALC guidelines. These are apparently being rolled out by the East Midlands Ambulance Service (NHS East Midlands 2011).

### **Conclusions: How useful might the headroom exercise have been?**

Although no monetary value was presented for this 'headroom', thinking about the device in terms of its potential impact on patients and the health service allowed for the identification of various sources of relevant evidence in the literature, and potential barriers to uptake. Many of the factors identified in sections 6 and 7 of the pro forma turned out to be very relevant for e-medICS, including

the main point made which was that, disregarding all other factors, the system would only work in practice if it had the backing of the clinical staff that would use it. From the small trial results, it seems that this is what has scuppered that adoption case for e-medICS. However, there has been one substantial development in the clinical context that may not have been predictable a decade ago; in 1999, the NHS was very keen to create a centralised bank of electronic health records, and the vision was that this would transform the way that patients were managed, making the most of the technology that is now available to us. The e-medICS was put forward as a way to optimise the management of patients and allow for patient records to be managed electronically. The company would probably not have been able to predict that, a decade later, this would still not have been rolled out nationally. This shows how important the clinical landscape is for the business proposition of a new product, and that sometimes it can change unpredictably.

Combining from the pro forma the 'developments', potential barriers to adoption, and 'research questions' identified, with the evidence identified from a UK trial on the emergency care of trauma patients, the case for e-medICS may have appeared at worst unlikely or at best uncertain (though I cannot judge what the developer would have made of these factors / questions, if indeed he had not considered them anyway). From the information I have found, e-medICS has not proven itself to be a cost-effective or efficient alternative to current management, and does not seem to have achieved widespread coverage in NHS ambulances.

This was an interesting example as in some ways e-medICS is a product delivered by the technology sector, and whilst it is important that the NHS makes the most of the technology that is available to improve patient management, procurement from this publicly funded service must be based on the value it creates for patients and the NHS. This was uncertain when carrying out the headroom analysis, and seems to be uncertain still.

It is difficult to know whether consideration of the headroom output would have influenced the decision of QinetiQ to develop e-medICS, but many of the questions were significant.

### 13. HeartSmart. *HeartSmart Limited*

<p><b>1. Description</b></p> <p><i>Diagnostic;</i></p> <p><i>Replacement;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing:</i> <i>October 2007</i></p> <p><i>Time perspective of this report: 2004</i></p>	<p>Patients who undergo major surgery or are being treated in intensive care units often require cardiac monitoring, due to the strain that these procedures place on the patient's heart. Cardiac output (which is sometimes called CO, or simply 'Q') is defined as the volume of blood that is pumped by the heart in one minute.</p> <p>The HeartSmart is a piece of software that uses algorithms to perform cardiac dynamic monitoring; results are reported in real time. The physician will input physiological readings into the software that are measured by standard pre-existing hospital equipment (e.g. a central venous catheter (CVC)). The physiological parameters required are: heart rate, central venous pressure, blood pressure and core body temperature.</p> <p>HeartSmart uses encoded algorithms defining the relationship between all key blood flow variables in order to produce important indexes of cardiac output, pressures and haemodynamic variables. These can be used to optimise patient blood flow and fluid management whilst the patient is in intensive care or undergoing surgery.</p> <p>The company envisages that HeartSmart could later be developed and marketed as hardware (where the algorithms are embedded into a microchip).</p>
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<p><b>2. Comparator</b></p>	<p>Many methods have been developed to measure cardiac output, and increasingly the emphasis of these developments has been on non-invasive methods.</p> <p>The reference standard for cardiac haemodynamic monitoring is pulmonary artery catheter thermodilution (PACTD). This is an invasive procedure, which involves a pulmonary artery catheter (PAC) (which is sometimes called the Swan-Ganz catheter) being inserted directly into the pulmonary artery to measure temperature. There are considerable risks associated with the technique, including arrhythmias, infections, thrombotic complications, and sometimes pulmonary artery rupture. An investigation by Walker and Waldmann (Walker &amp; Waldmann 1994) found that in the UK, there is considerable lack of standardisation for PAC use; this may impact its clinical utility.</p> <p>'Dilution' refers to the technique of measuring cardiac output by injecting an indicator and measuring its concentration in the blood after one circulation through the heart. Dye was initially the 'indicator' of choice. The PACTD technique uses temperature measurements, by using heated or cooled fluid as the indicator and measuring temperature change at different stages of the circulation.</p> <p>There are many alternative methods of cardiac output monitoring, including the following:</p>
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	<ul style="list-style-type: none"> <li>• Other indicator dilution techniques:             <ul style="list-style-type: none"> <li>○ Arterial (or ‘transpulmonary’) thermodilution: a less invasive method of thermodilution, where a thermistor-tipped catheter is inserted via the femoral artery. This has been found to be effective for burns patients, for whom fluid shifts can be great (Holm et al. 2001).</li> <li>○ Transpulmonary lithium dilution techniques.</li> <li>○ Pulmonary artery catheter based <i>continuous</i> thermodilution. Several products have been commercialised for this: Vigilance (Baxter), Opti-Q (Abbott), and TruCCOMs (Aortech). This continuous method was found to be effective compared with standard (‘bolus’) PACTD in a small trial by Medin et al (Medin et al. 1998).</li> </ul> </li> <li>• Echo-Doppler ultrasound: Measures blood velocity through the heart using ultrasound waves (‘doppler shift’).</li> <li>• Impedance cardiography (ICG): An electric current is used to measure resistance changes after each heart beat, which can be used with an ECG to generate haemodynamic data. A systematic search of the literature by Dark and Singer (Dark &amp; Singer 2004) for esophageal Doppler monitors found them to have high validity and high clinical agreement with PATCD in the monitoring of changes in cardiac output.</li> <li>• The Fick Principle: This describes the rate at which oxygen is consumed, and relates this to blood flow. A device (called NICO) has been developed by Novamatrix which uses this principle to non-invasively estimate cardiac output, just using measurements of airway gas.</li> <li>• Arterial Pulse Contour Analysis: Pulse pressure is (invasively) measured and used to estimate cardiac performance. Commercialised products that can achieve continuous cardiac monitoring using this method include PiCCO (Pulsion), PulseCO (LiDCO), and Modelflow (TNO/BMI).</li> <li>• Other comparators include MRI, electrical cardiometry, ultrasound dilution, and Finapres Methodology (‘volume clamp’ method).</li> </ul> <p>Despite this wide range of invasive, minimally invasive and non-invasive alternatives to PACTD, the consensus in the literature seems to be that PACTD is the established ‘gold standard’ for cardiac output estimation in critical care.</p> <p>The need for coronary output monitoring spans across many medical situations, in which a patient’s blood flow and fluid need to be optimised, including general intensive and neuro-intensive care units, open heart surgery, sepsis or shock, major general surgery, and the assessment of pressure in the pulmonary artery prior to liver operations. Clinical studies that investigate the outcome of patients that undergo cardiac monitoring using a pulmonary artery catheter (PAC) consider specific contexts (conditions or procedures). However, we can use these to give us some indication of the potential outcome of PACTD (our baseline) and to</p>
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	<p>speculate on the differences that could be made by HeartSmart.</p> <p>One cost-effectiveness study considered the hypothetical incremental cost/QALY of a PAC versus a no PAC strategy for patients experiencing COPD exacerbations that require mechanical ventilation, under the scenario that PAC-driven management results in a 5% improvement in survival (a speculative assumption) (Smith &amp; Pesce 1994). They calculate an ICER of \$77,407 and conclude that PAC for COPD exacerbations is expensive compared to alternative management strategies, unless PAC guided management were to improve survival by 8.7% or more.</p> <p>However, there is much discussion in the literature regarding whether PAC is in fact of any benefit in the management of patients. A cost-effectiveness study presented by Ramsey et al. (retrospective cohort study) looked at the use of PAC for patients undergoing coronary artery bypass graft surgery (Ramsey et al. 2000). They found that, after adjustment, the relative risk of in-hospital mortality was 2.10 for the PAC group versus the non-PAC group, total length of stay was 0.26 days longer for the PAC group, and hospital costs were \$1,402 higher (Ramsey et al. 2000).</p> <p>Sandham and colleagues (Sandham et al. 2003) report on an RCT conducted to examine the use of PAC in high risk surgical patients (60 years of age or older). They find no clinical benefit from PAC-guided therapy over standard care (which was allowed to include measurement of central venous pressure with a CVC). They found differences for in-hospital mortality or morbidity.</p> <p>Connors et al. (Connors, Jr. et al. 1996) present the findings of an observational study of the effectiveness of PAC in the care of critically ill patients (a mixed population, including medical and surgical patients in the ICU). Case-matching analysis was performed, and they found that patients that were catheterised had increased 30 day mortality (odds ratio of 1.24), an increased mean cost per hospital stay of \$13,600, and 1.8 more days in ICU.</p> <p>In response to these findings, Murdoch et al. examined the effect of PAC on mortality over 7 years in an ICU of a large British teaching hospital (Murdoch, Cohen, &amp; Bellamy 2000). They found that the use of PAC had a strong impact on mortality (42.9% versus 12.6% without PAC) if no adjustment was made for severity of illness. After adjustment, PAC had no association with increased mortality (Murdoch, Cohen, &amp; Bellamy 2000).</p> <p>On the other hand, a meta-analysis of the incidence of major morbidity in critically ill patients that are managed with PACs found that, in the studies considered, there was a statistically significant reduction in morbidity for PAC-guided management (Ivanov, Allen, &amp; Calvin 2000).</p> <p>Some of these studies question the usefulness of using cardiac monitoring to manage patients (at least using PACTD). The NHSC brief does not</p>
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	<p>indicate that, aside from reduced invasiveness / complications, HeartSmart would function any better than PACTD in its capacity to monitor cardiac output. Therefore, we must assume equivalent effectiveness, but that the risks posed by PACTD would be avoided by using the HeartSmart software instead of this procedure.</p> <p>By using PACTD as our baseline comparator, we assume that this <i>is</i> what is used in clinical practice, and thus what HeartSmart would replace. The literature varies in its assessment of PACTD, at best implying that morbidity is reduced, and at worst describing its use being associated with higher mortality, morbidity, and increased length of stay in hospital. The headroom method seeks to quantify the potential monetary opportunity for a new product within a specific market. This will be best explored in this case by considering two scenarios:</p> <ol style="list-style-type: none"> <li>1) Patient outcomes and cost of hospitalisation are equivalent for PACTD-monitored patients and HeartSmart monitored patients. Thus the only difference is the procedural cost of PACTD that is avoided</li> <li>2) The negative impact of PACTD on patient outcome (mortality) and hospitalisation costs (length of stay) may be avoided by using HeartSmart for cardiac output monitoring.</li> </ol>
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<p><b>3. Market size</b></p>	<p>What we would ideally use for this estimation is the number of PACTDs that are undertaken in the NHS every year; I could not find this. The NHSC briefing indicates in its ‘clinical need and burden of disease section’ that 200,000 central venous catheters (CVCs) are placed in the NHS every year (this estimate comes from NICE’s TA49 (NICE 2002)), but that the company believe this figure to actually be much higher. The measurements taken by CVC provide some of the required input measurements for HeartSmart, though their use seems to be associated with many motivations: haemodynamic monitoring, intravenous delivery (blood, drugs, etc), haemodialysis, nutrition, management of perioperative fluids etc. The placement of a pulmonary artery catheter seems to be diagnostic only, so it could be that a CVC is required alongside the PAC to make the indicated changes to optimise fluid and blood flow management.</p> <p>Although one might assume that the use of CVC would go beyond the use of PACTD for cardiac monitoring, I will use this estimate of 200,000 as the potential market size for HeartSmart, as this is what seems to be indicated by the NHSC briefing.</p> <p style="text-align: right;"><b>Market size per year (NHS): 200,000</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new</p>	<p>I am not sure whether CVCs are generally indicated for patients who undergo cardiac monitoring by PACTD. Therefore, I will show the health service cost effect in both cases.</p>
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<p>technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>According to the NHSC briefing, the total equipment cost of PACTD is £145 ('cost plus consumables') (no source was given, so it is assumed that this was company-knowledge). Besides this, the NHSC offers total monitor costs (£11,000-£15,000) and the cost of a service contract (£40,000)(no time span offered). Without more details of this cost (i.e. what does it include, does the headline figure of £145 include the amortised monitor/service costs, is the procedural cost of insertion included? etc), it is difficult to understand the true cost of PACTD to the NHS in the absence of any other estimate from the literature. Therefore, I will use the £145 'total equipment cost' figure offered by the NHSC as the estimate of PACTD cost per patient, whilst considering that, if not included, the monitor and service costs could add considerably to the headroom.</p> <p>Assuming that a CVC is normally used alongside PACTD, then the headroom in equipment costs would be the full £145.</p> <p>The cost of a CVC is also estimated in the NHSC briefing. The 'cost' is added to the 'consumables', to arrive at a 'total equipment cost' of £27. Alongside this, they present monitor costs of £3,800-£5,500 (again, no sources indicated or indication of what the figure of £27 includes). Therefore, per unit<sup>33</sup> there would be a saving of about £118 in switching from PACTD to CVC in cases where CVC would not be used concurrently with PACTD.</p> <p>For scenario 1 (outcomes and hospital costs of PACTD and HeartSmart are equivalent), this £145 (if CVC already used alongside PACTD) or £118 (CVC not used alongside PACTD) would be the headroom in health service costs.</p> <p>For scenario 2, we must add the health service costs associated with the adverse impact of PACTD on hospital length of stay. I will use the findings retrieved by Connors et al. where mean cost of hospital stay was raised by \$13,600 in PAC patients, equating to about £12,111 today (i)<sup>34</sup>.</p>
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<sup>33</sup> As CVCs are used for various purposes, it may be inappropriate to include the monitor costs for CVC anyway, as these may be needed in any case.

<sup>34</sup> The study by Connors et al (Connors, Jr. et al. 1996) included a mixed cohort of patients that attended ITU, including medical and surgical critically ill patients. Therefore, it may offer a more appropriate estimate than those studies that have considered a specific group of patients. However, it

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p><b>Scenario 1 &amp; CVC used with PACTD already:</b>  (Av. Per person) <math>\Delta SC = \text{£}0</math>  <math>P_1 = \text{£}145</math></p> <p><b>Scenario 1 &amp; and CVC investment required:</b>  (Av. Per person) <math>\Delta SC = \text{£}27</math>  <math>P_1 = \text{£}145</math></p> <p><b>Scenario 2 &amp; CVC used with PACTD already:</b>  (Av. Per person) <math>\Delta SC = -\text{£}12,111</math>  <math>P_1 = \text{£}145</math></p> <p><b>Scenario 2 &amp; and CVC investment required:</b>  (Av. Per person) <math>\Delta SC = \text{£}27 - \text{£}12,111 = -\text{£}12,084</math>  <math>P_1 = \text{£}145</math></p> <p><i>I can't tell whether or not monitor costs are included in the cost estimate of PACTD. If it isn't, then – as HeartSmart requires no investment in any capital equipment — this cost should be added to the headroom. As the monitor and service costs combined were up to £55,000, this indicates that these costs may <b>not</b> have been included in the 'total equipment cost' estimate. If this is the case, then this could add significantly to the headroom.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>The results of studies that consider the mortality effect of PAC vary greatly in result. Of those studies presented briefly above, Sandham (Sandham et al. 2003) finds no mortality impact, Ramsey (Ramsey et al. 2000) finds an increased relative risk of in-hospital mortality from PAC of 2.1, Connors (Connors, Jr. et al. 1996) presents an increase in 30 day mortality with an odds ratio of 1.24 compared with the no-PAC group, and Murdoch (Murdoch, Cohen, &amp; Bellamy 2000) finds that, after adjustment, PAC has no impact on mortality.</p> <p>Chittock and colleagues (Chittock et al. 2004) find that the use of a PAC may decrease mortality rates in those who are most severely ill, and increase it in those who are less ill. Yu et al. find no mortality</p>
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should be noted that this was the highest cost saving estimate that I found which, whilst maybe appropriate in the calculation of a 'headroom', may not be regarded as the most realistic estimate necessarily (as indicated, others found more moderate estimates).

	<p>impact from PAC in patients with severe sepsis (Yu et al. 2003), and Affesa and colleagues detect no mortality effect of PAC use on patients in intensive care either (Afessa et al. 2001).</p> <p>As we can see, these results are very variable. For Scenario one, we assume no impact on mortality (which seems to be the finding for most clinical studies). For Scenario 2, however, we want to model the monetary value of eliminating the risk that PACTD may pose on patients' lives due to its invasive nature, which could be avoided using HeartSmart. As we did with the service cost impact, it seems appropriate to take the most optimistic view for the value of HeartSmart, by taking the estimate from the literature that demonstrates the highest benefit to patients and the NHS from moving away from the use of PACs. It is Ramsey who provides the strongest case in this respect showing that, after adjustment, in-hospital mortality increased two fold for the PAC group. 2.8% of patients in the PAC group died, so let's assume that cardiac monitoring with HeartSmart rather than PACTD halves the mortality rate to 1.4%.</p> <p>To account for the quality of those lives saved accurately would be difficult as monitoring of cardiac output spans so many types of patients and illnesses. The median age of those patients (who underwent coronary artery bypass graft surgery) in the Ramsey study seemed to lie in the 60-69 bracket<sup>35</sup>. The median age of those admitted to the ICU of St James's University Hospital, Leeds between January 1990 and December 1996 (44% of which received PAC) was 56.3 years (Murdoch, Cohen, &amp; Bellamy 2000). Therefore, let's assume an average age of about 60. The Office of National Statistics (ONS) provide interim life tables which present the average person's expected years of life left at any given age (Office for National Statistics 2011). For expectation of life based on data for the years 2002-04, a 60 year old should expect to live a further 20.18 years if male or 23.43 years for women; let's assume a life expectancy of 22 years at the age of 60 for the general population. Of course, the underlying conditions which have led the patient to require the surgery or episode in ICU may mean that their life</p>
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<sup>35</sup> It should be noted that the use of this study is a proxy for potential impact, as this study related specifically to coronary artery bypass surgery rather than a more general investigation of cardiac output monitoring.

<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>expectancy should be reduced when compared to that of the general population. Let's speculatively consider that this figure is halved, so that the average life expectancy of a patient having received the intervention (cardiac monitoring) is around 11 years (underlying health condition will of course vary greatly among the target population, which makes this analysis highly speculative).</p> <p>To turn these into QALYs, we must apply a weighting to this estimate to account for the HRQoL experienced by the patients who are saved. For the general population, the weighted health state index for 55-64 year olds is 0.8, and 0.78 for 65-74 year olds (EQ-5D value sets) (Kind, Hardman, &amp; Macran 1999). Although this does not account for the underlying health condition of these survivors, I will not try to manipulate this figure given the lack of information upon which to base such a manipulation.</p> <p>However, as per NICE's reference case, life years gained in the future should be discounted at a rate of 3.5%. According to this principle, 11 years of life with a weighting of 0.8 is worth about 7.5 years today (ii).</p> <p>Overall, use of HeartSmart rather than PACTD could reduce in-hospital mortality from 2.8% to 1.4%, saving on average:  <math>7.5 \text{ years} \times 1.4\% = 0.11 \text{ QALYs per patient.}</math></p> <p>(This is all highly speculative, but is only illustrative anyway, as really we can see enough potential in the service costs alone to justify development)</p> <p style="text-align: right;"><b>Scenario 1:</b>  <b>ΔQALY= 0</b>  <b>(Av. per person) ΔQALY= 0</b></p> <p style="text-align: right;"><b>Scenario 2:</b>  <b>ΔQALY= 22,000</b>  <b>(Av. per person) ΔQALY= 0.11</b></p> <p><i>Pulmonary artery rupture as a result of PAC is a rare but fatal complication. An analysis of case reports to the U.S. FDA indicated 71 cases in the U.S. between 1991 and 2001, and found that the risk is greater in women than in men (Kaczmarek, Liu, &amp; Gross 2003). One study that explored the risk of pulmonary artery perforation advises that caution should be taken in</i></p>
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	<p><i>inserting PACs, and that their use should be avoided unless absolutely necessary (Sirivella, Gielchinsky, &amp; Parsonnet 2001).</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[RED]</b> There seem to be a great number of options for cardiac monitoring, and many more on the horizon (see section 2). The literature for cardiac output monitoring is extensive, and many clinical studies relate to specific technologies of the sort described in section 2. This shows that they are at an advanced stage of development, and are already looking to fill the space that PACTD now fills. Therefore, HeartSmart will be competing against all of these options rather than PACTD alone. A change in baseline comparator is likely to have a dramatic effect on the perceived headroom, especially if a non-invasive option were to prove effective and gain the favour of the clinical community.</li> <li>• <b>[GREEN]</b> It is unlikely that any other option for cardiac output monitoring is as cheap as what HeartSmart should turn out to be, as it requires no investment in capital equipment, no consumable costs, and no maintenance requirements.</li> <li>• <b>[AMBER]</b> The basis of this headroom analysis is the proposed avoidance of the potential complications associated with placement of a pulmonary artery catheter. However, there are also risks associated with placement of CVCs (pneumothorax, central-line associated bloodstream infections, thrombosis, arterial punctures, arteriovenous fistula, nerve injury, etc.) (NICE 2002). If these are in fact not used alongside PACTDs in the base case, then this could have a negative impact on the value generated by HeartSmart for patients and the health service. Cobb et al. find that both PACs and CVCs pose the risk of infection (Cobb et al. 1992). NICE seem to consider the reduction in CVC use to be a favourable outcome for an intervention.</li> <li>• <b>[GREEN]</b> NICE has issued guidance relating to the placement of CVCs in order to reduce complications associated with it (NICE 2002).</li> </ul>
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	<p>This could reduce the effect described above.</p> <ul style="list-style-type: none"> <li>• [AMBER] In one European study regarding the use / misuse of PAC, the authors suggest that: “As an alternative to expensive clinical trials on the pulmonary artery catheter, we propose that our limited financial resources for clinical investigation be invested in the development of innovative techniques that may reduce the need for pulmonary artery catheter in the future” (Vincent, Dhainaut, Perret, &amp; Suter 1998). This emphasises the potential space for HeartSmart, and its capacity to replace a procedure which is expensive and for which the evidence does not seem convincing.</li> <li>• [AMBER] In April 2002 ‘Pulse pressure wave monitoring for measurement of cardiac output’ was notified to NICE but was declared ‘not in remit’, and the reason given was that it was already an established procedure (NICE 2010e). This re-emphasises that the reference standard is not straightforward, and there are actually lots of options that are employed for cardiac monitoring.</li> <li>• [AMBER] Unlike other options that have been / are being developed for cardiac monitoring, I assume that the readings given will not be continuous (and will only update when the clinician re-enters the relevant physiological data). This may be seen as a disadvantage of HeartSmart compared with its competitors. Medin et al (Medin et al. 1998) find that continuous monitoring of cardiac output (using thermodilution) shows increased effectiveness over bolus comparators.</li> <li>• [AMBER] As HeartSmart is based simply on an encoded formula, then it may be that this is easy to replicate by another company or within the NHS. It may even seem unethical to be charged for the output of HeartSmart for each set of measurements.</li> <li>• [GREEN] The simplicity of HeartSmart is also a benefit, as there would be no significant change in clinical practice, and so no learning curve for staff or significant investment in training.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• Physiological parameters and CVC readings are to be inputted into the HeartSmart software manually. Is this a time intensive process?</li> <li>• A big risk that has been identified for this technology is the threat of a changing baseline. How does HeartSmart compare in cost and effectiveness with other up and coming options for cardiac monitoring? Is PACTD the relevant comparator (especially given the accumulation of literature that questions its usefulness)? Innovation in this area should be monitored.</li> <li>• If continued research into the clinical utility of PACTD confirms that PACTD does not have a beneficial impact on the management of patients during surgery or critical care, could HeartSmart be considered useful? What does it add to cardiac monitoring that is not achieved by CVC alone? (CVC alone is sometimes used as a comparator for PACTD in clinical studies).</li> <li>• How realistic is the market size estimated?</li> <li>• Update estimates of patient numbers if/when they become available.</li> <li>• Is CVC usually used alongside PACTD or not?</li> <li>• How much does PACTD cost? If the estimate used in this analysis is not correct, then so is the headroom.</li> </ul>
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**Notes by AC**

- (i) The difference in hospital costs for PAC and non-PAC patients was \$13,600 in 1996 prices.  
 The exchange rate in 1996 was about £0.65 to the US\$: \$13,600 = £8,840.  
 This must be inflated to today's (2004) prices using HCHS price inflator:

HCHS P&P Index 1996/7: 170.6  
 HCHS P&P Index 2004/5: 234.2  
 Inflation rate: 1.37

Hospital costs saved: £8,840 \* 1.37 = £12,111

- (ii) In order to express the QALY gain with today's reference point in mind, we must apply a discount rate of 3.5%. If every remaining year of life is experienced at a QALY of 0.8, then the total value of 11 years in this state would equate to the following:

$$\begin{aligned} \Delta QALY &= 0.8 + \frac{0.8}{1.035} + \frac{0.8}{(1.035)^2} + \frac{0.8}{(1.035)^3} + \frac{0.8}{(1.035)^4} + \frac{0.8}{(1.035)^5} + \frac{0.8}{(1.035)^6} + \frac{0.8}{(1.035)^7} + \frac{0.8}{(1.035)^8} + \frac{0.8}{(1.035)^9} \\ &+ \frac{0.8}{(1.035)^{10}} \\ &= 7.46 \text{ QALYs} \end{aligned}$$

## Headroom Notes (HeartSmart)

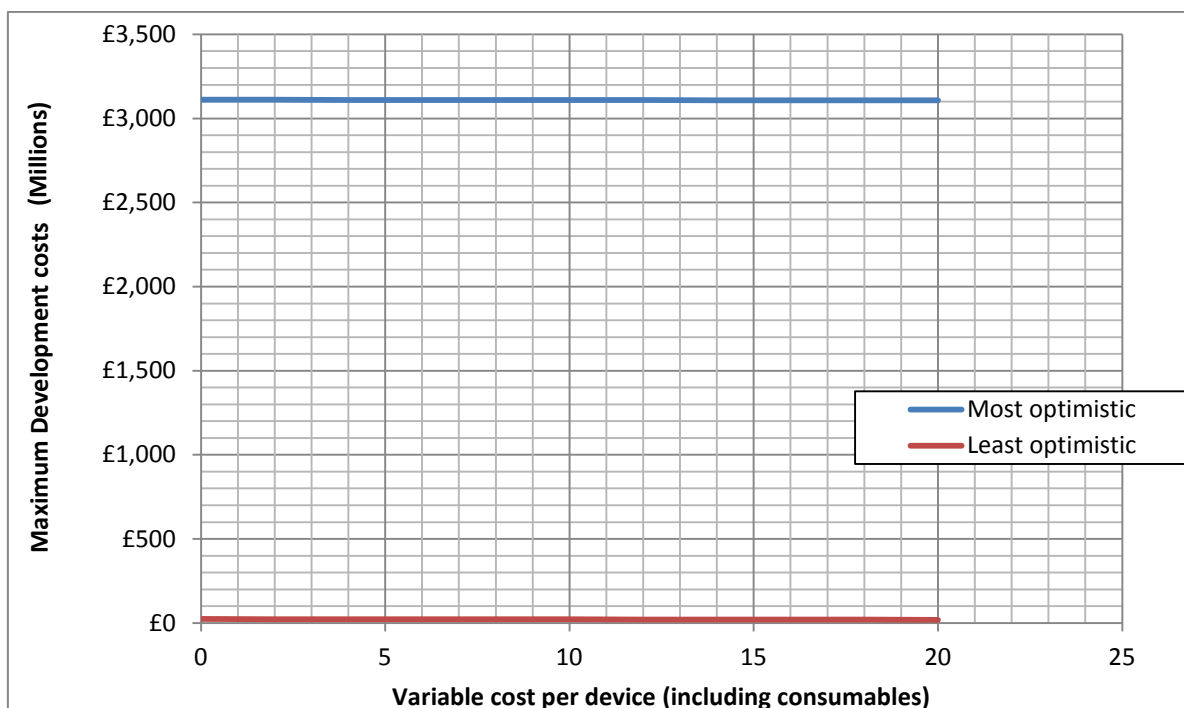
Here, the MRP represented the maximum reimbursable price for cardiac monitoring *per patient*. Without understanding the intended organisation / marketing of HeartSmart, I do not know how this relates to the reimbursement structure of the finished product (i.e. will the health service be charged per patient (as explored with headroom)? Per reading? Per license bought?) Unlike many services of this nature, the use of HeartSmart does not depend on an investment in capital equipment, and as such it is difficult to know how the company will choose to price the product.

In the least optimistic case (switching to HeartSmart would lead to no change in patient outcome or services costs in terms of patient stay etc, and placement of CVC (previously not indicated) would be required) the headroom per patient who needed cardiac monitoring was **£118**. This was simply the cost saving from no longer placing the PAC (minus the cost of placing the CVC). It should be noted that the cost of PACTD as expressed in the NHSC briefing was quite unclear, and that the equipment and service costs for PACTD (which could reach up to £55,000, but which would need to be amortised to reach a per patient figure) may need to be added. This could increase the Headroom figure further.

In the most optimistic scenario (switching to HeartSmart would reduce length of stay in hospital and reduce inpatient mortality, CVC is already used at baseline, and the NHS would be willing to pay £30,000 per QALY) the headroom per patient was **£15,556**.

This very wide gap in estimation shows the uncertainty in the assumptions made, which reflects the wide and divergent literature base for PACTD.

As for allowable development costs, even considering the least optimistic scenario these seem to be very large (in the region of £20 million), especially given the fact that the variable costs would be minimal for a piece of software.



## Follow-up (HeartSmart)

### Headroom Outcome and Market success

#### Does the MRP look realistic? Would it have indicated yes or no to development?

The headroom calculated per patient ranged from £118 to £15,556, depending on assumptions used for reduced length of stay, the need to apply a CVC where it was not used before, mortality, and WTP per QALY. The allowable development costs were very large (ranging from £3 million to £23 million). However, these supposed development costs should be taken with a pinch of salt as the estimated number of units was based on the use of CVCs in the NHS which, although indicated in the NHSC briefing as a proxy for HeartSmart use, may be an overestimate.

The information base to inform headroom assumptions was either sparse or inconsistent. This is why the estimates used were quite speculative, and why the range of headroom for most and least optimistic was so large, and why the exercise should be viewed as exploratory rather than definitive. Without getting too wrapped up in the detail, though, the health economic case for HeartSmart seems convincing when compared to what the company charge for the product. We knew that PACTD cost £145 a go (and this probably did not include the equipment and service costs which could reach £55,000 per unit), so even ignoring any of the potential benefits to arise from HeartSmart, it would be unlikely that the cost to produce the software for HeartSmart would exceed this value. Indeed, HeartSmart costs about £400 for set-up and installation, and £10-£15 per HeartSmart measurement (it is indicated that 3 to 4 measurements may be required). With no capital equipment costs, disposables, or maintenance required, the health economic case seems to be an obvious one if indeed HeartSmart does perform as well as or better than PACTD.

Having demonstrated the potential value to the NHS presented by HeartSmart it seems that, under the assumptions considered, the headroom would have indicated plenty of room for development.

### **Headroom would have indicated a positive development decision**

#### **Has there been a decision made on it by NICE? What was the outcome?**

NICE have not considered this particular device. NICE have produced guidance on other technologies for cardiac monitoring (see below).

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

HeartSmart is distributed in the UK by APC Cardiovascular, a UK based supplier of medical products. Dr Kenneth Warring-Davies, who is based at Bradford Royal Infirmary, was the inventor of the continuous cardiac dynamic monitoring (CCDM) software, HeartSmart<sup>36</sup>. Based on the locations of clinical trial data, it seems that HeartSmart has been used at least *alongside* PACTD (in order to check concordance of output) in 7 NHS trust hospitals (London, Cambridge, Bradford, Leeds, Sheffield, Scunthorpe and Grimsby). I have not been able to identify the extent to which it has or has not become part of routine clinical practice as an *alternative* to PACTD or other techniques.

Warring-Davies applied for a patent in 2003 (Berridge, Warring-Davies, Bland, & Quinn 2009), indicating that the 2004 time perspective may not have been the most appropriate.

HeartSmart is not mentioned in a 'Review of emerging cardiac technologies' provided by the Department of Health (Department of Health 2011a) (though this may be because this document is focused on services for sufferers of cardiac diseases, toward which cardiac dynamic monitoring is not exclusively focused).

#### **Have there been investigations into its clinical / cost effectiveness?**

I have found two journal publications relating to HeartSmart in the literature (both of which are authored or co-authored by HeartSmart's inventor Warring-Davies). Both consider the use of HeartSmart in a clinical setting by estimating cardiac output using standard PACTD and HeartSmart simultaneously, and comparing the results. The first, published in 2009, considers 45 patients undergoing cardiac surgery (Berridge, Warring-Davies, Bland, & Quinn 2009). They find that PACTD is in 'good agreement' with cardiac output monitoring using HeartSmart. The second paper (in Open Access Journal of Clinical Trials, 2010) considers trial data from 268 adult surgery or ICU patients that required PAC placement across 7 NHS trust hospitals, which allowed for the comparison of 2720 paired sets of cardiac index estimations (Warring-Davies & Bland 2010). Results suggest that 95% of paired measurements found HeartSmart values to be between 57% - 164% of PAC measurements

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<sup>36</sup> It was noted in the fill-in sheet that other cardiac monitoring options allowed monitoring to be continuous, and that HeartSmart not doing so may be perceived as a disadvantage. I am not sure whether the capacity for HeartSmart to offer continuous monitoring of cardiac variables is something that has since been incorporated, or whether it was simply not well described in the NHSC briefing.

(and that using the larger limit of agreement estimated between the two would imply that HeartSmart agrees with PAC as closely as it agrees with itself) (Warring-Davies & Bland 2010).

We can see from these trials that HeartSmart output generally agrees with the gold-standard. As trials have only tested the use of HeartSmart *alongside* PACTD, we are not able to observe the impact on clinical outcome of HeartSmart. However, if the accuracy of HeartSmart were to be deemed sufficient and it would require no investment in equipment or major re-training of staff, and would reduce the invasiveness (and presumably risks) of cardiac monitoring, then its case could only be favourable (in relation to PACTD).

In 2006 Harvey et al. produced an HTA on the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care (Harvey et al. 2006a). The study was a large multicentre RCT in a mixed setting across the UK, accompanied by an economic evaluation which was undertaken from an NHS perspective. PAC was compared with no PAC; in the control group patients were allowed to undergo cardiac monitoring by alternative means, which were employed in 66% of control group patients. The results corroborated the more conservative findings identified in the literature during the headroom analysis. There was no difference in hospital mortality or length of stay in hospital between the two groups, and the economic evaluation found that the expected cost/QALY that could be gained from withdrawing PAC from clinical practice would be £2,985 (this is because in the analysis the PAC group was associated with a slightly shorter LOS and slightly higher mortality). However, the cost of the PAC procedure itself does not seem to have been incorporated, only the time in ICU or the ward (this is not explained). In a cost-effectiveness study reported in the year prior to the full HTA (same data and results), the authors conclude that the withdrawal of PAC from routine clinical practice would be cost-effective (Stevens et al. 2005). This HTA suggests that 'scenario 1' in the headroom analysis may have been the most realistic.

Some of the same authors as the HTA (including Harvey S, lead author of both) provide a Cochrane review of the evidence for pulmonary artery catheters in the same year, 2006 (Harvey et al. 2006b). The results re-emphasise the variable findings of studies in the literature.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

It seems that PACTD is still considered the gold standard in clinical practice for haemodynamic monitoring; new technologies compare themselves with this technique (Warring-Davies & Bland 2010). However, the literature still indicates that new techniques and technologies continue to emerge and seem to be providing viable and effective alternatives to this 'reference standard'.

One technology in particular has shown particular potential, being recommended in March 2011 by NICE in a medical technologies guidance (NICE [Medical Technology Guidance] 2011) (though the committee note at the top of every report produced that "The specific recommendations on individual technologies are not intended to limit the use of other relevant technologies which may offer similar advantages"). The CardioQ-ODM oesophageal Doppler monitor uses a probe that is

placed in the oesophagus via the mouth or nose, which generates low-frequency ultrasound. The reflected signal can help determine flow velocity, and from this, other data can be generated. The CardioQ-ODM costs £11,000, plus the cost of a probe which is £67 to £118 per patient. Through reductions in hospital length of stay and complications due to better fluid management and a less invasive monitoring method, NICE estimate that implementing the guidance could generate £80,800,000,000 for the NHS (NICE 2011c). Interestingly, the comparator used by the committee seemed to be central venous pressure monitoring, against which CardioQ-ODM was said to generate £1,062 to £1,285 in savings.

This and other techniques seem to have become more common practice in recent years. Funk and colleagues (Funk, Moretti, & Gan 2009) wrote a review article in 2009 that considered the various options for minimally invasive cardiac output monitoring in the perioperative setting. They emphasise that the need for cardiac monitoring is strong and getting stronger, and that the limitations and complications inherent to PAC mean that clinicians are seeking minimally or non-invasive methods of monitoring cardiac output. They outline the advantages and disadvantages of esophageal Doppler, thoracic electrical bioimpedance, partial non-rebreathing systems, arterial pulse contour, lithium dilution, and trans-pulmonary thermodilution techniques (Funk, Moretti, & Gan 2009).

Given the far reaching research that is being undertaken in this area on alternative means of cardiac monitoring, and the largely neutral impact of PAC as presented by the literature, it seems that the appropriate baseline for HeartSmart is now not one, but many techniques.

### **Are there now many direct competitors?**

In their review (in which HeartSmart is not mentioned), Funk et al. conclude that of the monitors that are now available, the oesophageal Doppler and arterial pulse contour devices have the greatest potential for replacing PAC in standard practice. The arterial pulse contour method only requires an arterial line (rather than a central line [as used for CVCs], arterial lines are usually placed in smaller veins, for example in the wrist). Like HeartSmart, this works by using an algorithm in order to calculate the required indexes; though, signal processing and display devices seem to be required for this method.

### **Conclusions: How useful might the headroom exercise have been?**

As the information base for cardiac monitoring was in some areas sparse and in others plentiful but inconsistent, the resultant headroom analysis did not produce a definitive monetary opportunity for HeartSmart. It did, however, allow me to explore the potential health service value of the device, and how this would change when the assumptions used are manipulated. Hopefully this would have given the developer some appreciation of the important factors in the analysis, and how they can affect the overall health economic case for HeartSmart. As it happened, the health economic case under the perspective taken was an obvious one, as even the least optimistic scenario seemed to provide adequate headroom for HeartSmart. The perspective that *was* taken (regarding the

appropriate baseline) was challenged in sections 6 and 7 of the pro forma, and it is this that may be the most pertinent reason that HeartSmart does not seem to have a well established presence in the literature for cardiac monitoring. In the years since 2004, the alternatives to PAC have continued to grow, and the guidance recommending the use of the Doppler monitor actually indicated that CVC use alone was the relevant comparator.

As for the specific assumptions used, it seems that scenario 1 may have been the most relevant, as RCTs and systematic reviews that have since been produced for PAC have indicated that it is most likely to provide no benefit or harm for patient treatment. The HTA based on the large UK RCT (Harvey et al. 2006a) did not include the cost of PAC itself but did not indicate why; the basis of the headroom analysis for scenario 1 was simply the cost of PAC, which the NHSC indicated was substantial.

HeartSmart seems to be available in the UK (the company offer free trials), and used by various isolated centres (APC Cardiovascular 2011). The reason that it hasn't achieved widespread adoption across the NHS is likely to be because of the plethora of other options, one of which now has NICE approval, and also the requirement of CVC insertion (which seem to be out of favour given its inherent risks to the patient). Such barriers were identified in sections 6 and 7 of the pro forma. The 'headroom' for development would probably have been considered adequate without spending the hours trying to put a number to this, given the (relatively) high cost of PACTD and the low cost of a piece of software with encoded algorithms. Also, an expert in the area is likely to be aware of all of the other developments in the field.

The headroom method may have been a useful exercise for the developer of HeartSmart.

## 14. CT Angiography. *Various developers*

<p><b>1. Description</b></p> <p><i>Diagnostic;</i></p> <p><i>Replacement;</i></p> <p><i>NICE CG follow-up.</i></p> <p><i>Date of briefing:</i> <i>December 2006</i></p> <p><i>Time perspective of this report: 2003</i></p>	<p>Coronary Artery Disease (CAD) is the leading cause of death worldwide. It describes a condition where coronary arteries, which supply oxygen and nutrients to the myocardium (the muscle of the heart), become blocked. In England, angina (chest pain due to ischaemia of the heart generally caused by CAD) affects more than 1.4 million people, 300,000 suffer from heart attacks every year, and more than 110,000 people die from heart problems per year (Department of Health 2000). Coronary Heart Disease (CHD) accounts for about 3% of hospital admissions in England (Department of Health 2000), costs the UK £3.5 billion in health care costs (£7.9 billion including productivity losses and informal care) (British Heart Foundation 2003d), 79% of which is attributable to inpatient care (British Heart Foundation 2003a).</p> <p>In 2003 there were 53,261 percutaneous coronary intervention (PCI)<sup>37</sup> procedures undertaken in the UK (British Heart Foundation 2003c), and about 28,000 coronary artery bypass grafts (CABGs)<sup>38</sup> (British Heart Foundation 2003b). Angiography is the term used to describe the medical imaging technique that allows for investigation of coronary artery occlusion, in order to diagnose CAD and guide management and treatment.</p> <p><b>CT Angiography</b></p> <p>Multi-detector (or ‘multi-slice’) CT angiography (<b>MDCTA</b>) can measure the presence of coronary artery calcification, which indicates the presence of atherosclerosis – artery hardening. It combines the use of X-rays with advanced computer analysis, and allows for visualisation of the coronary arteries (non-invasively). MDCTA could produce a 3D image of the heart in less than 10 seconds, which can help the medical team detect the presence or lack of significant coronary stenosis (occlusion). It is thought that MDCTA could be used to diagnose CAD in patients with chest pain, and who have an intermediate pre-test probability of CAD; they may have no changes in ECG or an un-interpretable ECG. It could also be used for those patients that require angiographic data before surgery, in whom invasive angiography is not appropriate.</p>
<p><b>2. Comparator</b></p>	<p>The reference standard for evaluation of CAD is invasive coronary angiography (ICA) which involves coronary catheterisation. A catheter is inserted via the forearm, through the arterial system and into the major coronary artery. An x-ray contrast agent is then administered into the desired area to assess blood flow and visualise the artery openings (to assess occlusion, stenosis, thrombosis, etc) with an X-ray.</p> <p>The following is a list of other options:</p>

<sup>37</sup> PCI is more commonly known as angioplasty, and is the therapeutic procedure used to treat stenosis (narrowing) of the coronary arteries.

<sup>38</sup> CABG is a different therapeutic procedure whereby the stenotic arteries are bypassed by grafting by grafting vessels from elsewhere in the body.



	<ul style="list-style-type: none"><li>• Magnetic resonance angiography (MRA). This technique is already used for the evaluation of ventricular function, myocardial perfusion and mass. The test is non-invasive and does not use radiation, but for this indication would produce images of lower resolution and accuracy.</li><li>• Electron beam computed tomography (EBCT). Also non-invasive and uses lower radiation doses than MDCTA, but would have lower power.</li></ul> <p>In the national service framework produced for CHD in 2000 (Department of Health 2000), it is said that candidates for revascularisation who have evidence of extensive ischaemia or angina that persists despite medical therapy, should be referred for angiography (an ECG can help to determine these parameters, which records the electrical activity of the heart). Angiography would be followed by a quantitative assessment of urgency/risk/priority, which may be followed by revascularisation (either by CABG or PCTA (percutaneous transluminal coronary angioplasty)).</p> <p>MDCTA could offer a less invasive, lower risk, and probably much cheaper alternative to ICA. The reason that it is not being proposed for wider use (i.e. only in patients who have an intermediate pre-test probability of significant coronary stenosis, and for whom ICA would otherwise be indicated) is because of the risk of high-dose radiation involved.</p> <p>Diagnostic imaging is constantly evolving, with techniques continually improving in speed and accuracy; CT scanners are no exception to this. MDCTA is therefore not a brand new technology (which would be rare in the area of diagnostic imaging), but is being proposed for diagnostic imaging of CAD where an invasive ICA would otherwise be indicated. Therefore, this headroom analysis (which does not relate to one particular scanner, but to the practice of MDCTA more widely) investigates the monetary opportunity for MDCTA, and so explores whether there is enough of a reimbursement opportunity in the market to support the development of new and improved MDCTAs. It could be that developments / advances in this technology are what is needed in order to make them acceptably accurate and able to replace the reference standard in clinical practice, ICA. Therefore, this analysis could be seen as providing the maximum reimbursement opportunity for MDCTAs that perform as well as the reference standard, from which a developer could determine the feasibility of development.</p> <p>There is already some early data on the use of CT for non-invasive angiography (Achenbach et al. 2000; Harbel R &amp; Steinbigler P 2001). Some results of trials comparing invasive to non-invasive CT angiography demonstrate a sensitivity of 76-91% and a specificity of 84-97% (Harbel R &amp; Steinbigler P 2001). De Feyter et al, in a recent (2003) review of multi-slice CT conclude that “further technical improvements are necessary to</p>
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	<p>make CT a clinically reliable diagnostic tool” (de Feyter et al. 2003). By comparing MDCTAs directly to ICAs in their performance (and ignoring issues of sensitivity and specificity), we will be exploring the economic case for these further development (using the top end of the possible performance of MDCTAs).</p> <p>The need for non-invasive angiography was highlighted by a study by Haberl et al, in which only 53% of those investigated by means of invasive coronary angiography actually had significant stenosis (Haberl et al. 2001). This is supported by a postal questionnaire that was undertaken to survey directors of public health in the UK, which found that the mean ratio of invasive treatment to angiography was 1:2 (Gunnell &amp; Harvey 1996).</p> <p>The NHSC briefing is not absolutely clear whether ICA would still be indicated for those patients in whom CAD is detected non-invasively. In other words, the brief does not make clear whether MDCTA would be used as a ‘rule out’ method to ensure that those that <i>don’t</i> have significant CAD do not undergo invasive angiography, or whether it is proposed to work just as well as ICA in the assessment of the heart prior to revascularisation. One cost-effectiveness analysis for alternative test strategies for CAD models a situation where if non-invasive tests are positive than they would be followed by ICA (Garber &amp; Solomon 1999). With regards to angiography prior to cardiac surgery, the NHSC briefing indicates that MDCTA could be used in patients for whom invasive angiography has either not worked or is unsafe. Therefore, I will assume that the assessment of a patient with MDCTA (which would replace current ICA as first-line investigation CAD) would be followed by an ICA for those patients where severe occlusion is indicated and therefore who would require revascularisation. The sources cited above indicate that about half of those currently investigated with ICA result in cardiac surgery. Therefore, I will assume that by investigating <i>all</i> CAD patients (that currently undergo ICA) with MDCTA first, half of these patients will avoid ICA and the other half will have to undergo ICA subsequently.</p>
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<p><b>3. Market size</b></p>	<p>The NHSC indicates that around 93,470 ICAs are performed per year in England. However, this was based on 2005 data (beyond my time frame). Assessing the Department of Health’s schedule of reference costs for the year 2002 (published 2003) (Department of Health 2003), ‘Angiography’ comes under a couple of seemingly relevant HRG code labels: ‘Cardiology’ which had 22,311 attendances, and ‘Vascular Surgery’ which had 8,532 attendances’. The sum of these is 30,843, which is only a third of those reported by the NHSC for 2005. The only thing that brings the estimate up to the 90,000 level is by including the 50,275 Ophthalmology (eye) angiographies, which are clearly not relevant. Gunnell and Harvey (Gunnell &amp; Harvey 1996) estimate that in 1996 in the UK, coronary angiographies were undertaken at a mean rate of 1,010 per million of the population, indicating that about 50,500 ICAs are undertaken every year in England (considering a population of about 50 million).</p>
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	<p>On the other hand, these figures would seem to underestimate the market size if we are considering that <i>half</i> of ICAs lead to revascularisation, and that about 81,261 revascularisation procedures are undertaken every year in the UK (adding together CABG and angioplasty statistics from the British Heart Foundation reported above).</p> <p>Therefore, it seems to be difficult to obtain a clear picture of market size. Also, it may not be appropriate to consider the market size in its absolute sense, as this headroom analysis sets itself within the space for MDCTAs in general, a space which is likely to be filled by many different companies. Therefore, it would be more appropriate to consider this example exclusively on a per unit basis. It is clear from the estimates above that there is a large market for imaging for the diagnosis and management of CAD.</p> <p style="text-align: right;"><b>Market size per year: ? (large)</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>The potential headline advantages of MDCTA over ICA are that it would be less invasive, lower risk, quicker, and probably cheaper. The baseline assumption from a healthcare cost perspective for this analysis is that half ICAs can be avoided by first using MDCTA to assess CAD.</p> <p>The important input for this is therefore the cost to the NHS of an ICA procedure. The NHS reference cost database for 2002 (Department of Health 2003) provides the national average unit cost for specific HRG-coded interventions. For ‘angiography’ under the cardiology label (HRG code E02op) and vascular surgery label (HRG code Q02op), the average cost is £278 and £379 respectively. The NHSC briefing indicated that ICAs could cost between £134 and £1,600. With the reference cost data being at the lower end of this range, and not knowing what was included in these costs, an estimate from a UK-based study in the literature was sought.</p> <p>Underwood and colleagues (Underwood et al. 1999) investigated the economics of myocardial perfusion imaging in various centres across Europe. For the cost of coronary angiography (ICA), they used the average costs from three UK centres (judged to be the most consistent from the study), which included the cost to the NHS of consumables, labour, fixed costs (amortised according to patient throughput, and including maintenance of equipment), capital charges, and also overnight stay (1996 figures). The total cost of ICA was £1,100, which in today’s (2003)</p>
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<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>prices, is £1,419 (i).</p> <p>If half of ICA procedures can be avoided, then the average cost per patient of those who now undergo ICA would be halved.</p> <p style="text-align: right;"><b>(Total) ΔSC= -</b> <b>(Av. Per person) ΔSC= £710</b></p> <p style="text-align: right;"><b>P<sub>1</sub>=(included above)</b></p> <p><i>Use of MDCTA rather than ICA for those patients who do not turn out to have severe CAD, may mean that the complications associated with ICA are reduced. I have not found any estimates that monetarise these complications, but the case for MDCTA should be strengthened when considering its less invasive nature.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>CAD is associated with significant risk to life (it is the leading cause of mortality in the UK) as well as a reduced QoL.</p> <p>Kuntz et al. describe quality adjustment weights for sufferers of angina (a major outcome of CAD), which ranges from 0.89 for mild to 0.78 for severe (Kuntz, Tsevat, Goldman, &amp; Weinstein 1996).</p> <p>Another cost-effectiveness study that considers different diagnostic strategies for CAD uses standard gamble to assign health utilities of 0.87 for no symptoms, 0.81 for mild symptoms, and 0.67 for severe symptoms (Kuntz, Fleischmann, Hunink, &amp; Douglas 1999).</p> <p>However, these QoL indicators have only been used to compare the outcome of patients that undergo different diagnostic tests that, due to variable performance, lead to different <i>treatment</i> strategies (which impact the quality and length of life of the patient). I have found no cost-effectiveness analyses that have considered any QALY loss for the procedure itself. Therefore, as I am assuming that treatment outcome would be the same for MCDTA + ICA (proposed strategy) and ICA alone (current practice), then I will assume that there is no effect on patient outcome.</p> <p style="text-align: right;"><b>ΔQALY= -</b></p>
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<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p style="text-align: right;"><b>(Av. per person) ΔQALY= -</b></p> <p><i>Intuitively, there is a great advantage in presenting a strategy whereby all those patients that currently undergo invasive angiography <b>unnecessarily</b> no longer will. The risk to patients that is inherent to invasive procedures would be reduced significantly, but again, I have found no figures to quantify this risk. It should be noted, though, that there may be some safety issues with the high doses of radiation associated with MDCTA.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [AMBER] If the treatment strategy following diagnostic imaging is revascularisation (e.g. by angioplasty), then it may be that the intervention could be performed straight after the diagnostic test. If the diagnostic test were to be conventional invasive angiography, then this transition may be swifter and more cost-effective (avoiding the <i>full</i> cost of ICA plus revascularisation). An investigation by Panchamukhi and Flaker (Panchamukhi &amp; Flaker 2000) found that catheter intervention (angioplasty) performed at the same time as the <i>diagnostic</i> cardiac catheterization, is safe, effective, and significantly reduces hospital stay and costs. Indeed, interest has been raised in “diaventioanal” catheters that can function in both diagnostic and interventional capacities (Chatelain et al. 1994). This would not be possible for MDCTA, as the procedure is dissimilar.</li> <li>• [AMBER] There are actually lots of alternative strategies of non-invasive angiography in development. The NHSC produced a technology briefing on these emerging imaging techniques for coronary heart disease in 2001, of which MDCTA was one. Others included: myocardial ultrasound, nuclear medicine (SPECT, Pet) and MRI (MR spectroscopy, contrast MRI, coronary MR angiography). This headroom analysis can really be seen as an analysis for any of these options, depending on which turns out to be the most effective (which, as it happens, seems to be MDCTA). However, it is important to note that in such a busy area of development, any single technique is unlikely to achieve universal</li> </ul>
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	<p>coverage.</p> <ul style="list-style-type: none"> <li>• [GREEN] The results presented by Underwood et al (Underwood et al. 1999) for myocardial perfusion as a non-invasive imaging test showed that savings arose mainly from excluding CAD without the need for invasive angiography, supporting the hypothesis for this headroom analysis.</li> <li>• [AMBER] However, this and other cost-effectiveness analyses demonstrate the potential of other methods of non-invasive imaging for CAD (Garber &amp; Solomon 1999;Kuntz, Fleischmann, Hunink, &amp; Douglas 1999;Patterson, Eisner, &amp; Horowitz 1995;Underwood et al. 1999). Whilst the case for these other techniques has not, it seems, been deemed sufficiently convincing to replace ICA as the gold standard at the moment, this may change in the future.</li> <li>• [AMBER] One cost-effectiveness analysis comparing exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for the diagnosis of CAD find that, for patients with a high pre-test likelihood of CAD (&gt;0.7), (invasive) coronary angiography shows the lowest cost/effect or cost/utility given current levels of diagnostic accuracy and resulting outcomes. Non-invasive tests showed lower costs than angiography when pre-test CAD was &lt; 0.5 (Patterson, Eisner, &amp; Horowitz 1995). This makes sense when considering that those with a greater likelihood of significant CAD and therefore surgical treatment may need an ICA anyway. This may indicate that MDCTA would be indicated for a smaller number of patients than what is presumed in this analysis. This notion is upheld by Bohme et al who indicate that some CAD patients would need to be assessed invasively, and so would not profit from the CT scan (Böhme et al. 2003).</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor</p>	<ul style="list-style-type: none"> <li>• Given the fact that innovation in this area is constantly moving; will future changes in current practice change the baseline for coronary angiography?</li> </ul>
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<p>during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• Would these scanners be used in areas other than CAD? This would change the context of the analysis and significantly widen the relevant market. The headroom analysis just considers the use of a device in a specific context.</li> <li>• How quickly and to what extent will MDCTA be further developed / improved over time?</li> <li>• To what extent are angiography and angioplasty conducted in the same sitting? This may have an effect on the supposed cost-effectiveness of non-invasive imaging like MDCTA.</li> <li>• To what extent does the risks associated with ICA impact NHS costs and patient outcome? Is there a significant mortality risk?</li> <li>• What are the risks of the high-dose radiation associated with MDCTA, and can these be quantified? Would they be sufficiently great so as to reduce the chances of adoption?</li> <li>• How realistic is it to assume that MDCTA would work as well as ICA in the detection of CAD? For the purposes of this analysis we have ignored issues of sensitivity and specificity. Lee et al (Lee et al. 2002) show that the rate of false negatives in diagnostic strategies for CAD is very important when considering the cost-effectiveness of these strategies.</li> <li>• For what proportion of patients is invasive CA not appropriate?</li> <li>• Would there be any patients for whom imaging with CT angiography weren't possible?</li> <li>• It may be that MDCTA is most cost-effective when acting as a 'rule out' tool for those patients who do not have high probability of CAD. What proportion of those currently undergoing ICA does that represent?</li> <li>• The whole monetary valuation in this headroom analysis is based on the supposed cost of ICA. Is the figure of £1,100 that was employed (as indicated by Underwood and colleagues) the best estimate? If instead I were to have used the cost</li> </ul>
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	indicated by the NHS reference cost database, which was about £330 on average, then the headroom for MDCTA would have become just <b>£165</b> per test.
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### Notes by AC

- (iii) The total cost of ICA in 1996 prices was £1,100. This can be inflated to today's prices using the HCHS price inflator:

HCHS P&P Index 1995/6: 166.0

HCHS P&P Index 2002/3: 213.8

Inflation rate: 1.29

Cost of ICA (2003): £1,100 \* 1.29 = £1,419

### Headroom Notes (CT Angiography)

Given the fact that...

1. The total market size was uncertain
2. There may be many products that fill the space in the market for MDCTA, and
3. MDCTA is a piece of equipment, and understanding the allowable headroom per *device* rather than per person would require an understanding of the machine's throughput...

...I did not relate the headroom to the implied allowable development costs. I was also unable to derive an MRP (maximum reimbursable price per device) because of point 3.

What the headroom analysis does deliver is, under the assumptions outlined, the headroom per patient of a strategy using MDCTA before ICA. This headroom was £710, and represents the maximum cost that the NHS should be willing to pay to put one patient through a scan with a MDCTA machine. As the cost estimate used for ICA was inclusive of all component costs of the procedure, this £710 must include total NHS costs for the new imaging technique including hospitalisation, labour costs, equipment etc. Although the equipment costs for MDCTA are not likely to be small (and may take up most of this 'headroom'), the total service costs implicated for the use of MDCTA, which must also be considered within this £710 figure, may be reasonably modest as the process is said to deliver results in just 10 minutes and, given its non-invasive nature, patient recovery time it likely to be short.

The issues raised in the 'developments' and 'research questions' sections should be considered alongside this figure in order to appreciate the likelihood of this 'maximum reimbursement' being achieved. Especially worth considering is the research question which examines the effect of taking a different estimate of ICA cost. This may reduce the headroom per patient dramatically, to just £165. The developer should consider which of these is the more likely / appropriate estimate.



## Follow-up (CT Angiography)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

No MRP per se was delivered (as the MDCTA scanner would be a piece of equipment that would be used by an unknown number of patients), but a headroom was found of £710 per patient. This represented the cost saving to the NHS of avoiding half of the invasive coronary angioplasties (ICAs) that were previously undertaken.

As described in the pro forma, this headroom analysis was performed not on the basis of one particular product to have been invented by one particular company, but on the monetary opportunity in the market for developments in CT angiography. Indeed, the NHSC technology briefing that was produced in 2006 provided information on four developers of these scanners: LightSpeed VCT from GE Healthcare, Brilliance 64 from Philips Medical Systems, Somatom Sensation 64 from Siemens Medical Solutions, and Aquillon 64 from Toshiba America Medical Systems. There are likely to be others. All present the same offering in general terms, with slight variations in slice number, resolution and reconstruction time.

The NHSC briefing indicates that the purchase cost of a MDCTA (64-detector (or 'slice') CT scanner) is around £600,000 to £1.2 million. Considering the equipment costs alone and relating this to the headroom calculated, this would require a throughput of about 170 to 340 patients per year per scanner to recover costs, if the machine were to last 5 years (completely speculative, and ignores service costs involved in undertaking the scan and reviewing the results). The feasibility of this would depend on distribution-level decisions, and how many scanners would be required to practically service all patients (in their respective locations) that would require it.

An HTA that was conducted from a UK perspective which presented a systematic review of the clinical and cost effectiveness of CT angiography, used in its modelling a cost of £206 per test with MDCTA (Mowatt et al. 2008). This is well below the headline headroom of £710, indicating ample room for development. If, however (as presented in the 'research questions') we were to have used the cost estimate for ICA from the NHS reference costs, then the headroom would have been just £165; this is below the transpiring cost of MDCTA, indicating that under that assumption, the reimbursement opportunity may not have been deemed sufficient (depending on how close to the unit cost to the manufacturer the £206 is).

**Headline headroom estimation would most likely have indicated ample room for development. However, the output of sections 6 and 7 should have also been considered alongside this in the development decision; one issue to be presented was the effect of using a different source for the estimation of ICA cost. If this had been considered appropriate, then this might have changed the decision outcome.**

**Has there been a decision made on it by NICE? What was the outcome?**

In 2010 NICE produced a clinical guideline (95) for ‘Chest Pain of Recent onset’ (NICE 2010a). In it, they recommend that for high risk CAD, ICA should be used as the first-line diagnostic investigation. CT angiography is recommended to assess people with a probability of CAD of 10-29% and a calcium score of 400 or less. Those patients with a calcium score of 400 or more were deemed too difficult to image with the earlier generation (64-slice) CT scanners that were assessed. It was noted in a research recommendation that the use of CT angiography should be investigated as a more general ‘rule out’ strategy for CAD.

It has become clear upon follow-up that the ‘64 slice’ MDCTAs, which did not yet exist at the time of headroom (and indeed were the newest version at the time of the NHSC briefing publication in 2006), are now labelled ‘earlier generation’ CT scanners. NICE’s new diagnostic assessment programme have drafted guidance for *new* generation cardiac CT scanners (consultation period ended October 2010, and it is due for publication in January 2012). They (provisionally) support their use in the NHS in England as first-line imaging of people with suspected or known CAD, in whom imaging is difficult with earlier generation CT scanners, and whose estimated probability of CAD is 20-29% (NICE 2011d).

**Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

I assume that CT angiography *has been* (or at least will be) incorporated into clinical practice in the NHS, as per NICE recommendations.

An internet search for the MDCTAs that were indicated in the NHSC brief indicate that they seem successful (and have since been upgraded), for not only CAD but also other diagnostic capacities. As described above, the systems have already moved on and developed, and the NICE diagnostics guidance in fact considers the use of the very four products that were presented by the NHSC, but updated and advanced:

Company	64-slice MDCTA	‘New generation’ CT
GE Healthcare	LightSpeed VCT	Discovery CT750
Phillips Healthcare	Brilliance 64	Brilliance iCT
Siemens AG Healthcare	Somatom Sensation 64	Somatom Definition Flash CT Scanner
Toshiba Medical Systems	Aquillon 64	Aquillon ONE

When examining patient-facing websites such as the information offered to CAD patients by NHS choices (NHS Choices 2011b) and the British Heart Foundation (British Heart Foundation 2011), CT angiography is not mentioned under the possible diagnostic tests outlined. In both, those that are mentioned are ECG, x-rays, echocardiogram, blood tests, (invasive) coronary angiography, radionuclide tests, and MRI scans. As there are so many different alternatives in coronary imaging, and each seem to have specific advantages or disadvantages in particular settings, it may just be that the list is too long and indications too specific to incorporate all of these potential options at a

general level (or that the official guidelines that incorporate these other techniques are less than a year old).

### **Have there been investigations into its clinical / cost effectiveness?**

There continues to be a strong presence in the literature of imaging techniques for CAD.

In 2008 the NIHR produced an UK-based HTA which involved a systematic review of the clinical and cost-effectiveness of CT angiography against ICA (Mowatt et al. 2008). The authors, Mowatt and colleagues, conclude that the proportion of ICA that might be replaced by MDCTA is uncertain, but that it would mainly be at the diagnostic end (rather than for revascularisation assessment). They find that its main use would be to rule out significant CAD, and that it is unlikely to replace ICA in the assessment of patients for revascularisation, especially as angiography and angioplasty are often conducted at the same time (Mowatt et al. 2008) (as noted as a potential factor in the headroom analysis). They found CT angiography to be highly sensitive in pooled estimates (99%), and a high negative predictive value. Results varied between studies, with one finding that the use of MDCTA did not significantly affect the number of ICAs undertaken subsequently, and another finding that in the 6 months following MDCTA, ICA was avoided in 82% of those patients who would otherwise have undergone ICA. On the cost side, Mowatt et al. use as a base case cost for ICA of £320 (very close to the estimate derived from the NHS reference cost database in the headroom analysis). They do acknowledge that higher estimates have been identified in the literature, and use the same source that I did (Underwood) in a sensitivity analysis. They conclude that the results suggest a scope for avoiding unnecessary ICAs.

Cost-effectiveness analyses for MDCTA are generally positive. One study by Amemiya & Takao use a Markov model to explore its cost-effectiveness and find that using CT angiography as first-line examination for men of 60 years of age at risk of stable CAD achieved similar QALY gains to conventional ICA, but cost less (Amemiya & Takao 2009). Kreisze et al (Kreisze et al. 2009) find that CT angiography is a cost-effective rule-out strategy for symptomatic patients who are at low/intermediate risk of CAD. Two decision analytic cost-effectiveness analyses that were undertaken from a U.S. healthcare payer perspective (Khare et al. 2008; Ladapo et al. 2008) find CT angiography to be either cost-effective or (more often) cost saving for patients with low-risk chest pain.

There are a multitude of papers comparing the various imaging technologies to each other in the context of CAD, but perhaps the most relevant, up to date, and inclusive study into the clinical and cost-effectiveness of CT angiography is that presented by the diagnostics assessment programme within NICE (to be published officially January 2012). This assessment was performed with data pertaining to the new generation scanners listed above, which are quicker, involve a reduced radiation dose, and are more accurate in specific patient groups than the older 64-slice versions. The scanners were investigated in terms of their cost and effectiveness for the imaging of patients for whom it was difficult or impossible to image, reasons for which include patients who are obese, have high heart rates, arrhythmias, intolerance to  $\beta$ -blockers, or previous stent implants or bypass grafts. ICA was considered to be associated with a (small) risk of complications such as stroke, non-fatal myocardial infarction and death. The results of the economic evaluation show that these new

generation cardiac CTs are cost-effective for difficult to image CAD patients, and that strategies that include them yield equivalent QALYs and are cost saving (NICE 2011d).

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

There are many imaging technologies for CAD, which have an increasing role to play in this area, and which are being constantly developed and advanced. Although ACI seems to be the main technique used in many cases (i.e. where likelihood of CAD is high, and especially where revascularisation is being planned), various imaging options are employed, and have a role to play / are recommended for particular circumstances. Clinical Guideline 95 (NICE 2010a) for 'Chest pain of acute onset' describes the role of the various techniques, including CT angiography, and the role of new generation CT scanners is described in the Diagnostic guideline (NICE 2011d).

#### **Are there now many direct competitors?**

There are many other techniques, many of which have a specific role to play in the imaging of CAD patients who fulfil certain criteria (see CG 95 (NICE 2010a)). Indeed, many of these are described by the National Horizon Scanning Centre. In 2001 a briefing was published for 'Imaging in Coronary Heart Disease' which described many of these (NHSC 2001a), and subsequently MRI imaging (NHSC 2007b) and MRA imaging (NHSC 2007a) have been considered specifically by the NHSC (in 2007) for CAD patients. This indicates that the sector is continually developing, and that the available technology comes in a variety of forms. In essence, the headroom analysis (being non-specific in its nature) was relevant to them all.

### **Conclusions: How useful might the headroom exercise have been?**

In the headroom pro forma, it was noted that MDCTA was not a brand new technology, having been developed from earlier CT scanners (even though these weren't in relation to CAD specifically). Therefore, the purpose of the headroom analysis was to evaluate the space for developing the technology further, on the basis that advancing the technology to a level that could bring its performance closer to that of ICA may be what is required to achieve market coverage. By considering the role of invasive CA as the mainstay of clinical practice in this area, MDCTA was tested in the headroom analysis as a 'replacement' of this as the first-line imaging strategy. As the headroom analysis considered only the factors and costs associated with ICA, which could be avoided if the technique were to be replaced, it could be applicable for any of the non-invasive angiographies that are being developed.

It has become clear in following up the device that technological developments in this area is very fast moving, and even the CT angiographies that were 'on the horizon' in 2007 have already been

improved and updated to newer versions which are quicker, more accurate, and produce less radiation. The headroom approach took the optimistic view that CT angiography could replace ICA in its first-line diagnostic capacity (whilst noting that ICA would still be required for those patients being considered for revascularisation). However, it was also indicated in the 'developments' and 'research questions' sections why this might not be the case, e.g. that for those with higher risk CAD it might be more appropriate to proceed straight to ICA, or for those cases where angiography and angioplasty might be conducted at the same time, etc. These considerations turned out to be completely relevant.

By presenting the monetary value of the 'best-case', the value of iterative developments, which may eventually achieve diagnostic equivalence between CT and ICA, is articulated. This seems to make sense in a market of continual development.

The headroom, which overall seemed conducive to a positive development decision, relates favourably to subsequent cost-effectiveness analyses that have found MDCTA to be cost-effective (albeit in relation to specific sub-populations). It was also encouraging to note that the large UK-based HTA considered many of the same sources of evidence that had been identified for the headroom analysis in a short time-frame and with a date restriction of 2003 for searches. Also, most of the issues / uncertainties that were articulated by the 'research questions' were appropriate and important.

What isn't considered by a headroom analysis is that, in this sort of area, developments are likely to be organic rather than the result of a specific early economic evaluation; companies are likely to want to ensure that they stay at the forefront of technological innovation. Also, in this particular case, the technology involved is useful not only for imaging CAD patients, but would most likely be useful in a much wider set of diagnostic capacities. The headroom method focuses on its application to one particular market.

## 15. Stapled Haemorrhoidectomy. *Ethicon Endosurgery (Johnson & Johnson)*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Replacement;</i></p> <p><i>NICE IPG and TA follow-up.</i></p> <p><i>Date of briefing: January 2001</i></p> <p><i>Time perspective of this report: 1995<sup>39</sup></i></p>	<p>Haemorrhoids, sometimes referred to as piles, are swollen or inflamed blood vessels that are located in or around the anus or lower rectum which can be internal or external. They are often associated with itching, mucus discharge, pain, and bleeding when passing stools.</p> <p>Haemorrhoids are classified into stages of severity, of which there are four. Third and fourth degree haemorrhoids involve prolapse of the haemorrhoids, and may indicate the need for surgical removal (usually after having tried less invasive management methods).</p> <p>Prevalence of haemorrhoids is very difficult to ascertain and estimates vary greatly. Johanson and Sonnenberg estimate a prevalence rate of 4.4% among U.S. citizens (Johanson &amp; Sonnenberg 1990). They tend to occur in older people (though not exclusively), and certain risk factors including diet and specific events like childbirth increase the likelihood of haemorrhoids (a study of women at Birmingham maternity hospital found that 18% of women reported haemorrhoids following childbirth, half of which reported them occurring for the first time (MacArthur C, Lewis M, &amp; Knoz E G 1991)).</p> <p>Stapled haemorrhoidectomy<sup>40</sup> uses an intraluminal circular stapling device which is introduced into the anal canal; the staples are applied and the redundant tissue is removed. It is intended for third and fourth degree haemorrhoids. It is thought that procedure could be carried out as a day-case, be less painful than conventional haemorrhoidectomy, and reduce recovery time.</p>
<p><b>2. Comparator</b></p>	<p>Small haemorrhoids are quite common and often don't require any treatment at all. For those that do require treatment, the options available vary in type and invasiveness depending on the severity of the haemorrhoid. Treatment could start with the administration of creams or the prescription of laxatives.</p> <p>For grade two or three haemorrhoids, the following strategies are sometimes employed. They all aim to reduce symptoms and obstruct the blood flow to the haemorrhoid:</p> <ul style="list-style-type: none"> <li>• Banding: A very tight elastic band is placed around the haemorrhoid inside the anus in order to cut off the blood supply, allowing it to fall off within about seven days of treatment.</li> <li>• Sclerotherapy: An injection is administered into the blood vessels around the anus, which reduces the swelling.</li> <li>• Infrared coagulation: A probe is inserted into the anus and emits infrared light onto the affected tissue, which burns and shrinks the haemorrhoid (often used for grade one or two haemorrhoids).</li> </ul> <p>Surgery is usually reserved for grade three or four haemorrhoids.</p>

<sup>39</sup> A date limit of 1995 has been chosen as the device was introduced into the UK in 1998

<sup>40</sup> Haemorrhoidectomy is also known as haemorrhoidopexy.

	<p>The main method employed is standard haemorrhoidectomy, which involves the surgical removal of the haemorrhoid, with or without closing the wound that is left. The gold standard in UK clinical practice, and thus the most appropriate ‘comparator’ for this new device, is haemorrhoidectomy using the Milligan-Morgan technique. The operation is generally performed under general anaesthetic. It can be performed as a day-case procedure, but normally requires an inpatient stay (of about 3 days, according to the NHSC briefing).</p>
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<p><b>3. Market size</b></p>	<p>In the NHSC briefing, the estimated number of haemorrhoid removal operations is 26,514, over half of which (14,373) are undertaken as day-case procedures (according to 1998/99 HES data). This does not seem to uphold the assertion made in the briefing that most conventional haemorrhoidectomies require an inpatient stay of around 3 days. Being unable to identify the source for the 98/99 estimates, I searched the hospital episode statistics (HES) database to find an estimate of haemorrhoidectomies undertaken and the proportion of these that are undertaken as day-case procedures. The first date for which haemorrhoid procedure data was available that I could find was for 1999/2000. Although this was past my date restriction, I thought it would be important for the headroom analysis to understand the likely / feasible effect size of stapled haemorrhoidectomy, by making sure I understood the current landscape for current treatment.</p> <p>For 1999/2000, HES data indicates that 10,292 excision procedures for haemorrhoids were undertaken (HES code H51); there were 22,772 ‘destruction of haemorrhoid’ procedures (H52) and 1,676 ‘other’ surgeries for haemorrhoids (H53) (HES 2000b). Codes H52 and H53 must relate to procedures such as rubber banding, sclerotherapy, and coagulation. The day-case count for all <i>excision</i> operations in 1999/2000 was 12%, indicating that 88% involved an inpatient stay.</p> <p>This obviously differs from the information given in the NHSC briefing, but it may be that they considered the summary data file that reports headline figures (including other types of haemorrhoid treatment) rather than the break-down of interventions. The main procedures database includes ‘Operations on haemorrhoid (H51-H53)’, which in 1999/2000 was 27,392, of which 57% were day case (HES 2000a). This is very similar to the figures used in the NHSC briefing, and would be inappropriate to use as this would include data for non-excision surgery, thus inflating the relevant market size as well as providing an inaccurate estimation of day-case procedures in current surgical haemorrhoidectomy. Therefore, I will use the estimations presented above for haemorrhoid excision procedures.</p> <p style="text-align: right;"><b>Market size per year: 10,300</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in</p>	<p>The principle proposition of stapled haemorrhoidectomy on the health service costs is the reduced time in hospital for patients.</p>
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<p>service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>The NHSC indicates that theatre time for stapled haemorrhoidectomy and the conventional method would be approximately the same, so I will assume that the operating theatre costs for the two procedures are equivalent. Aside from the cost of the device itself (for which we are finding the headroom), the following factors would impact positively or negatively on service costs to the NHS:</p> <ul style="list-style-type: none"> <li>• (<i>Saving</i>) The cost of sutures used for conventional haemorrhoidectomy is approximately £1.</li> <li>• (<i>Cost</i>) Surgeons may recommend the use of prophylactic (preventative) antibiotics prior to stapled haemorrhoidectomy.</li> <li>• (<i>Cost</i>) Training of surgeons would be required for stapled haemorrhoidectomy.</li> <li>• (<i>Saving</i>) Stapled haemorrhoidectomy can be undertaken as a day-case.</li> </ul> <p>Without knowing the type of antibiotic that might potentially be prescribed (cheap or expensive), and to what extent they would be prescribed, I will ignore this potential cost, and presume it to cancel the saving from sutures that are used for conventional haemorrhoidectomy.</p> <p>Training of staff will be required, and must be conceptually incorporated into the headroom calculated (it is often the case that training is provided by the manufacturers of a new device anyway).</p> <p>So, the most important cost-saving factor that must be calculated is the potential impact of stapled haemorrhoidectomy on the cost of hospital stay for recovery post-surgery. By reducing the level of pain and shortening recovery time, it is thought that stapled haemorrhoidectomy could be carried out as a day-case (the patient does not require the use of a hospital bed overnight).</p> <p>An article published in the Lancet in 1964 discussing hospital length of stay for patients undergoing surgical procedures at the Aberdeen Royal Infirmary (Campbell &amp; Dudley 1964) found an average inpatient stay after a haemorrhoid operation of 5.4 days. As hospital care and the surgical procedure for haemorrhoids has improved over the years, so has the recovery prospects for patients undergoing haemorrhoidectomy. The NHSC briefing indicates</p>
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	<p>that the average LOS for those undergoing a conventional haemorrhoidectomy who require an in-patient stay is about 3 days. Conventional haemorrhoidectomy can also be carried out as a day-case, but the proportion of operations for which this happens is uncertain.</p> <p>Given the estimations presented in section 3, I will use the assumption that currently, conventional haemorrhoidectomy is performed as a day-case procedure in about <b>10% of cases</b> (baseline estimate). I will also test the assumption that 50% of current haemorrhoidectomies are undertaken as day-cases to account for possible improvements in current practice.</p> <p>It is unlikely that a patient will be sent home straight after a haemorrhoidectomy even in a day-case scenario, so I will assume that on average two days' worth of hospital costs would be saved by a patient being operated on in a day-case scenario as compared with an in-patient stay, at a price of £300 per day (as indicated by the NHSC)<sup>41</sup>. I will also assume that <i>all</i> stapled haemorrhoidectomies are performed as day-cases<sup>42</sup>.</p> <p>If one patient who would currently undergo conventional haemorrhoidectomy with a 3 day in-patient stay, were to instead receive stapled haemorrhoidectomy which is performed as a day case, £600 in hospital costs would be saved.</p> <p>If 10% of those currently undergoing conventional haemorrhoidectomy are treated as day-case procedures (Scenario 1), then switching all patients to stapled haemorrhoidectomy would save the following in hospital costs for the 'average' patient:  <math>£600 * 0.9 = £540</math></p> <p>If 50% of those currently undergoing conventional haemorrhoidectomy are treated as day-case procedures (Scenario 2), then switching all patients</p>
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<sup>41</sup> The NHSC indicates that much of the information provided in the briefing is from Ethicon. Without having provided a source for the £300 cost estimate for a hospital day, I will presume this to be a company estimation. The estimate is comparable to other estimates in the literature (NHS reference costs started being reported in 1998)

<sup>42</sup> The briefing indicates that in cases where in-patient hospital stay is required, stapled haemorrhoidectomy would reduce the length of this hospital stay. However, it is implied that most will be day-case procedures, and two days of hospital stay saved seems like a reasonable average marginal impact under either scenario.

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>to stapled haemorrhoidectomy would save the following in hospital costs for the 'average' patient: £600*0.5= £300</p> <p><b>Scenario 1 (basecase estimate)</b>  <b>(Total) ΔSC= £5.56 million</b>  <b>(Av. Per person) ΔSC= £540</b></p> <p><b>Scenario 2 (testing the effect of improvements in current practice)</b>  <b>(Total) ΔSC= £3.09 million</b>  <b>(Av. Per person) ΔSC= £300</b></p> <p><i>The cost of antibiotics which may potentially be prescribed with stapled haemorrhoidectomy has not been included.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>The reason that surgery is only indicated for those patients with third or fourth degree haemorrhoids is that, as well as the associated costs, the procedure can be very painful. It is thought that stapled haemorrhoidectomy would be less painful for patients, reduce recovery time, and return patients to their normal activities quicker.</p> <p>It is recommended that patients take a week or so off work for the wounds to heal after having undergone surgical haemorrhoidectomy, and that pain may last for a few weeks<sup>43</sup>.</p> <p>After stapled haemorrhoidectomy, it is likely that patients will still need some recovery time, but that the period of pain experienced would be shorter and less acute. I found no estimations of QoL for haemorrhoids or related procedures in the literature. In order to estimate the effect of this in terms of QALYS, I use the findings of Williams (Williams 1995), who presents the time trade-off tariff for each combination of health states within the EQ-5D questionnaire, which was estimated from a large study of the UK population (3,395 people). For each of the five health dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), there are three levels (no problems, some / moderate, or extreme problems).</p>
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<sup>43</sup> I could not find any precise estimation of recovery duration in the clinical literature. Therefore, this information was retrieved from a patient-facing website (NHS Choices). This information should easily have been accessible in 1995 for those working in the field.

	<p>To get a rough estimate of the additional QALYs associated with an improved recovery period, let's assume that stapled haemorrhoidectomy is associated with two fewer weeks in a health state of 11221 (perfect health apart from 'some problems performing usual activities' and 'moderate pain or discomfort'). This health state is said to be associated with a quality of life tariff of 0.76. To translate this into QALYS we must multiply the impact on QoL (<math>QoL_2 - QoL_1</math>) by the time in which this improvement is experienced (2 weeks = 0.038 years):</p> <p><math>(1 - 0.76) * 0.038 = 0.00912</math> QALYs.</p> <p>This would be gained by all patients.</p> <p style="text-align: right;"><b><math>\Delta</math>QALY= 94 QALYS</b> <b>(Av. per person) <math>\Delta</math>QALY= 0.00912</b></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p>	<ul style="list-style-type: none"> <li>[GREEN] A meta-analysis of haemorrhoidal treatment modalities found haemorrhoidectomy to be significantly more effective than manual dilation of the anus, rubber band ligation and sclerotherapy (MacRae &amp; McLeod 1995). The authors conclude that rubber band ligation should be used in the first instance; haemorrhoidectomy shows better response rates but is associated with more pain and complications. This recommendation is upheld by others (Murie, Mackenzie, &amp; Sim 1980). If stapled haemorrhoidectomy could reduce the pain experienced by patients and complications associated with the procedure, then it may overcome this barrier, and be recommended in more cases than haemorrhoidectomy is currently.</li> <li>[AMBER] A clinical trial and economic evaluation conducted in 1977 which considered day-case surgery for haemorrhoidectomy, found that complications were twice as likely in the day-case group compared with the long-stay patients (Russell et al. 1977). Day patients also received more visits from the district nurse, and had more</li> </ul>
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<p>AMBER: Potential threat</p> <p>GREEN: Further supports the case for the new technology</p>	<p>GP consultations following the surgery. Although the economic evaluation was old-fashioned<sup>44</sup>, this may indicate that further care outside the hospital setting may be required for day-case patients. However, rather than simply reducing the length of stay in hospital for patients undergoing the same procedure (as in the study by Russell and colleagues), the assumption made in this analysis is that stapled haemorrhoidectomy reduces length of hospital stay because its impact on patients in terms of morbidity and complications is lower than conventional haemorrhoidectomy.</p> <ul style="list-style-type: none"> <li>[GREEN] Drug costs may be reduced for stapled haemorrhoidectomy patients due to its lower morbidity implications (patients are often prescribed narcotics following haemorrhoid surgery) (Kilbride, Morse, &amp; Senagore 1994). Cost of pain management in primary care may be reduced following stapled haemorrhoidectomy.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>Is it sensible to assume that all stapled haemorrhoidectomy procedures are undertaken as a day-case procedure? If not, what assumption would be more appropriate, and how would this impact the estimation of 2 hospital days saved per patient?</li> <li>What are the quality of life implications for pain following surgery, and how would this be altered with the new procedure? Search for any developments in the literature that test for this parameter, and adjust the QALY estimates accordingly.</li> <li>What is the likely cost of antibiotics that might be prescribed before stapled haemorrhoidectomy? If these costs are significant, then they should be subtracted from the headroom figure.</li> <li>This analysis has assumed that conventional and stapled haemorrhoidectomy are equally as</li> </ul>
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<sup>44</sup> For example, it was suggested that the cost saving from reduced length of stay could be limited to the expenditure on provisions and laundry, and that this net saving could be cancelled out if actually the recovering surgical patients help nursing staff by carrying out small tasks on the ward (Russell et al. 1977).

	<p>effective as each other at removing the haemorrhoid, by implicitly assuming equivalent complication and recurrence rate. Is this appropriate, or could stapled haemorrhoidectomy be associated with increased / decreased complications and later recurrence?</p> <ul style="list-style-type: none"><li>• Would the device be easy to copy?</li></ul>
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### Headroom Notes (Stapled Haemorrhoidectomy)

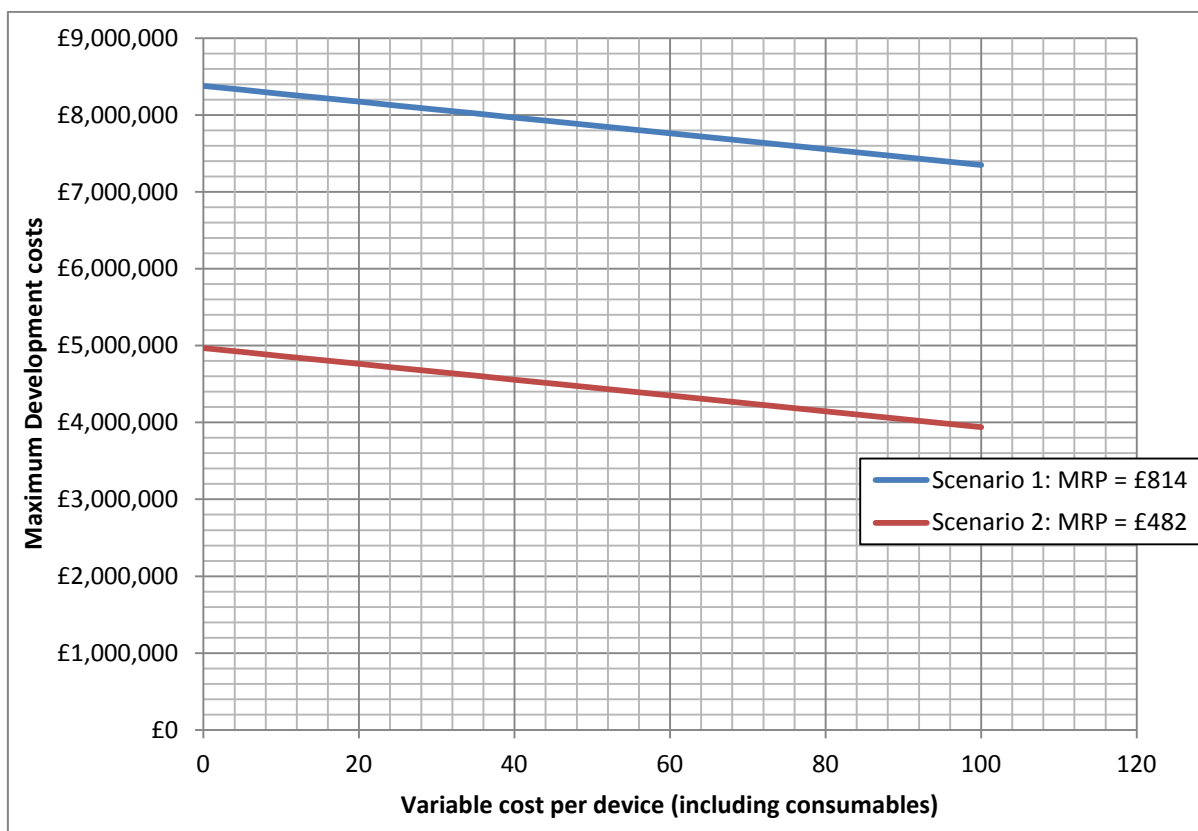
By considering the possible cost-saving and QoL-enhancing effect of stapled haemorrhoidectomy versus conventional haemorrhoidectomy, the MRP in the basecase is £772 to £814 (depending on a £20/£30,000 WTP). This assumes the following things about stapled haemorrhoidectomy versus conventional haemorrhoidectomy:

- 2 hospital days are saved,
- Recovery time is 1 week rather than 3, and
- Conventional haemorrhoidectomy is undertaken as a day case in 10% of cases, and
- All stapled haemorrhoidectomy procedures are undertaken as a day-case.

To examine the effect of stapled haemorrhoidectomy in the context of improved current practice, I also tested the effect of assuming that half of all current procedures are undertaken as a day-case, in which case the headroom was £482 to £574.

These figures must include the provision by the company (or NHS) of training to hospital staff on the use of the product, calculated on a per unit basis. Also, if antibiotics will be used systematically with the procedure, then this should also be subtracted from these figures.

The analysis yielded the following prospects for development costs / profit.



## Follow-up (Stapled Haemorrhoidectomy)

### Headroom Outcome and Market success

#### Does the MRP look realistic? Would it have indicated yes or no to development?

The MRP for stapled haemorrhoidectomy under the basecase was £772 to £814. Incorporating an improvement in current practice resulted in a minimum MRP of £482 (see pro forma sheet and headroom notes for assumptions made). Assuming that variable costs of production were £100 or under, then the maximum allowable development costs would have been at least £7.4 million in the basecase (assuming full market coverage).

The NHSC briefing indicates that the price of the Ethicon stapling device is £256 per unit. Unless the cost of training staff (and possibly antibiotics if indicated) were more than £200 for each procedure undertaken, then even when incorporating huge improvements in the current procedure, the MRP would still have been sufficient to cover what is now charged for the device. In the technology appraisal conducted by NICE for the device, a price of £420 is indicated. The basecase headroom (£772 to £814) would likely still have left ample room for development at this price, but depending on changes in assumptions made about impact on hospital length of stay, this (probably more reliable) estimated price of £420 for the stapler device would make it a closer call.

**Headroom would have most likely indicated a positive development decision**

### **Has there been a decision made on it by NICE? What was the outcome?**

In December 2003, NICE produced an Interventional Procedure Guidance (IPG 34) on the use of circular stapled haemorrhoidectomy. In it they conclude that “Current evidence on the safety and efficacy of circular stapled haemorrhoidectomy appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance” (NICE 2003b). They emphasise that clinicians wishing to undertake the procedure should be trained and mentored.

NICE have also produced a technology appraisal for the device, which was published in September 2007 (NICE 2007b). In their list of ‘consultees and commentators’, there are two companies under manufacturers/sponsors: Ethicon Endo-Surgery (Johnson&Johnson), and Tyco Healthcare UK Ltd. Upon reading the appraisal, the committee make it clear that the recommendations refer to the circular stapler produced by Ethicon Endo-Surgery, and that there was no evidence to recommend the Autosuture stapler with STRAM kit adaptor (which is the model produced by Tyco Healthcare). Stapled haemorrhoidectomy is recommended as an option for people in whom surgical intervention is appropriate in the treatment of prolapsed internal haemorrhoids.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

In 2000, the Australian Safety and Efficacy Register of New Interventional Procedures- Surgical (ASERNIP-S) produced a review of stapled haemorrhoidectomy and categorised the procedure as category C (safety and efficacy not proven) (NHSC 2001b). Since, and with the increased availability of data, the device has been recommended by NICE as a safe and effective procedure (NICE 2003b), as well as a cost-effective one (NICE 2007b).

Stapled haemorrhoidectomy is mentioned in all the patient-information websites that I have come across (Patient UK, NHS Choices, etc), and the device is presented, along with many other stapling devices, on the Ethicon Endo-Surgery website. Given the plethora of clinical trials presented in the literature for stapled haemorrhoidectomy, I believe it to be used in many countries for the treatment of patients with haemorrhoids. I don’t believe it to have replaced conventional haemorrhoidectomy entirely.

### **Have there been investigations into its clinical / cost effectiveness?**

There is much literature on stapled haemorrhoidectomy. The following is a brief summary of some of the important research undertaken for the procedure.

#### ***Clinical Effectiveness***

In the IPG NICE guidance published in 2003, specialist advisors to the committee indicated that stapled haemorrhoidectomy was as effective as the surgical alternative (but that long-term data was needed to confirm durability). They also suggested that safety concerns were theoretical and mostly unsupported by trials (NICE 2003b).

The Cochrane collaboration produced an intervention review for stapled haemorrhoidectomy versus conventional surgery in 2006 (Jayaraman, Colquhoun, & Malthaner 2006). In it, data was sought from all published RCTs. The main findings were that although pain seemed to be reduced (this effect

was not always being significant), stapled haemorrhoidectomy was associated with higher risk of recurrence and prolapse; it was concluded that if recurrence and prolapse are the most significant clinical outcomes, then excision should remain the 'gold standard'. A review of this was produced in 2010 to include more recent evidence (Lumb, Colquhoun, Malthaner, & Jayaraman 2010). The conclusions of the previous review were upheld: stapled haemorrhoidectomy was associated with higher long-term risk of recurrence and additional operations. There were non-significant trends in favour of stapled haemorrhoidectomy in pain, pruritis ani and faecal urgency.

Many individual studies confirmed the overall consensus that stapled haemorrhoidectomy carries a significantly higher risk of recurrence and additional operations (Giordano et al. 2009). Individual studies also found that hospital stay and pain were significantly reduced with stapled haemorrhoidectomy versus conventional (Milligan-Morgan) haemorrhoidectomy (Khan et al. 2009).

### *Cost-effectiveness*

The two main cost-effectiveness studies for stapled haemorrhoidectomy from an NHS perspective are those provided by NICE (NICE 2007b) and the NIHR HTA (Burch et al. 2008).

In 2007, NICE provided a technology appraisal which recommended the use of stapled haemorrhoidectomy, as discussed above. Upon reading the report in more detail, it is clear that many factors went into this decision from a cost-effectiveness perspective. On the clinical effectiveness side, the committee found the following:

- Less pain was associated with stapled versus conventional haemorrhoidectomy for the 14 days post-procedure.
- There was little difference long-term pain difference (21 days and 1 year or later)
- Stapled haemorrhoidectomy was associated with shorter wound healing time and quicker return to normal activity.
- Bleeding was reduced 14 days postoperatively, but not at 6 to 8 weeks or 12 weeks.
- The evidence seems to indicate greater chances of prolapse and re-intervention.
- Postoperative complications were not statistically different.
- The overall message from QoL studies is that there is no statistically significant difference between stapled and conventional haemorrhoidectomy;
- However, statements from patients and clinical specialists indicated that stapled haemorrhoidectomy was "considerably less painful" than the alternative, and that patients have a much speedier recovery time.

On the cost-effectiveness side, NICE considered the cost-utility study submitted by the manufacturer, and also conducted their own. That of the manufacturer, which took a one year time horizon and an NHS perspective, found a cost of £191 and an incremental QALY of 0.009 for stapled versus conventional haemorrhoidectomy, leading to an ICER of £22,416 per QALY. The cost-utility analysis conducted by the NICE assessment group took a 3 year time horizon (and incorporated a wider definition of symptoms, complications and re-interventions) and found an incremental cost for stapled haemorrhoidectomy of £19, and 0.001 *fewer* QALYs. Stapled haemorrhoidectomy was



therefore dominated. However, NICE also considered the opinions of a 'clinical specialist' and 'patient expert', who indicated the high value placed by patients on the benefits of stapled haemorrhoidectomy. As well as considering that patients who undergo conventional haemorrhoidectomy are probably more likely to seek pain management in primary care (leading to increased costs), they also considered the opinion of advisors that, for patients, the risk of re-intervention was less important than the expectation of a high-level of postoperative pain. They also heard that less time in hospital and an earlier return to normal activities was important for patients, and that according to the clinical expert "the recurrence of prolapse after haemorrhoidectomy varied on a case by case basis and in his experience of clinical practice recurrent prolapse was uncommon after stapled haemorrhoidectomy" (NICE 2007b). Also, upon reconsideration of the important issue of utility (and the big impact this had on the overall ICER), they were persuaded that there *was* a clear utility benefit in favour of stapled haemorrhoidectomy, and therefore "on balance" the utility estimated by the manufacturer (0.009) was plausible.

Burch and colleagues (Burch et al. 2008) produced a systematic review and economic evaluation for stapled haemorrhoidectomy from the perspective of the NHS in 2008. The findings are similar to those presented above. The authors find that in the early postoperative period most trials find less pain following stapled haemorrhoidectomy, but that by day 21 the difference is minimal. Healing was quicker, but prolapse was more likely. Stapled haemorrhoidectomy was associated with shorter operating times, hospital stay, and return to normal activity. There was no overall difference in the rate of complications between the two procedures. The cost and QALY implications calculated are exactly those used in the NICE guideline for the year before, indicating that this HTA fed into that decision making process. The assessment concludes that conventional and stapled haemorrhoidectomy have very similar cost and QALYs. They indicate that the cost of the staple gun (£420) is offset by the savings in hospital stay; if this price were to change, then so would the conclusions of the economic analysis. The authors conclude that the clinical evidence and economic evaluation indicate that the choice between the two procedures could be based primarily on the preferences and priorities of the patient and surgeon.

### *Suitability of headroom assumptions*

By being able to examine the factors that went into the economic evaluation which was used by NICE to make a decision on whether to recommend stapled haemorrhoidectomy (by considering the full HTA that was published a year later), I can compare these parameter inputs to those presumed in the headroom evaluation, to see to what extent these transpired to be relevant or not.

Retrospective case studies: 15. Stapled Haemorrhoidectomy

	Headroom	HTA	Comments
<b>Market size</b>	10,300	8,000	The HTA also used HES data for code H51 (excision of haemorrhoid), but relating to the years 2004-2005. This shows that the decision to use my own search rather than the estimation in the NHSC briefing was appropriate.
<b>Impact of stapled haemorrhoidectomy on hospital LOS</b>	Reduction of 2 days in those incurring hospital stay (basecase: 0% vs. 90%)	Ethicon's model: reduction of 1 day in those incurring hospital stay (57% vs. 27%) Assessment centre model: average reduction of LOS of 1.17 days (1.43 days rather than 2.66 days)	The headroom analysis assumed that <i>all</i> stapled haemorrhoidectomies were conducted as a day-cases. This has turned out to be over-optimistic.
<b>Cost of a hospital day</b>	£300	Ethicon's model: £224 Assessment centre model: £256	The cost estimation of a hospital day used in the headroom analysis was too large.
<b>QALY difference</b>	+0.009	Ethicon's model: +0.009 Assessment centre model: -0.001	Utility was estimated in both HTA models by mapping visual analogue scale (VAS) scores to SF-36 data. The NICE TA decision concluded that, based on the evidence presented by specialists as well as the output of the assessment centre model, the QALY gain estimated by Ethicon seemed feasible. Amazingly, this was exactly the same QALY impact as that estimated in the headroom analysis. Although the basis upon which Ethicon estimated this QALY gain was very different, it was encouraging to see that, in this case, the very rough estimate derived in the headroom analysis using a simple manipulation of EQ-5D value inputs, was a match to what was subsequently found for utility effect <sup>45</sup> .

The main limitations in the headroom calculation were the assumptions that all stapled procedures would be undertaken as a day-case, and that effectiveness (in terms of subsequent prolapse and re-intervention) would be the same. Of course this sort of assumption is relevant for the headroom method as, before development, the effectiveness will be unknown and it is appropriate to estimate the value of what you think *could* be achieved. The factors that did transpire to negatively affect the economic case for stapled haemorrhoidectomy *were* raised as issues / questions in sections 6 and 7 of the headroom analysis.

<sup>45</sup> It should be noted that the assumptions upon which the calculations were based were not the same, but it happened in this case that they led to exactly the same estimate of QALY gain. This at least shows that the rough method of QALY estimation proposed has the *potential* to be a useful judge of utility impact.

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

There is still plenty of literature being produced in relation to what I have considered in this analysis as 'conventional' haemorrhoidectomy – the Milligan-Morgan technique of open haemorrhoidectomy. This includes a 2011 paper written on a study which looked at how to improve the pain prospects associated with the surgery (Ba-bai-ke-re et al. 2011).

One 2010 paper considers excisional haemorrhoidectomy to still be the reference standard, being the most commonly performed procedure (McKenzie et al. 2010). However, the source used for this claim is a study from 1995 (which in fact I included as part of my headroom analysis (MacRae & McLeod 1995)). However, the Cochrane review produced in 2010 also refers to the Milligan-Morgan open haemorrhoidectomy as the current 'gold standard'. Whilst stapled haemorrhoidectomy has gained worldwide approval over the last 10 years (Cosenza et al. 2011), it has not *replaced* conventional haemorrhoidectomy entirely. This is also what is implied on patient-facing websites such as NHS choices.

### **Are there now many direct competitors?**

There are still many options available for the treatment of haemorrhoids, and surgical intervention is still only considered for haemorrhoids of third/fourth degree, and usually where other less invasive methods have failed. In terms of direct competitors, one other stapling device was identified (by Tyco Healthcare), but the use of this one does not seem so prevalent based on its coverage in the clinical literature.

In May 2010 NICE issued an interventional procedures guidance suggesting that the use of haemorrhoidal artery ligation (also for grade 3 or 4 haemorrhoids) was an efficacious alternative to conventional / stapled haemorrhoidectomy (NICE 2010b). The procedure ties off the blood supply to the haemorrhoids by stitching the blood vessels.

## **Conclusions: How useful might the headroom exercise have been?**

The 'headroom' generated by the analysis is likely to have indicated a positive development decision (though this depends on whether my interpretation of potential effect was correct- if the developer actually had more reserved ideas for impact on LOS than I used, then the development case may have been less certain). Stapled haemorrhoidectomy is used, but it has not replaced conventional haemorrhoidectomy entirely.

What made this case interesting was the ability to follow-up with a NICE technology appraisal, and relate the headroom analysis to this subsequent appraisal. The most important factors that were omitted from the (quantified) headroom analysis, which meant that the health economic effect was over estimated, were the incidence of prolapse and re-intervention, and the ability for stapled haemorrhoidectomy to be undertaken as a day case. These issues were highlighted in the research questions section as topics that should be explored.

Surprisingly, the estimate of QALY impact that was calculated by the manufacturers by extrapolating RCT data and converting to SF-36 scores was identical to that estimated in the headroom analysis (0.009 QALYs). The assumptions that went into the estimations were not the same; in the headroom analysis I simply assumed that 2 week's worth of 'moderate pain' and 'some problems with normal activities' were transformed into perfect health, whereas the Ethicon model took a year's time horizon, incorporated probability of prolapse, and involved a complex mapping task to convert to a utility score. Nevertheless, the fact that the estimate derived in the headroom analysis was in line with one that was later accepted by NICE as a plausible estimate of QALY impact for stapled haemorrhoidectomy, is encouraging (though with just this one case, the good prediction achieved with this method could be considered a fluke).

A comparison between the assumptions made in the headroom analysis and those used in the HTA which were based on the clinical literature, is presented above. An interesting finding from this follow-up is NICE's decision to recommend the procedure despite showing that, health economically, it is most likely *dominated* by conventional haemorrhoidectomy (i.e. more expensive and worse) when using assumptions based on the current evidence base.

Much like in a headroom evaluation, where the developer is encouraged to consider sections 6 and 7 as additional un-quantified indicators of likely clinical / cost-effectiveness and incorporate consideration of these into their decision, NICE also seem to undertake such an exercise. Even though the economic evaluation found that stapled haemorrhoidectomy was dominated by current practice, consideration of patient/clinician preference, as well as other factors such as the potential for reduced primary care costs for pain management (this was also flagged up in the headroom evaluation as a factor to consider), meant that NICE decided to recommend the procedure. This demonstrates the importance of factors that can't be quantified, which can still influence **buying** decisions, and should therefore also be considered in the **development** decision.

Overall, I think the headroom analysis would have presented a useful insight into the market opportunity for stapled haemorrhoidectomy.

## 16. Transpupillary thermotherapy. *Iridex*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>New Indication; (incremental development for company)</i></p> <p><i>NICE IPG follow-up.</i></p> <p><i>Date of briefing: July 2002</i></p> <p><i>Time perspective of this report: 2000<sup>46</sup></i></p>	<p>Age-related macular degeneration (AMD) is an affliction of the centre portion of the retina, the macula, and is responsible for the eye's detailed central vision. It is one of the biggest causes of vision loss in people over 50. Degeneration of the macula occurs when small clot-like formations form in the cells below the retina, which can stop the flow of nutrients to the retina. AMD can be dry form (all AMD starts as dry form), or wet form. Although just 10% of AMD cases are wet form, they account for 90% of blindness in the AMD population. Wet-form occurs when tiny new blood vessels from the choroid (a deep layer of tissue) grow up beneath the retina and are very fragile (also called choroidal neovascularisation, CNV). These fragile new vessels can leak and bleed, and eventually a scar forms in the middle of the central vision, causing a blind spot in a person's central vision. AMD can affect just one eye, or both eyes at different rates.</p> <p>It is thought that over 30% of people over 75 years of age in England have AMD. A paper published in 1996 estimated that about 50% of cases of registered blindness was attributable to AMD, and that the number of cases had an upward trend over time (Evans &amp; Wormald 1996). O'Shea describes AMD as accounting for 95% of blindness or partial sight registrations in the UK (O'Shea 1998). CNV (wet-form AMD) affects 247,000 people per annum in England. Of these, only a small proportion suffer from classic CNV whilst 88% are afflicted with occult CNV, which is where the vessels may be growing in different directions and cannot be seen clearly upon examination (unlike classic CNV where there is a well defined stalk of vessels and a localised leak). There are currently no treatment options for people with occult CNV, so prospects for these patients tend to be poor.</p> <p>Transpupillary thermotherapy (TTT) would be a new treatment option for AMD patients with CNV (i.e. wet-type AMD, classic or occult). The particular benefit of this treatment would be that it could be used to treat those AMD patients for whom current methods of treatment are not viable (specifically, those with CNV of the occult type). TTT uses a low intensity infrared laser beam (with an OcuLight SLx or OcuLight SL) with a large spot slit lamp adaptor, to heat the problematic blood vessels, with the objective of preserving central vision.</p>
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<sup>46</sup> I have chosen a timeframe of 2 years prior to the briefing because the laser equipment was actually CE marked in 1998, and is for use not just as part of the TTT procedure, but also for conventional photocoagulation. It is to be paired with a large spot slit lamp adaptor for TTT, so really the headroom is for this new technique, for which the laser equipment must be bought. As the laser equipment has already been developed and indicated for other ophthalmic uses, I will use a timeframe of the year 2000.

<p><b>2. Comparator</b></p>	<p>Conventional laser coagulation is the accepted treatment for CNV, which uses an intense light beam to burn the blood vessels and seal the leak. Photodynamic therapy is an emerging treatment for AMD, for which there is currently a lot of research being undertaken. This involves a drug called verteporfin being injected into the arm, which binds to the problematic blood vessels in the eye. A low-energy laser is then directed at these vessels, which should clot them and prevent further damage by stopping the leakages. The drug used for this is expensive. Early results from trials have shown that photodynamic therapy can safely reduce the risk of vision loss for patients with classic CNV from AMD (Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group 1999).</p> <p>The very important problem with the current options for CNV patients is that none are applicable for those with occult CNV, which represent about 88% of all CNV patients. This is why I have described TTT as a 'new indication'.</p>
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<p><b>3. Market size</b></p>	<p>In order to keep the analysis simple I will assume that treatment for patients with classic CNV, for whom conventional treatments are appropriate, will remain the same. The impact of TTT will be considered for those 88% of CNV patients who suffer from occult CNV, a condition with no other treatment alternatives.</p> <p style="text-align: right;"><b>Market size per year: 217,000</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>Conventional laser photocoagulation is the mainstay in clinical practice for CNV patients. Unfortunately, the majority of patients with this condition have occult CNV, which may not be treated with current methods. The principal benefit of TTT is that it could treat the otherwise untreatable. As there is no indication in the NSHC briefing that TTT would work better than current means of treatment, I will assume that TTT would be as useful for occult CNV patients as conventional laser photocoagulation is for patients with classic CNV.</p> <p>I have identified one cost-effectiveness study for conventional laser photocoagulation for subfoveal choroidal neovascularisation in patients with AMD. In it, the authors use markov modelling to compare laser photocoagulation therapy with the natural course of CNV (Brown et al. 2000). The cost perspective taken for this analysis was that of the Health Care Finance Agency (U.S.). The total cost estimation for laser photocoagulation was \$1,047. This included initial outpatient consultation (\$126), photocoagulation procedure (\$733) and fluorescein</p>
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<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p>angiography with interpretation and report, around 3 weeks and 5 weeks after treatment (2x\$94 = \$188).</p> <p>As the process of treatment and patient care is likely to be similar for conventional laser and TTT treatment (the procedures are not dissimilar), the resource utilisation for the general patient pathway, outside of the treatment session itself, is likely to be similar.</p> <p>As we are considering TTT for the treatment of patients who would not otherwise be considered for treatment, all costs required to treat these patients would represent <i>additional</i> costs to the NHS, rather than a shift in the allocation of resources. We can estimate the likely resource requirements for everything other than the procedure itself (for which we are estimating the 'headroom') using the costs reported above. Outside of the TTT procedure itself, the cost to the health service of caring for a CNV patient undergoing treatment (assuming these would be similar across countries and health services) would be about \$314 (initial consultation plus follow up appointments). This is equivalent to £207<sup>47</sup>.</p> <p>These treatment costs are incurred in the initial year of treatment, so no discounting is required.</p> <p style="text-align: right;"><b>(Total) ΔSC= £44,919,000</b> <b>(Av. Per person) ΔSC= £207</b></p> <p><b>P<sub>1</sub>= (not appropriate, as no disinvestment will occur)</b></p> <p><i>I have not added to this figure the procedural service costs associated with undergoing TTT. Therefore, these would have to be considered within the headroom figure delivered.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-</p>	<p>There are some questions raised in the literature about how QoL (and the measurement of this parameter) and ophthalmology fit together. A survey of experts conducted in 1998 found that UK Ophthalmologists appear to be unfamiliar with QoL measures, despite the fact that they have become the standard means of assessing and comparing health care interventions (Hart, Chakravarthy, &amp;</p>
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<sup>47</sup> Using an exchange rate of \$1.52 to the £ (the average across the 12 months of the year 2000) (HM Revenue & Customs 2011).

<p>effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>Stevenson 1998). Most respondents deemed QoL measures to be of little importance for AMD, with distance and near visual acuity being the most highly rated measures.</p> <p>Brown (Brown 1999) presents the only attempt I have found in the literature within this timeframe of measuring the QoL associated with vision. He presents an evaluation of various QoL measures for vision acuity loss, and finds the time trade-off method to be the most useful and appropriate.</p> <p>It is the same author that, a year later, produced the cost-effectiveness analysis for laser photocoagulation introduced above. The extent to which TTT treatment of CNV could affect a patient's QoL would be very difficult to guess / estimate by indirect means, as would the timeframe according to which these changes might happen. Therefore, it seems appropriate to approximate this impact by using data obtained from treating classic CNV patients with conventional laser coagulation. Brown et al. (Brown et al. 2000) use patient outcome data from a trial conducted by the Macular Photocoagulation Group (Macular Photocoagulation Study Group 1993), in which 371 patients were randomized to laser treatment or no treatment. The mean age at randomization was 74.4 and follow up was available for 4 years. The visual acuity data for these years showed that in the first three months, visual acuity was decreased in the treatment group compared with the control group, but that the net utility change from treatment was positive after the first year. The change in visual acuity was reported over the four years, and these were converted into QALYs by Brown and colleagues by using the results of the QoL elicitation using the time trade-off method, as reported in his previous paper (Brown 1999). The net utility change over the four years for treated versus non-treated CNV patients was 0.028, but markov modelling was used to extrapolate the results over the remaining years of expected life per patient (a further 7 years). The overall QALYs gained from treatment versus no treatment was 0.257 which, discounted at a rate of 3%, is equivalent to 0.186<sup>48</sup> (Brown et al. 2000).</p>
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<sup>48</sup> The rate of discount that should be used is 3.5% (the same as the discount rate for costs). However, the authors only provide the QALY gain discounted at the rates of 1%, 3%, 5% and 10%.



<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p style="text-align: right;"><b>ΔQALY= 40,362</b> <b>(Av. per person) ΔQALY= 0.186</b></p> <p><i>The most important aspect of this technology is that it may offer the opportunity to treat patient who at the moment have no hope of vision preservation. Any reimbursement decision is likely to consider this proposition favourably, and may be willing to pay a premium for this.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [GREEN] There is much emphasis in the literature on the lack of treatment options for patients with occult CNV (Howe 1995). A technique (like TTT) that could overcome this big gap in current care for patients with AMD should be very sought after and well received by the health service.</li> <li>• [AMBER] The OcuLight laser instrument that has recently been developed by the company is for use in various clinical applications including, it seems, conventional laser coagulation. It is very likely that others do or can produce very similar devices, and so the TTT technique may be mimicked and marketed by others if it proves to be successful in the treatment of CNV patients.</li> <li>• [AMBER] There seems to be plenty of innovation in the area of CNV treatment. Treatments identified in the literature search include teletherapy (Hart et al. 1996) and proton beam irradiation (Flaxel et al. 2000). With much development in the area, it may be sooner rather than later that other methods are found to treat occult CNV by other means.</li> <li>• [AMBER] A (small) number of investigations in the literature consider other options for the treatment of patients with occult CNV, for whom current treatment offers limited benefit. One study finds that radiation therapy should not be generally used for patients with occult CNV (Weinberger et al. 1999). Another such investigation is into the efficacy of indocyanine green angiography (ICGA)-guided laser photocoagulation. Brancato and colleagues</li> </ul>
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As the net utility gain over the last 7 years of life are said by the authors to be “variable” (Brown et al. 2000), I cannot calculate accumulated discounted value myself.

	<p>(Brancato et al. 2000) find that the technique <i>may</i> improve or stabilise visual acuity in some eyes with occult CNV, but that further investigation is needed. Weinberger et al show similar preliminary findings (Weinberger, Knabben, Solbach, &amp; Wolf 1999).</p> <ul style="list-style-type: none"> <li>[AMBER] Transpupillary thermotherapy is already referenced in the literature in relation to the treatment of choroidal melanoma. This indicates potentially a much wider market, but also raises the issue that this is probably a technique that may be performed by a number of different devices.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>How would the cost of performing TTT relate to the cost of conventional laser coagulation and photodynamic therapy? If costs could be reduced and effectiveness is equivalent or better, then TTT could overtake these other techniques as the treatment of choice for all CNV patients.</li> <li>For what other indications might the equipment be used? This will affect market size.</li> <li>Is it feasible to assume that the vision gain associated with treating occult CNV patients with TTT is equivalent to that gained treating classic CNV patients with laser coagulation? (this is the assumption that we make in this analysis)</li> <li>Would there be any other costs involved in the application of TTT that have been omitted here?</li> <li>Would just one treatment be necessary or would multiple treatments be required?</li> </ul>
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## Headroom Notes (Transpupillary thermotherapy)

Headroom	
WTP: £20,000	WTP: £30,000
<b>£3,513</b>	<b>£5,373</b>

The ‘headroom’ presented above represents the value that the NHS should place on improving the vision prospects of occult CNV patients. Netted from this are some of the service costs that would be involved in pre and post care for TTT.

In this example, the service costs estimated are all incurred rather than saved as in most other examples. This is because TTT offers a treatment option for those patients who were previously untreatable. Although some service costs have been accounted for, those that would be associated with the procedure itself have not been accounted for, so must be considered within this figure. In other words, the developer must ask himself whether £3,513 - £5,373 would reasonably cover the cost to the health service of carrying out the procedure itself (i.e. the clinician and theatre time involved) *and* whether what is left over of this 'headroom' figure would be sufficient to cover what would be the amortised cost of using the device. Again, this is difficult for me to consider in concrete terms without understanding the likely throughput of the device, and so the 'cost per patient' of using it.

Note: This estimation represents a headroom 'per patient'. If multiple procedures would be required, then this figure would have to cover all of these.

## Follow-up (Transpupillary thermotherapy)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

A per patient headroom of £3,513 - £5,373 was calculated for Transpupillary thermotherapy (TTT). This represents what the NHS should be willing to pay to treat one patient with TTT, given the assumptions used in the headroom analysis, but should include the service costs associated with the procedure itself.

The NHSC briefing indicates that the laser and delivery device would cost £25,000 as a one off lump sum. A cost estimate per individual treatment/patient is not given. I have found no other cost estimates for TTT, and without understanding the distributional and patient throughput implications of treating all occult CNV patients, I do not know if this would have covered costs (one device would have to treat at least 8 patients in its lifetime). An economic evaluation undertaken from an NHS perspective for photodynamic therapy (PDT) (which was to inform NICE's technology appraisal for the procedure) estimated that the cost per treatment was £1,181 (Meads et al. 2003). Given the high cost of the verteporfin drug required for this procedure (£850), the cost of TTT would be very unlikely to exceed this cost, indicating that the headroom presented may well have shown ample room for development. Having said this, the HTA seems to indicate that for PDT, patients would undergo at least 3 PDT treatments in the first year alone. If this is the case for TTT, then the headroom must cover all treatments.

An announcement by IRIDEX that TTT had achieved Medicare reimbursement (U.S.) in Mississippi detailed that the allowable cost (from a reimbursement perspective) for the procedure was \$800 (Internet Wire 2004). Again, interpretation of this in relation to the headroom calculated would require knowledge of how many procedures would be required in total per patient, but it seems likely to fit within the headroom indicated (assuming that procedures required per patient are less than

five or six, which seems likely). Given the cost per patient treated with PDT fits within the headroom (which is likely to be more expensive than TTT given the drug required), and that the device would hopefully be used to treat more than seven or eight patients in its lifetime, headroom is likely to have indicated a positive development decision.

**Headroom result uncertain due to lack of information, but is likely to have indicated a positive development decision.**

### **Has there been a decision made on it by NICE? What was the outcome?**

As indicated by early research outlined in the pro forma, there is a lot of treatment innovation in the area of AMD. This is reflected in the number of NICE appraisals / guidelines that are relevant to this disease. To date there have been two technology appraisals (photodynamic therapy, and ranibizumab and pegaptanib) and six interventional procedures guidance (epiretinal brachytherapy, implantation of miniature lens systems, limited macular translocation, macular translocation with 360° retinotomy, radiotherapy, and Transpupillary thermotherapy).

The interventional procedures guidance for TTT, IPG 58, was produced in May 2004 (NICE 2011e). Current safety and efficacy evidence for TTT was insufficient to allow the procedure to be recommended.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

I have found evidence that TTT is reimbursed for wet AMD in some parts of the U.S. (at least 17 states as of 2003) (Business Wire 2003;Internet Wire 2004). However, some recommend TTT for different indications. For example, the CIGNA<sup>49</sup> medical coverage policy stipulates that TTT is provided but only for retinoblastoma or small choroidal melanomas; they do not cover TTT for the treatment of CNV associated with AMD as “such treatment is considered experimental, investigational or unproven”(CIGNA HealthCare 2008). Other health insurance providers have the same policy for TTT (Aetna 2011).

From the Iridex website, it is clear they produce many laser devices, including the OcuLight SL/SLx (used for the delivery of TTT). However, these infrared laser devices are for use not only for TTT but also other retinal treatment procedures, like photocoagulation.

I have found no clinical literature on the use of TTT in a UK setting. On the NHS choices website which provides patient information for the treatment of macular degeneration, TTT is not mentioned as one of the potential options to be considered (NHS Choices 2010c). For wet AMD, the first treatment described is PDT, followed by drugs, followed by a list of ‘possible treatments’ which include implanting lens systems, macular translocation, and laser photocoagulation.

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<sup>49</sup> CIGNA is a private healthcare provider, based mainly in the UK and large providers of managed employee healthcare benefits and services.

### **Have there been investigations into its clinical / cost effectiveness?**

I have found no cost-effectiveness analyses or economic evaluations for TTT.

As for the clinical effectiveness of the procedure, with the information available in 2004, NICE were unable to recommend the procedure for use in CNV patients (NICE 2011e). Therefore I will briefly summarise the important results of clinical effectiveness since that time.

As indicated in the NHSC briefing and therefore in the headroom analysis, the real benefit of TTT would have been to allow for the treatment of patients with occult CNV. It was thought that no other therapy was relevant to this population. However, a study presented by Odergren and colleagues in 2010 (Odergren et al. 2010) finds that TTT and PDT appear to be equally as effective for stabilising visual function for patients with occult CNV. It is noted, however, that the study was underpowered and also that the drug ranibizumab has shown impressive results for *all* types of CNV, so neither laser procedure should be considered as first-line treatment (Odergren et al. 2010).

One study reports that TTT carries a small but significant risk of immediate and severe vision loss—risk factors identified were haemorrhage disc size and laser power (Mason, III et al. 2008).

A prospective randomised controlled pilot study for the use of TTT in occult CNV patients (full text unavailable so I was unable to see whether Iridex equipment was used) was conducted in 2006 (Myint, Armbrecht, Mon, & Dhillon 2006). The authors concluded that TTT appeared to have no benefit in preventing vision loss.

During my follow up searches, I found reference to TTT (using the OcuLight laser by Iridex) being tested for use in AMD in 1999 (Reichel et al. 1999), indicating that my time frame was not as early as it should have been.

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

In 2000 (the time perspective of the headroom analysis), conventional laser photocoagulation was considered the 'gold standard' for AMD patients. This is no longer the case. A Cochrane review produced in 2007 (and reviewed in 2009 with the same conclusions) considers laser photocoagulation for the treatment of neovascular AMD, and concludes that whilst being the first treatment in this area, laser photocoagulation should no longer be recommended for CNV patients given the risks attached to the procedure and the appearance of newer and better treatment modalities or different laser techniques (Virgili & Bini 2007). PDT seems to be the most widely referenced treatment on patient information sites like NHS Choices. In September 2003 NICE recommended PDT for wet AMD patients, but only those with no sign of occult CNV (NICE 2003c).

As mentioned, there was no gold standard in 2000 for patients with *occult* CNV. This seems to have changed as well, with PDT proving to be just as effective for these patients in one study undertaken (see above). In a technology appraisal produced for the drug ranibizumab, NICE recommend it as a treatment option for all wet AMD patients (NICE 2008b). Ranibizumab has generated positive results in clinical trials for all types of CNV; more effective than another type of drug verteporfin (Brown et

al. 2006). A study that compared ranibizumab to a placebo found that after 2 years, vision loss was prevented in the treatment group and visual acuity rose; patients in the study included those with classic *and* occult CNV (Rosenfeld et al. 2006).

The appearance of new treatment options in this area seems to be common, as well as the further development of current treatments, including TTT. A 2011 publication considers the functional outcome of TTT with different spot sizes using the OcuLight by Iridex (though for the treatment of a different condition) (Shah, Narendran, & Kalpana 2011).

#### **Are there now many direct competitors?**

As of 2002, the FDA had approved three ophthalmic lasers for TTT: the OcuLight SLx (Iridex Corp, CA), the Nidek DC-3000 (Nidek Inc, CA) and the GaAIAs diode laser (Candela USA, MA) (CIGNA HealthCare 2008).

The main source of competition for TTT therapy are other forms of treatment, which at the moment appear to have a stronger clinical grounding for use in wet AMD patients.

#### **Conclusions: How useful might the headroom exercise have been?**

The source of 'headroom' in this example was predominantly the QoL benefit to patients, who currently had no treatment options. Unfortunately it was difficult to interpret this headroom without information on the procedural service cost implications of the therapy (on the day of treatment), how many treatments would be needed per patient, and the distributional and equipment longevity details (and what this would mean for the equipment cost per *patient*).

Although it was difficult to interpret the economic analysis from information provided in the NHSC briefing alone (this may have been a more informative process to the manufacturer), the main reason for its poor uptake in the UK is its limited clinical efficacy; I did not identify any economic analyses, presumably due to the limited clinical support for the procedure. The headroom method economically evaluates a new device by considering the price it might fetch under the assumption that it will work. In this case, TTT doesn't produce the clinical outcomes it set out to, and other treatment options seem to be more viable. The baseline has changed as other treatments have now been recommended for patients with occult CNV. Although the efficacy of other new treatments can't be predicted from an early stage, it was clear from the literature at the time that there were many new treatment options on the horizon.

However, as indicated, the device (rather than the technique specifically) is used for a wider range of ophthalmic applications, and as such still appears to be a viable product.

**17. Citrasate dialysate. Health Tec Medical Ltd. (License from Advanced Renal Technologies (ART), USA)**

<p><b>1. Description</b></p> <p><i>Device<sup>50</sup>;</i></p> <p><i>Incremental Development;</i></p> <p><i>No NICE follow-up.</i></p> <p><i>Date of briefing: August 2006</i></p> <p><i>Time perspective of this report: 1999<sup>51</sup></i></p>	<p>People that require haemodialysis are those with chronic or acute renal failure who require the assistance of a dialysis machine to remove waste products and water from their blood. A dialysis solution is used as part of the extracorporeal circuit, which often contains heparin. Heparin is an anticoagulant and prevents clotting in the dialyser circuit, which can lead to a reduced dose of dialysis delivered and increased blood loss. Heparin, however, is contraindicated in some patients.</p> <p>Citrasate dialysate is a citric acid concentrate which can be used as part of standard bicarbonate dialysis solutions. It represents an incremental development to standard dialysis solutions, which could improve efficiency of dialysis and lead to fewer complications than standard acetic acid-based dialysate fluids. It can also work as an anticoagulant for those patients who can't tolerate heparin. There would be no changes to all other dialysate chemicals, and no system or equipment changes would be required.</p>
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<p><b>2. Comparator</b></p>	<p>Comparator dialysate fluids include standard acetic acid or bicarbonate dialysate formulations (of which there are many types). Heparin is added where anticoagulation is needed because there is a clotting risk, and is used routinely (SIGN (Scottish Intercollegiate Guidelines Network) 1999). Low molecular weight heparins are starting to emerge as an alternative to heparin, which are considered to potentially offer therapeutic benefit and reduced complications. Heparin is considered to be relatively safe and effective, though its long term use can be associated with complications including thrombocytopenia (heparin-associated thrombocytopenia: HIT), lipid abnormalities, increased risk of haemorrhage, and allergic reactions (Saltissi, Morgan, Westhuyzen, &amp; Healy 1999).</p> <p>Where heparin anticoagulation is contraindicated, measures that can be used are:</p> <ul style="list-style-type: none"> <li>• Periodic line flushes. This is thought to be relatively ineffective and cumbersome.</li> <li>• Regional citrate anticoagulation. High concentrations of citric acid are infused into the venous line to prevent and clear blockages. This can be difficult to administer, expensive, and unsuitable for out-patients.</li> <li>• Danaparoid can be used in patients where heparin is contraindicated. It is thought not to be suitable for all patients, and is expensive. One clinical study from 1997 compares heparin to Danaparoid and</li> </ul>
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<sup>50</sup> There is some confusion in the literature regarding the categorisation of dialysis fluids. However, within the rules set out for the classification of medical devices by the European Commission (European Commission 2010), 'haemodialysis concentrates' are included under Rule 3: Non-invasive devices that modify biological or chemical composition of blood, body liquids, other liquids intended for infusion. These belong to Class IIb.

<sup>51</sup> I have found trials for Citrasate dating back to the year 2000, so I have chosen to predate this by one year.

	<p>concludes that Danaparoid is the drug of choice (van Barlingen, van Beek, Erkelens, &amp; de Bruin 1997). Another small study of two individual cases finds that Danaparoid is a safe and effective substitute for heparin as an anticoagulant in haemodialysis (in this case where that patient had developed HIT) (Ben Ami, Rachmimov, &amp; Berliner 1999).</p>
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<p><b>3. Market size</b></p>	<p>According to the NHSC briefing, the company estimate that about 35% of patients on dialysis could receive Citrasate. Approximately 13,000 people are on haemodialysis in England and Wales, which implies a potential market of approximately 4,500.</p> <p>There are probably only around 100 patients in the UK in whom heparin is contraindicated, but these patients need to use (heparin-free) dialysis throughout their lives.</p> <p style="text-align: right;"><b>Market size per year:</b>  <b>4,500</b> (if used for all relevant patients)  <b>100</b> (if used only for those who cannot use heparin)</p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>I have found only a limited number of cost estimates for dialysate fluids:</p> <ul style="list-style-type: none"> <li>• The NHSC briefing indicates that the lowest price for acetate acid dialysate is 35p/litre.</li> <li>• One study which compares heparin with low-molecular-weight heparin (LMW) reports a cost per treatment of US\$24.22 for Clexane (LMW) and US\$20.51 with sodium heparin (standard heparin) (Saltissi, Morgan, Westhuyzen, &amp; Healy 1999). It is not clear what these costs include.</li> <li>• A review produced by the NHS HTA programme (MacLeod et al. 1998) presents a cost analysis for bicarbonate dialysate (to which Citrasate would theoretically be added) and acetate dialysate. They conclude that bicarbonate dialysate is both the most widely used and the most preferable, being of similar cost and associated with fewer complications. The total cost of the bicarbonate dialysate fluid ranges from £5.40 to £9.45 per session (depending on type) and £4.90 to £6.30 for the acetate dialysate. However, this difference is neutralised when considering the cost to the health service of complications.</li> </ul> <p>In its costing analysis, the HTA implies that acid must be added to the bicarbonate dialysate but not to the acetate dialysate (the cost for this was included in the estimates above).</p> <p>I will assume that it is this acid addition that Citrasate</p>
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	<p>dialysate is proposing to replace. The cost for this acid element of the dialysate fluid in the HTA was £2.45 to £3.15 per session.</p> <p>There are two elements to the health economic case for Citrasate. The first is to be a more efficient and effective dialysis fluid than standard acetic based ones. The second is for it to act as an anticoagulant. As heparin is considered to be effective and inexpensive, I will assume that this would be continued to be employed for anticoagulation in haemodialysis. However, for those in whom heparin is contraindicated, Citrasate could replace heparin-substitute strategies, such as the use of danaparoid.</p> <p><b>Scenario 1(a):</b> Citrasate dialysate is to be used with standard bicarbonate dialysis solutions for haemodialysis (no specific targeting of the therapy to patients in whom heparin is contraindicated).</p> <p>For this scenario, I will simply assume that Citrasate is to be used as the 'acid' addition to bicarbonate dialysate solutions. The headroom for this will simply be the cost of current acid required for the dialysate, which is about £3 per session (MacLeod et al. 1998)</p> <p style="text-align: right;"><b>Market size = 4,500</b> <b>P<sub>1</sub> = £3</b></p> <p><b>Scenario 1(b):</b> The NHSC briefing implies that the incorporation of Citrasate could promote more efficient dialysis (though is in reference to acetate fluids rather than bicarbonate). If it is intended that the addition of Citrasate could further improve the efficiency of bicarbonate solutions, one could reasonably assume that the difference in cost of complications to staff etc. may be similar to the difference in complication cost between standard acetic and standard bicarbonate fluids (which perform better than acetic ones). The maximum difference in cost of complications (provided in the HTA (MacLeod et al. 1998)) between these two standard dialysates is £0.62 (highest estimate for acetate) minus £0.11 (lowest estimate for bicarbonate). Therefore, we will assume that, in the best case scenario, Citrasate might save about 50p in complications costs per patient per session.</p> <p style="text-align: right;"><b>Market size = 4,500</b> <b>ΔSC = £0.50</b> <b>P<sub>1</sub> = £3</b></p>
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<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p><b>Scenario 2:</b> Citrasate dialysate is directed at those who cannot use heparin and who require anticoagulation; this is relevant for about 100 patients in the UK.</p> <p>Danaparoid seems to be the most widely recognised means to treat these patients, so provides the relevant comparator for Citrasate. According to the NHSC briefing, one expert has suggested that replacing danaparoid in the small number of patients who use it could save their unit around £10,000 per year.</p> <p>Although in many publications it is referred to as 'expensive', I have found no direct estimate of the cost of danaparoid per session. As all other components of the procedure remain the same, the cost of danaparoid itself would be the only cost saved if Citrasate could replace it with equal effectiveness. Therefore, the cost of danaparoid would represent the headroom for Citrasate within this scenario, but I can find no details of this price.</p> <p style="text-align: right;"><b>Market size ≈ 100</b> <b>P<sub>1</sub> = £?</b></p> <p><i>If Citrasate can improve the efficiency of dialysis over and above that of other bicarbonate dialysis fluids, then this could imply reduced extracorporeal flushing (saving staff time), and reduce the time required to deliver the required dialysis dose.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>Haemodialysis presents an interesting and difficult challenge for QoL measurements; whilst this renal replacement therapy acts as a lifeline for the many patients that use it, the impact of this very regular and intensive therapy on the lives of those that use it is substantial. There have been many attempts in the literature to address this issue (Killingworth &amp; van den Akker 1996; Maxwell &amp; Fitzpatrick 1998).</p> <p>As Citrasate dialysate represents an incremental development of currently used dialysate fluids, it is unlikely to pose any significant and measurable impact on QoL.</p> <p style="text-align: right;"><b>ΔQALY= -</b> <b>(Av. per person) ΔQALY= -</b></p> <p><i>If Citrasate were to work more effectively than current fluids, this could mean shorter dialysis sessions, and also reduced blood loss.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [GREEN] Citrasate dialysate is to be added to standard bicarbonate dialysis solutions. A comprehensive review of the literature undertaken from an NHS perspective was produced last year, 1998. The systematic review indicated that bicarbonate has largely replaced acetate solutions in haemodialysis in the UK (MacLeod et al. 1998). The report indicates that bicarbonate dialysis is preferable due to its associated reduction in adverse symptoms, and similar costs. Citrasate dialysate is compatible with these recommended solutions, and aims to promote their efficiency further.</li> <li>• [AMBER] There are other alternatives to heparin that are being investigated and could prove to be more effective: low molecular weight heparins (LMW). A review produced two years ago in 1997 outlines their benefit over unfractionated heparin (Nurmohamed, ten Cate, &amp; ten Cate 1997). There may be some therapeutic advantages over unfractionated heparin, and possibly fewer complications. Citrasate may need to prove itself to be as effective an anticoagulant as these.</li> <li>• [AMBER] Some of these low molecular weight heparins have been shown to provide a safe and effective anticoagulation for those in whom heparin has caused HIT (heparin induced thrombocytopenia) (Rowlings et al. 1991), and to show a lower complications rate (Warkentin et al. 1995). This may change the treatment option for those in whom heparin is contradicted, moving away from danaparoid (supposedly very expensive) to other, perhaps cheaper modes of treatment, such as low molecular weight heparins.</li> <li>• [AMBER] Some authors find 'no anticoagulation' to be safe and effective in some cases.</li> </ul>
<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating</p>	<ul style="list-style-type: none"> <li>• The main assumption made is that, in the case of scenario 2, Citrasate will work equally as well as other more expensive anticoagulants such as danaparoid. The feasibility of this assertion must be investigated.</li> </ul>

<p>to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• What is the cost of danaparoid? Given that the above can be qualified, this will be the 'headroom' in scenario 2.</li> <li>• Is it thought that Citrasate could improve the efficiency of dialysis as compared with bicarbonate dialysis, or acetic dialysis? (I.e. is scenario 1(a) or 1(b) the more likely?</li> <li>• Could the improvements brought about by Citrasate translate into any quality of life improvements for patients?</li> <li>• Would standard heparin still be used in patients who use Citrasate dialysate? If not, then a small premium may be added to represent the disinvestment in heparin when using Citrasate.</li> </ul>
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## Headroom Notes (Citrasate dialysate)

There were many unknowns for this case, including, crucially, the price of the danaparoid, which is what Citrasate may possibly replace for anticoagulation in those who cannot use heparin.

In the straightforward case of Citrasate replacing the acid that is added to standard bicarbonate solutions, the headroom (and indeed the MRP, as there would probably be no impact on service costs) would be about £3. If the developers believed this to be a reasonable price, then this would be likely to justify a development decision. If it is thought that Citrasate could improve the efficiency of dialysis compared with bicarbonate dialysate, then the MRP would be £3.50. This is in reference to the price that could be charged *per patient per session*.

To consider allowable development costs would require information on the number of haemodialysis sessions a patient will go through in a lifetime.

## Follow-up (Citrasate dialysate)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The headroom analysis in this case was fraught with uncertainties, and the benefits that could be brought about by Citrasate dialysate (as compared with standard bicarbonate rather than acetic solutions) was not clear. However, under various assumptions / scenarios, the MRP of Citrasate dialysate per patient per session was estimated.

Presuming that Citrasate incorporated into the to the haemodialysis process for all relevant patients, then some 4,500 patients may use Citrasate. Without knowing more about the number of sessions undertaken by the average patient over their lifetime, I cannot calculate how many sessions this would equate to in total. Per patient per session, the MRP was estimated to be about £3, and this

was simply based on the price of the acid that is currently added to bicarbonate dialysate solutions. If it were thought that Citrasate could improve the efficiency of dialysis further, then it was estimated that it would fetch a price of around £3.50.

One major proposition of Citrasate in terms of value was its capacity to act as an anticoagulant for patients in whom heparin was contraindicated, as current means of treating these patients are expensive. However, I was unable to identify the price of danaparoid, the main (and probably most expensive) alternative. I assume that this information would have been more accessible to the developer of Citrasate. In this context, it would simply have been assumed that the NHS should be willing to pay *up to* what they already pay for danaparoid. Of course, the prospect of cost-saving would be attractive for uptake, and it is unlikely that the developer could choose to set a different price according to who it was being used for.

The NHSC briefing indicates that Citrasate dialysate would cost £1-2 per litre. They do not make clear how much fluid is required per session. Various anti-coagulation strategies are discussed in one paper that was published in 2008, which includes Citrasate and danaparoid (Faratro, D'Gama, & Chan 2008). The cost of both is presented: Citrasate being \$6.75 'per jug' and danaparoid being \$18.78 'each'. Units are unclear. On one medical supplies website, Citrasate is priced at about \$40, based on '48 cases' (Dial Medical Supply 2011). Again, it is difficult to know how these would translate into a cost per haemodialysis session. The company's own website indicates that Citrasate liquid is available in individual-dose gallon jugs, packaged four per case (Advanced Renal Technologies 2009). This would imply a cost of \$40 / (48\*4) = \$0.21. This is much lower than the estimate 'per jug' used in the study reported above.

**Headroom unclear given lack of detailed pricing knowledge (both for the estimation of headroom and for the assessment of its adequacy). If it is produced at a price of under £3 per session, then headroom would probably have been favourable.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

Citrasate for renal dialysis was considered for potential technology appraisal but was rejected by the panel in July 2007 (NICE 2009b). NICE has produced various appraisals and guidelines for kidney failure and haemodialysis, but none deal specifically with dialysis fluids.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

Citrasate dialysate received FDA approval in June 2000 (FDA 2000), but did not receive EU regulatory clearance (by issue of a CE mark) until 2007. In the FDA approval letter Citrasate dialysate is referred to as a device, but it is viewed by others as a drug (Flanigan 2000).

The product was developed by Advanced Renal Technologies (ART) in the U.S., and Health Tec Medical Ltd. has exclusive rights for its sale in the UK. Citrasate seems to be on the product list of many medical suppliers, who are located across the world. Uptake seems to have been quite slow, with the EU clearing Citrasate 7 years after it was available in the U.S. A publication from 2008, in which Citrasate was used for nocturnal haemodialysis, indicated that the product was still not approved by 'Health Canada' (Faratro, D'Gama, & Chan 2008).

Citrasate dialysate is not mentioned in a number of relevant guidelines (at least in its anticoagulant capacity), such as that produced by The Renal Association (UK) in 2009 (Mactier, Hoenich, & Breen 2009). They mention that bicarbonate dialysate should be used as the buffer. Although its presence in the literature is reasonably limited (though there have been some publications which include the use of Citrasate, including one published in 2010 (Hanevold, Lu, & Yonekawa 2010)), it has a strong online presence. This may be unsurprising given its very specific nature. Health Tec Medical Ltd. (the UK supplier) confirmed by telephone that they supply Citrasate to 6 NHS units, and that this user base is expected to grow.

### **Have there been investigations into its clinical / cost effectiveness?**

On sales websites for Citrasate, 'tangible' benefits that are emphasised are reduced clotting (and subsequent equipment changes) and reduced heparin use and nursing time. Under the 'intangible' benefits are improved patient treatment, decreased time, lower blood loss and adverse side effects, and fewer saline flushes (Dial Medical Supply 2011). They also emphasise the 'costly pharmaceutical alternatives to heparin'.

Whilst the product is marketed with its capacity for anticoagulation at the forefront of benefits, Citrasate is not included in most of the literature that addresses anticoagulation in haemodialysis. Most of the literature addresses heparin and low-molecular-weight (LMW) heparin. Many articles refer to regional citrate infusion among the other treatment options, rather than Citrasate dialysate (Fischer 2007; Hetzel et al. 2011; Mactier, Hoenich, & Breen 2009).

There are some clinical trials that consider Citrasate specifically. One is by Ahmad and colleagues, who find that that use of Citrasate dialysate increases the delivered dose of dialysis (Ahmad, Callan, Cole, & Blagg 2000). The same author has been involved in many poster presentations and other papers that report positive Citrasate results (he has 'equity interests' in the company ART). The other published paper declares that Citrasate dialysate is associated with increased solute removal (Kossmann, Gonzales, Callan, & Ahmad 2009). A different paper that considers the use of Citrasate in relation to haemodialysis in children, concluded that Citrasate was well tolerated and reduced but did not eliminate the need for heparin (Hanevold, Lu, & Yonekawa 2010). Cheng and colleagues find in a feasibility study that citrate-enriched dialysate (using Citrasate) is feasible, and offers a simpler approach compared with intermittent saline flushing (Cheng et al. 2011).

One review of the literature which concludes that (although heparin should remain the mainstay of clinical practice for anticoagulation in haemodialysis), after development of HIT (heparin-induced thrombocytopenia) it is appropriate to use one of the following: direct thrombin inhibitors, regional citrate infusion, citrate dialysate, or heparin-free dialysis (Cronin & Reilly 2010).

In clinical studies that do not focus specifically on anticoagulation in haemodialysis, Citrasate tends to have positive results. One study concludes that whilst coagulation was not affected by citrate-based versus acetate-based bicarbonate haemodialysis, efficiency was improved, as was acid-base status, haemodynamics and tolerance (Gabutti et al. 2009).

The only study I have found which relates to the cost of Citrasate is not a cost-effectiveness study per se, but reports on the treatment outcomes and costs for one patient who tried many alternatives to heparin for home haemodialysis, after having developed HIT (Faratro, D'Gama, & Chan 2008). The cost per patient per treatment for home haemodialysis (including staffing time and supplies) was \$103.85 for standard heparin, \$127.37 for Citrasate dialysate, and \$141.41 with danaparoid (Faratro, D'Gama, & Chan 2008).

## **Has the landscape described changed significantly?**

### **What is current gold standard clinical practice now? Has this changed?**

Most of the literature addresses heparin and low-molecular-weight (LMW) heparin, many finding that healthcare resource use is reduced with LMW heparin, which makes up part of the price differential (Pettigrew et al. 2011); one study conducted from a UK perspective found that, although LMW heparins had been recommended over unfractionated heparin in the European Best Practice Guidelines, the LMW heparin Tinzaparin achieved comparable safety and efficacy compared with standard heparin, and equal total cost of therapy (Bramham, Varrier, Asgari, & Makanjuola 2008).

One review published in 2010 concludes that unfractionated heparin is still the treatment of choice as the performance of LMW does not justify its extra cost (Cronin & Reilly 2010). It was noted that although LMW heparin was not used widely in the U.S., in Western Europe it is the 'norm' (Cronin & Reilly 2010). A Cochrane review is currently under development comparing the two.

As for patients in whom heparin is contraindicated, various methods seem to be employed (as outlined in the headroom analysis). A large survey sent to all renal units in the UK was reviewed in a study published in 2007, which found that for patients with HIT, the most commonly used treatment method was with Danaparoid (Hutchison & Dasgupta 2007). This was the same baseline as that which was considered in the headroom analysis. However, it wasn't until 2007 that Citrasate dialysate was available in the UK.

The gold standard of clinical practice seems to be similar to what it was in 1999 (the time perspective of the headroom analysis, apart from the increased use of LMW heparins).

### **Are there now many direct competitors?**

All of the studies that I have identified (and websites that I have found) that relate to citrate fluids in general have all been in relation to Citrasate dialysate. As expected, the use of LMW heparins has increased, and in some cases are employed where unfractionated heparin is contraindicated. There are still many options for dialysate fluids and anticoagulant techniques, among which is Citrasate dialysate.

**Conclusions: How useful might the headroom exercise have been?**

The results of the headroom method were difficult to interpret given the lack of precise costing, price, and procedure data. Whilst the potential for reimbursement was outlined, it could not be quantified (at least under scenario 2) without knowing the price of danaparoid. There was no cost-effectiveness study for Citrasate in the literature to compare assumptions and findings with the headroom analysis.

The literature search undertaken for the headroom analysis identified one source for service cost saving estimates, which could potentially have been considered, but otherwise it was simply the price of current options that was used (one of which could not be found). This would probably have been useful, but is likely to have been considered in any case.

Citrasate dialysate is not used systematically across the NHS, but is employed by some units and therefore does appear to be a treatment option.



## 18. Tension Free Vaginal Tape (TVT). *Ethicon*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>Replacement Technology;</i></p> <p><i>NICE follow up (CG)</i></p> <p><i>Date of briefing: June 2000</i></p> <p><i>Time perspective of this report: 1996<sup>52</sup></i></p>	<p>TVT is a minimally invasive technique which seeks to eliminate urinary incontinence. It will be performed under local anaesthesia, take 25-30 minutes and require an average of 6 hours in hospital.</p> <p>Stress incontinence (the most common cause of urinary incontinence (UI) in women) is the involuntary loss of urine upon physical exertion, which could simply be coughing or changing position. It is defined by the International Continence Society as the involuntary loss of urine occurring when, in the absence of bladder wall contraction, the bladder pressure exceeds the urethral pressure. The condition can cause significant physical and psychological difficulties, thus reducing QoL. It is thought that around 2.5 million women in the UK suffer from stress incontinence.</p> <p>TVT reinforces the pubourethral ligaments. A mesh tape is attached under the urethra (like a sling / hammock) to keep it in the right position. It is inserted via the vaginal wall, looped in a u-shape around the mid-urethra, and the ends are cut off in abdominal subcutaneous tissue (accessed through the abdomen).</p>
<p><b>2. Comparator</b></p>	<p>Colposuspension surgery is the relevant comparator for treatment of stress incontinence after conservative treatments (pelvic floor muscle training, electrical stimulation, and pharmacological intervention) have failed. The Burch colposuspension is the gold standard - a surgical intervention which involves repositioning the bladder neck by lifting and stitching the front wall of the vagina onto a ligament behind the pubic bone.</p> <p>TVT is less invasive and takes less time, and so is likely to be better accepted by patients, and reduce service delivery costs. A recent study (1996) found significant changes in voiding function after Burch colposuspension, and outflow obstruction appeared to be a significant potential complication (Wall &amp; Hewitt 1996). A systematic review of the effectiveness of current surgical management for stress incontinence indicates that about 85% of women are continent one year following colposuspension (Black &amp; Downs 1996). We will assume that the TVT procedure will have the same outcomes as this more invasive surgical intervention (there is nothing in the briefing to suggest that it would work better).</p>

<sup>52</sup> The three year rule I have employed elsewhere has been extended to four years in this case. This is because the briefing has been written on what seems to be a well established technique in 2000. The briefing refers to a publication which is a 3 year follow up of TVT, published in late 1999 (Ulmsten, Johnson, & Rezapour 1999). A publication from 1995 on non-surgical therapy for stress incontinence did not include this new sling procedure (Bourcier & Juras 1995). Therefore, I choose the year 1996 for my time perspective.

<p><b>3. Market size</b></p>	<p>Around 4,000 ‘stand-alone’ colposuspensions are carried out each year, and it is thought that all women undergoing these procedures could be considered for TVT.</p> <p style="text-align: right;"><b>Market size (NHS England) per year: 4,000</b></p> <p>However, it is thought that if this procedure were to be taken up, then the threshold for patients being referred to surgical intervention may become lower as TVT offers a much less invasive option compared to current surgical intervention. The upper estimate of this population size is the following, as presented in the NHSC briefing:</p> <p style="text-align: right;"><b>Market size (NHS England) per year: 100,000</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>There are only a limited number of cost estimates in the literature for open Burch colposuspension (assumed to be the ‘gold standard’) predating 1996. One estimates that the procedure is associated with a direct cost to the health service (U.S.) of \$6,370 (Hannah &amp; Chin 1996), or £4,085<sup>53</sup>. They find that an average hospital stay of three days is required for this procedure.</p> <p>Another estimate is made by Kung and colleagues (Kung, Lie, Lee, &amp; Drutz 1996), who find that abdominal colposuspension costs Can\$5692.3 (1994 Canadian dollars), which is £2,852 in today’s (1996) prices (i).</p> <p>The NHSC briefing provides a couple of estimates for the cost of open colposuspension, one being £1,350 (what is included in the figure is not detailed) and the other being £2,500 (according to the ‘consulted expert’).</p> <p>Colposuspension is performed whilst the patient is under general anaesthesia and looks to involve an inpatient stay of about 3 days. This is in contrast to TVT, which is performed under local anaesthesia, takes about 30 minutes, and is performed as a day case (time in hospital should be limited to around 6 hours).</p> <p>With cost estimates of current practice ranging from £1,350 to £4,085, and with no access to the full reports and details of these figures, I will assume that a colposuspension costs the NHS about £2,700 – the average of these four estimates.</p>
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<sup>53</sup> This was converted using the average exchange rate across the 12 months of 1996 retrieved from (X-rates 2011), which was \$0.64132 to the £.

	<p>By switching from colposuspension to TVT, the majority of this cost should be avoided, as a large portion of it is made up by the hospital stay that is required following major surgery.</p> <p>Without having access to a comprehensive evaluation of the costs of colposuspension in order to help me isolate the costs associated with the various aspects of patient care, I will assume that the overall cost for the colposuspension procedure that is avoided is £2,700 (as described above), and this whole cost would be avoided with TVT. The total headroom must therefore include the cost of undertaking the TVT procedure as well as the device itself<sup>54</sup>.</p> <p>Of course, for those who would not have initially undergone surgery for UI, the redirected costs would be much smaller, and are likely to be surpassed by the cost of TVT. The QALY impact of undergoing TVT rather than more conservative treatments must make this monetary difference up. A trial which compared the costs and outcomes associated with inpatient and outpatient continence programmes for UI (bladder retraining and physiotherapy) found that the costs associated with the outpatient programme were much smaller (£66 per patient treated versus £126) and the outcomes just as good (Ramsay et al. 1996).</p> <p>Assuming that some of the patients who would otherwise undergo conservative management such as that described by Ramsay and colleagues now undergo TVT, we may assume that £66 could be saved per patient per year<sup>55</sup> (assuming that the health service employs this more efficient means of treating patients— in an outpatient setting).</p> <p style="text-align: right;"><b>1: TVT replaces colposuspension.</b> <b>Patients: 4,000</b></p> <p style="text-align: right;"><b>(Total) ΔSC= £10,800,000</b></p>
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<sup>54</sup> I have been unable to isolate these procedural costs from the headroom estimate due to the lack of NHS reference costs or other UK cost information that I have been able to find from sources that were available in 1996.

<sup>55</sup> I choose a one year time frame for this scenario, as it may be that a patient's symptoms would have progressed such that surgery would have been considered in time: as I do not know the relevant time frame, I consider its value over a one year time period only.

<p><i>Describe any potential costs/savings that you haven't quantified.</i></p>	<p style="text-align: right;"><b>(Av. Per person) ΔSC= £2,700</b></p> <p style="text-align: center;"><b>2: Patients who would otherwise be treated by conservative means may now be treated surgically with TVT. Patients: 96,000</b></p> <p style="text-align: right;"><b>(Total) ΔSC= £6,336,000</b> <b>(Av. Per person) ΔSC= £66</b></p> <p><i>The above figures must include the procedural cost implications of TV, including staff time, equipment, etc. The training of staff to use this technique must also be considered.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>In the case of application 1, we assume that TVT simply replaces all current colposuspension procedures, with the same effectiveness. For this, I assume that the QALYs implicated are the same<sup>56</sup>.</p> <p>For those who relied previously on conservative management alone, but who would benefit from surgery with TVT, there is likely to be a QoL implication. The assumption here is that previously symptoms would have needed to be strong before surgery was considered. With TVT, the (milder) UI symptoms of the 96,000 who could now be treated with TVT, could be alleviated.</p> <p>In the absence of any QoL assessments in the literature of this or comparable ailments, I estimate the impact of urinary incontinence by manipulating what may be the relevant EQ-5D parameters and estimating their value using the study presented by Williams (Williams 1995). Of the five health parameters in the EQ-5D questionnaire<sup>57</sup>, those that seem to be the most pertinent for urinary incontinence are probably 'usual activities' 'pain/discomfort' and 'anxiety/depression'. Assuming that in all other ways the patient is in full health, the range of utility values that one could attribute to urinary incontinence ranges from 0.883</p>
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<sup>56</sup> Although recovery time is likely to be much shorter for TVT versus open colposuspension (and thus have a positive impact on QALYs), to estimate this may be impractical, especially given my lack of understanding of the recovery prospects for patients having undergone TVT. The developer is likely to have had a better idea of this, even at this very early stage. However, this is probably not crucial at this stage, given the fact that the case for development is likely to be an obvious one, given the cost saving potential of the procedure alone.

<sup>57</sup> Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression. Note- manipulation of these parameters is speculative.

	<p>to 0.689, assuming that any problems in these areas are moderate rather than severe<sup>58</sup> (ii). By simply adding the value of a shift change from level two to level one in the three potentially relevant health categories, this would lead to an impact of 0.23 on the QoL scale. Therefore, I will assume that TVT for patients who would have previously been managed conservatively would lead to an incremental QALY of 0.2 per year. This means that if the patient is otherwise in full health, urinary incontinence might be associated with a QoL weighting of 0.8. This, however, assumes that patients gain no useful control of their symptoms after being treated by conservative therapy. Although the NHC brief indicates that those extra 96,000 patients who could now be treated with TVT are those who do not respond to conservative therapy, I will also test the headroom result for a more modest gain of 0.1 per year, to account for where conservative management leads to some symptom improvements (but only half of what could be achieved by undergoing TVT), or accounting for a more modest baseline level of health.</p> <p>TVT is intended as a permanent treatment for UI. However, without knowing the clinical pathway and progression of those that would before have been treated conservatively (e.g. average age of the patient, percentage recovery rate of those treated conservatively, or proportion of those patients who would develop further symptoms and subsequently be referred to colposuspension), I will take just a one year timeframe.</p> <p style="text-align: right;"><b>1: TVT replaces colposuspension.</b> <b>Patients: 4,000</b></p> <p style="text-align: right;"><b>ΔQALY= -</b> <b>(Av. per person) ΔQALY= -</b></p> <p style="text-align: right;"><b>2(a): Patients who would otherwise be treated by conservative means may now be treated surgically with TVT. Patients: 96,000</b></p>
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<sup>58</sup> If patients had symptoms within the 'severe' category for any of these QoL parameters, the patient would probably have been within the group of 4,000 patients already being treated with surgical colposuspension.

<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p style="text-align: right;"><b><math>\Delta</math>QALY= 19,200<sup>59</sup></b> <b>(Av. per person) <math>\Delta</math>QALY= 0.2</b></p> <p style="text-align: center;"><b>2(b): Patients who would otherwise be treated by conservative means may now be treated surgically with TVT. Conservative therapy improves UI symptoms but only half as much as TVT would.</b> <b>Patients: 96,000</b></p> <p style="text-align: right;"><b><math>\Delta</math>QALY= 9,600</b> <b>(Av. per person) <math>\Delta</math>QALY= 0.1</b></p> <p><i>Due to the invasive nature of the current gold standard, patients are likely to prefer TVT to colposuspension. Although this preference is difficult to capture in a QALY (and so has been ignored), it is likely to have an impact on the clinician's / patient's decision. Also, the recovery time is likely to be much shorter. On the other hand, for those who would otherwise have been treated conservatively TVT is unlikely to be pain-free, but the disutility associated with the procedure itself has been ignored by this analysis.</i></p> <p><i>Another potentially problematic assumption is that patients treated with TVT (who were previously managed conservatively) will resume a status of 'full health'. Given the likely age of the patients treated and other co-morbidities they might suffer from, this might not be appropriate.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p>	<ul style="list-style-type: none"> <li>[GREEN] In 1996 the Department of Health instigated and reported on a research project for the development of methodologies to identify urinary incontinence and set targets for health gain. Also in this year they published "Costs of incontinence to individuals and to services, and users' perceptions of quality and effectiveness of services. Second stage feasibility study". (Unfortunately neither report is electronically downloadable). This demonstrates current interest in improving outcomes for these patients (Department of Health 2011c).</li> </ul>
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<sup>59</sup> This is 96,000 \* 0.2 (as I treat the replacement of colposuspension with TVT as simply a cost-saving enterprise for those other 4,000 patients).

<p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• [AMBER] Other techniques are being investigated as alternatives to open Burch colposuspension. One such technique is a modification to the standard treatment: laparoscopic colposuspension, where the operation is performed through small keyhole cuts in the abdomen. One cost-effectiveness study finds laparoscopic Burch to be more cost-effective than open abdominal Burch, costing Can\$2,938 rather than Can\$5,692 (Kung, Lie, Lee, &amp; Drutz 1996). Developments in this area may shift the comparator for TVT to a procedure that is relatively less invasive than open Burch colposuspension.</li> <li>• [AMBER] There may be other relevant treatment comparators or competitors for TVT. The most directly relevant of these 'other options' identified in the literature seem to be those that are referred to as Sling procedures (Falconer, Ekman-Ordeberg, Malmström, &amp; Ulmsten 1996; Zaragoza 1996). Without knowing more about the technicalities of either TVT or these other sling procedures, I do not know how (or if) these will differ.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon?</p>	<ul style="list-style-type: none"> <li>• The analysis presented here assumes that TVT is equally as effective as our comparator, Burch colposuspension surgery. Is this appropriate? Might complications be reduced by TVT?</li> <li>• In order to keep the analysis relatively simple, and to take an optimistic view at this very early stage, the analysis assumes that where TVT is used to treat patients who would previously have undergone <i>conservative</i> management, success rate is 100%. Is this realistic, or should a down-weighting be applied to account for those patients who may not respond positively to the procedure?</li> <li>• Is a one year time frame for the QoL benefits associated with TVT as compared to the current clinical pathway for moderate UI patients appropriate?</li> <li>• To what extent is conservative management successful? The two estimates made in this analysis assume either a null (patients begin and end the year with a QoL weighting of 0.8 with conservative management) or modest success</li> </ul>
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	<p>rate (that conservative management would raise QoL by 0.1, half the change that could be achieved by TVT). The study I have found that estimates the success rate of conservative management is by Ramsay et al. who estimated that 63% of women were cured (or improved such that they required no further treatment) (Ramsay et al. 1996). This many indicate that this analysis has overestimated with incremental effect of TVT on patient QoL over conservative management techniques. This should be investigated in the light of continually evolving research.</p> <ul style="list-style-type: none"> <li>• Is 'full health' an appropriate baseline for QoL estimations?</li> <li>• To what extent would the less invasive nature of TVT provide an incentive to switch from colposuspension to TVT? By considering this change as cost-saving only (for those 4,000 who will currently be managed surgically), the value of TVT may be underestimated.</li> <li>• Is a potential patient population of 100,000 too optimistic?</li> <li>• The estimated QoL gain associated with switching from conservative treatment to TVT is very speculative. The literature should be monitored regularly for QALY estimates of UI treatment.</li> <li>• It was also difficult to obtain a reliable and consistent picture of costs for colposuspension. The literature should be monitored for more data as it becomes available, particularly any attempts to estimate this from a UK perspective. The DH project mentioned above may prove useful in this respect (Department of Health 2011c).</li> <li>• How does TVT differ from other sling procedures currently being investigated in the literature?</li> </ul>
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**Notes by AC on workings**

Information used is from the NHSC briefing notes unless otherwise stated

- (i) The cost of colposuspension according to Kung and colleagues (Kung, Lie, Lee, & Drutz 1996) needs inflating to 1996 prices as well as converting from Canadian dollars to pound sterling.  
The average exchange rate for the 12 months of 1994 was 0.4795 Can\$ to the £ (X-rates 2011).  
Can\$5692.3 (1994 Canadian dollars) was equal to £2,729 in 1994

This must be inflated to 1996 prices, which is done using the HCHS price inflator:



The earliest date I can find for the HCHS index is 1995/6. In order to try to estimate the inflation index between 1994 and 1996, and will use the inflation rate between 1995 and 1997 as a proxy:

HCHS P&P Index 1995/6: 166.0

HCHS P&P Index 1997/8: 173.5

Inflation rate: 1.045

Cost of abdominal colposuspension (1996): £2,729 \* 1.045 = £2,852

- (ii) By manipulating what seem to be the relevant health parameters within the EQ-5D framework, we get the following utility values:
- 11112: **0.848** 'Moderately anxious or depressed'
  - 11121: **0.796** 'Moderate pain or discomfort'
  - 11211: **0.883** 'Some problems performing usual activities'
  - 11212: **0.812** 'Some problems performing usual activities' 'Moderately anxious or depressed'
  - 11221: **0.760** 'Some problems performing usual activities' 'Moderate pain or discomfort'
  - 11122: **0.725** 'Moderate pain or discomfort' 'Moderately anxious or depressed'
  - 11222: **0.689** 'Some problems performing usual activities' 'Moderate pain or discomfort' 'Moderately anxious or depressed'

## Headroom Notes (TVT)

For TVT, two 'headroom' scenarios were presented. The first was for where TVT would directly replace colposuspension, the current gold standard. For this (which would be applicable for about 4,000 patients), the headroom was **£2,700**, which is simply the estimated cost of a colposuspension procedure.

For the other 96,000 of the potential 100,000 market in the UK, TVT would be replacing conservative management. To estimate the potential value of this to the health service, the cost of conservative management was added to the value of the estimated QALY gain. This would be **£4,066** if the NHS were willing to pay £20,000 per QALY and **£6,066** if the tariff were £30,000 per QALY<sup>60</sup>. However, this assumes that conservative management does not significantly improve UI symptoms. If we assume that conservative management does improve symptoms, but only half as much as TVT would, then the headroom changes to **£2,066 - £3,066**.

The headroom estimates must cover the cost to the health service of implementing the TVT procedure, and therefore should be considered as the headroom per procedure rather than per device per se (i.e. not an MRP). Thus, as well as the device itself, this must cover the cost to the

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<sup>60</sup> The fact that the headroom for treating those patients who currently do not undergo costly surgical procedures is larger than the headroom for those that do does not seem completely logical. The reason for this result is that I have assumed a substantial QALY gain for these patients. I have also presented the headroom for a more modest QALY gain.

health service of staff time, hospital stay (about 6 hours), other equipment or local anaesthesia costs, as well as staff training etc.

Extrapolation into development decision analysis was not undertaken due to the inability to identify the potential health service procedural costs, and therefore lack of MRP.

The analysis has been presented in two parts, according to style of current management, but of course these would not be considered by the company in isolation. For example, it is unlikely to be the case that TVT be directed only to those 96,000 patients for whom the procedure may be relevant, but who do not currently undergo colposuspension. Therefore, these figures should be considered side-by-side and not as absolute values; price discrimination for TVT according to the patient and their current treatment alternative is unfeasible.

## Follow-up (TVT)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The headroom analysis seems to present a favourable opportunity for TVT. Having considered the cost of colposuspension, as well as the potential for increased QoL for those who would previously have received conservative management, the minimum headroom estimated was £2,066, but reached £2,700 for those who would currently undergo colposuspension treatment, and just over £6000 under very favourable assumptions of QoL gain for those who are currently managed by conservative treatment. This was to cover all of the hospital costs for the procedure as well as any device used that is supplied by Ethicon for the TVT procedure. Given the high estimated cost of colposuspension, the much shorter hospital stay that would probably result from TVT, and what is likely to be a relatively simple piece of kit, the economic case for TVT at this the development stage seems to be a relatively straightforward one. Cost estimates of the procedure in the literature from a UK NHS perspective include estimates of £1,058 (Kilonzo et al. 2004; Manca, Sculpher, Ward, & Hilton 2003), £1,114 (Cody et al. 2003), £1,135 (Imamura et al. 2010), and £2,044 (Jacklin, Duckett, & Renganathan 2010). These mainly fall below even the minimum headroom figure, indicating that the headroom would have presented adequate room for development.

Thinking about the problem on a more primitive level, comparing TVT directly to colposuspension and noting the shorter hospital stay and less invasive nature of the procedure, the saving in health service cost would seem very likely to outweigh the cost to the company of producing the tape and application device required to apply TVT (especially if it can be performed as a day case, as indicated in the NHSC briefing).

Interpretive answer: **Headroom appears adequate to support a development decision.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

In February 2003 NICE produced a technology appraisal for TVT for use in women with stress incontinence. This was replaced in October 2006 by a clinical guideline on the management of urinary incontinence in women, CG40 (NICE 2006a). In this guideline, retropubic mid-urethral tape

procedures using a 'bottom-up' approach with macroporous polypropylene meshes (i.e.TVT) are recommended for the treatment of UI where conservative management has failed. Open colposuspension, and autologous rectus fascial sling are the recommended *alternatives* 'when clinically appropriate' (NICE 2006a). This indicates that TVT has replaced colposuspension as the gold standard method of surgical intervention. Sacral nerve stimulation is recommended for UI due to detrusor over activity (again, where conservative management has failed). Also recommended within this guideline (to be considered after traditional TVT due to less outcome data) are synthetic slings with a retropubic 'top-down' or transobturator foramen approach. Ethicon produces TVT-Obturator (TVT-O) which matches this description.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

TVT was launched by Ethicon in 1999, and was one of the first minimally-invasive surgical treatments for stress UI (Ethicon 2010a). In England, uptake has been fast. In 1997/8, 8,000 surgical operations were undertaken for stress UI over a 12 month period. Annual surgical interventions increased by 16% for 2004-2005, despite a 90% fall in the number of colposuspensions and needle suspensions and a 50% reduction in bladder neck buttress, sling and periurethral injections (NICE 2006a). This difference has been made up by the rapid introduction of TVT, and other similar tape procedures. This has also led to a decrease in hospital bed days for UI surgery, falling from over 5 days in 1998/9 to under 3 days in 2004/5.

HES data (hospital episode statistics for the NHS) for the year 2010-11 shows that TVT was carried out on the NHS for 6,451 patients (HES 2012). This shows that surgical intervention for stress UI has risen (TVT is just one of the options), but not to the extent of what was considered possible in the NHSC briefing and headroom analysis, which was 100,000 relevant patients.

From the Ethicon website, it is clear that the company have since expanded their portfolio of products in this area, with five variations of the TVT. The 'gold standard' retropubic TVT system is the product that was first introduced and to which most clinical data seem to relate. The product(s) are said to be used worldwide, in treating over one million women for stress UI (Ethicon 2010b).

#### **Have there been investigations into its clinical / cost effectiveness?**

There has been much investigation in the literature on the clinical and cost-effectiveness of TVT.

As indicated by NICE's positive recommendation decision, the clinical data indicates that TVT is a safe and effective way to treat women with stress UI. The study with the longest follow-up period (11 years) shows that TVT is safe and effective, with 77% being (subjectively) 'cured', 20% improved, and 3% that were failures (Nilsson, Palva, Rezapour, & Falconer 2008). In the studies reviewed by NICE that went into the decision to recommend TVT over colposuspension, TVT tended to perform in a similar way or slightly better than colposuspension, but TVT procedures consumed fewer hospital resources (hospital stay, duration of catheterisation and operating time) and were associated with a faster recovery (NICE 2006a). The model presented by the systematic review and HTA that NICE used for its technology appraisal projected the cost and QALY implications of TVT and colposuspension over 10 years after surgery, and showed the QALY implication to be very similar, but that TVT was a cost saver (Cody et al. 2003). This supports the perspective taken by the headroom analysis for these

patients (the 4,000 who would otherwise undergo colposuspension). Given the paucity of data available in 1996, the exact cost of colposuspension to the NHS was difficult to find; the £2,700 estimate that was used seems to overestimate its actual cost, which is about half this amount. The average cost of colposuspension among the UK studies that I have found since is about £1,340. However, this is not likely to have had an impact on the economic case for TVT, as the potential saving in healthcare resources was clear. Having said this, the proposal made in the NHSC briefing that TVT might require an average LOS of 6 hours seems overly optimistic; Manca and colleagues (Manca, Sculpher, Ward, & Hilton 2003) find an average LOS for TVT of 2.29 days, versus colposuspension which involved an average LOS of 6.67 days (study published in 2003).

The mean length of stay presented in the HES data from 2010-11 for TVT was 1.4 days (median: 1 day) (HES 2012). About a third of all cases (2,125 out of 6,451) were treated as a day case. This shows that as time has gone the procedure has become much faster.

Manca and colleagues (Manca, Sculpher, Ward, & Hilton 2003) find that there is a mean cost saving of £243 with TVT as compared to colposuspension, that the QALY differential between the two procedures is 0.01, and that TVT had a 95% chance of being more cost-effective than colposuspension (at a WTP of £30,000). Kilonzo et al. (Kilonzo et al. 2004), Wu et al. (Wu, Visco, Weidner, & Myers 2007), and Valpas. et al (Valpas, Rissanen, Kujansuu, & Nilsson 2006) all conclude that TVT is more cost-effective than colposuspension (though the comparison for Valpas is laparoscopic colposuspension rather than open).

The more difficult of the perspectives taken in the headroom analysis was that of the patients who were currently managed conservatively. The data for TVT procedures shows that the 100,000 estimate for potential patient population is, at the moment, a huge overestimation, though TVT does seem to have lowered the threshold for surgical intervention (with 4,000 patients undergoing the 'gold standard' colposuspension back then and 6,500 now undergoing TVT, notwithstanding the other types of surgical intervention that are currently also undertaken). For this, what were regarded as the relevant EQ-5D parameters were manipulated and an impact of 0.2 was estimated for the cure of stress UI (an impact of 0.1 to the QoL weighting was also considered). Research in the literature into the patients' QoL before and after treatment for stress UI indicates that this presumption of a return to 'full health' in all of these parameters was overoptimistic. Whilst in other headroom analyses I have used QoL data for the UK population according to age as the baseline, this was more difficult in this case as I was trying to measure a *difference* rather than an absolute. The literature upholds the estimate made in the headroom analysis for the QoL value for women with incontinence: about 0.8. In the systematic review used by NICE to assess the cost-effectiveness of TVT, a value of 0.8 was used for incontinent women, and 0.85 for continent women (Cody et al. 2003). These figures are around the same ballpark as QALY numbers estimated by others, for example Kilonzo et al. (Kilonzo et al. 2004) who find a utility value of 0.82 with cure and 0.78 with incontinence, and Manca et al. who (using the EQ-5D questionnaire) find a EQ-5D value at baseline of 0.778 and 0.806 at 6 months after treatment. Tincello and colleagues (Tincello et al. 2010) describe the characteristics and comorbidities of stress UI patients, which may go some way to describing the baseline health state of these patients.

## Has the landscape described changed significantly?

### What is current gold standard clinical practice now? Has this changed?

The clinical landscape for stress UI has changed somewhat since 1996; open colposuspension is no longer the 'gold standard' treatment (though it remains an option). There has been no update to the NICE clinical guideline since it was published in 2006. NICE recommend that where conservative management does not offer the patient symptom control, a 'bottom-up' tape procedure (such as TVT) should be considered; open colposuspension and fascial sling procedures are recommended as alternatives where appropriate. Other forms of tape procedures (e.g. TVT-O) are also considered to be appropriate options. Laparoscopic colposuspension is not recommended by NICE.

Tape procedures such as TVT are also described as the first-line surgical option on the patient-facing website NHS Choices (NHS Choices 2010b).

### Are there now many direct competitors?

I have not seen the use of the term TVT in relation to any other medical companies. Without a better knowledge of the area, I am uncertain to what extent direct competition is a factor. When searching the NHS supply chain catalogue (NHS 2012) for TVT, only Johnson & Johnson products are brought up (Ethicon is a subsidiary of Johnson & Johnson). Ethicon seem to have developed (and continue to develop) many variations of the device, with minor changes / enhancements to its user control, mesh used, precision, allowing for a single incision, etc. There are now five products within Ethicon's TVT range, which reflects the company's work to stay dominant in the field (Ethicon 2010b).

## Conclusions: How useful might the headroom exercise have been?

For TVT, a range of headroom values were presented based on various assumptions made and populations described. For the simplest case, where TVT would simply replace the current gold-standard at the time (colposuspension) the headroom was relatively straightforward and was simply the cost of colposuspension surgery to the NHS. Although the relevant NHS costing estimates could not be disaggregated from this, the potential for the cost saving was clear, and given the relatively straightforward nature of the device itself, the case for development seemed to be a clear one. Indeed, the potential for cost saving has come to bear in reality, with TVT now having overtaken colposuspension as the first-line surgical treatment for stress UI.

In the headroom analysis, the more conceptually difficult population to consider were those not currently managed surgically. For these patients, QoL estimates had to be made (subjectively, given the lack of data in the literature). Although the estimate of the QoL weighting associated with stress UI turned out to be remarkably accurate, the return to 'baseline' was misjudged in the headroom analysis, and the incremental benefit created by TVT (or any 'cure') was overestimated (see above for discussion of this).

As the economic case for TVT was quite strong and, in the end, straightforward (in its cost saving potential alone), it is difficult to say whether the headroom approach would have contributed any novelty or extra information to the decision-making process. Many of the difficult or pertinent factors that were raised in the research questions were pertinent to this example upon follow-up.

## 19. Penile cuff test, CT3000. *MediPlus Ltd.*

<p><b>1. Description</b></p> <p><i>Diagnostic;</i></p> <p><i>'Another Option';</i></p> <p><i>No NICE follow-up</i></p> <p><i>Date of briefing: July 2005</i></p> <p><i>Time perspective of this report: 2002</i></p>	<p>Lower Urinary Tract Symptoms (LUTS) are a common problem for men; incidence increases with age. Symptoms include problems with both storing and voiding urine. The most common cause of LUTS is benign prostatic hyperplasia which, whilst not malignant, can cause significant morbidity. The decision to intervene medically or surgically is dependent on severity of symptoms and responsiveness to alternative means of management.</p> <p>The CT300 is a non-invasive pressure flow analysis for men, which indirectly measures intra-vesical pressure using controlled inflation of a flexible cuff which is placed around the penis during the voiding of urine, until the flow is interrupted. Cuff pressure at this point reflects bladder contraction pressure. The CT3000 is thus a diagnostic technique that could be used to screen men with lower urinary tract symptoms (LUTS) before more lengthy, invasive and expensive studies are undertaken. The results of the test can indicate suitability for prostatectomy.</p> <p>The CT300 system would consist of a PC, printer, customised trolley, flow meter, and the CT300 machine itself. A single disposable penile cuff would be required per test.</p>
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<p><b>2. Comparator</b></p>	<p>The current 'gold standard' diagnostic tests for obstruction of the bladder outlet are invasive urodynamic studies (sometimes called cystometry). These invasive and costly investigations involve urinary catheterisation and a rectal manometer.</p> <p>Currently, the best non-invasive method is peak urinary flow rates, but these cannot distinguish between obstruction and bladder muscle weakness (detrusor hypocontractility). It is thought that the presence of detrusor hypocontractility (rather than obstruction) is often a reason for prostatectomy failure, and thus part of the reason for poor success rates for prostatectomy.</p> <p>Other types of non-invasive test identified in the literature include:</p> <ul style="list-style-type: none"> <li>• Total prostate volume, or central zone prostatic volume (though the latter has been found by Corica et al. to be no more useful than the former (Corica et al. 1999)).</li> <li>• Imaging techniques. These are outlined by the American College of Radiology (Bluth et al. 2000). However, imaging does not play a major role in the current assessment of patients with LUTS (though it may play a larger role in the future) (Grossfeld &amp; Coakley 2000). Imaging is mainly used to exclude the presence of malignant prostate tumour (Aarnink &amp; Wijkstra 1999).</li> </ul> <p>The use of current testing methods (notably the two main ones: cystometry and peak flow rates) varies greatly according to location /</p>
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	<p>urologist. One study of men who underwent prostatectomy in four regions of England in the mid 1990s found that only 50% had their urinary flow rates measured (despite the fact that this is recommended) (Emberton et al. 1995), and a much smaller percentage undergo invasive testing. This variable (and often underused) screening approach is further exemplified by a survey of the management of patients presenting with bladder outflow obstruction conducted in Scotland in 1991 (Lloyd &amp; Kirk 1991). Of the 46 respondents to the postal questionnaire, 36 (78%) had access to a urine flow meter, and 32 (70%) had facilities for cystometry. Of those that did have access to a urine flow meter, 13 (36%) measured urine flow rates in all patients, and 14 (39%) said they did so frequently. Of those with the facilities required to undertake cystometry, all used it 'only occasionally' in men with suspected outflow obstruction (Lloyd &amp; Kirk 1991) (this was, however, 10 years ago).</p> <p>It is thought that around a third of men who currently undergo prostatectomy do not benefit from the procedure (Emberton et al. 1996). Bladder pressure flow analysis using the CT3000 is proposed to increase the overall success rate of prostatectomy by improving the targeting of prostatectomy, as compared with current diagnostic strategies (which sometimes involves neither flow rates nor invasive urodynamic studies).</p> <p>The reason that I have decided to call the CT3000 non-invasive bladder pressure test 'another option' in relation to current practice, it that the briefing is not absolutely clear how the CT3000 would replace or add to the diagnostic strategies that are used at the moment. The fact that the number of invasive tests performed by urologists could be reduced is mentioned, but it is not proposed to replace them entirely, and the device is also mentioned in its use as an addition to other non-invasive tests. Therefore, I assume that the CT3000 offers urologists another way in which bladder obstruction can be diagnosed (either with or instead of current bladder function tests), and that as a result the success rate of prostatectomy is increased from 70% (as is the case currently) to 90% (assumption provided by the NHSC briefing, presumably stipulated by the developer). With the current number of prostatectomy procedures being around 30,000 per year in England and Wales, this could lead to 6,667 procedures being prevented each year (assuming that the <i>number</i> of successful procedures remains constant)<sup>61</sup>.</p>
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<p><b>3. Market size</b></p>	<p>In England and Wales 30,000 prostatectomy procedures are currently undertaken each year. It could be assumed that this corresponds to the approximate number of patients eligible for the CT3000 penile cuff test, though without understanding how exactly the device would be incorporated into current practice, this may be difficult to approximate. However, if it is to be incorporated into the management of patients across the NHS, then we may assume that all (approx.) 550 urologists should purchase one system. As the main cost element of the CT3000</p>
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<sup>61</sup> This estimate was provided by the developer in the NHSC briefing.

	<p>would be the piece of equipment itself rather than the disposable 'cuff', it makes sense to consider the investment on a per unit rather than per patient basis.</p> <p style="text-align: right;"><b>Market size per year (NHS England &amp; Wales, number of units required to cover all relevant patients ): 550</b></p>
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<p><b>4. Health Service</b></p> <p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (<math>P_1</math>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>The main assumption for this headroom analysis is that 6,667 prostatectomy procedures could be avoided each year if the CT300 penile cuff test were available to urologists for the diagnosis of bladder obstruction (thus increasing the chance of a good outcome from prostatectomy). According to the Department of Health's NHS Reference costs for 2000-2001, a prostate transurethral resection procedure costs a mean of between £1,411 and £1,592 (according to recipient age and presence of complications or comorbidities) (Department of Health 2002). I will therefore assume that a prostatectomy costs the NHS about £1,500 per procedure.</p> <p>The CT3000 test requires around 15 minutes of preparation/operation time by a junior technician or health care assistant per test, costing the health service around £3.50<sup>62</sup>. It will require 5 minutes a day from a senior technician for calibration. Half a day of training would be required when the equipment is first introduced. As these service costs are all relatively small, and are very likely to be outweighed by disinvestment in other bladder function tests that would result from the introduction of the CT3000 (which are not being quantified here), I will ignore these costs. However, these should be considered in relation to the headroom that is identified; if the headroom is modest, then these may have an impact on a development decision.</p> <p style="text-align: right;"><b>(Total) ΔSC per year= £10,000,500</b> <b>(Av. Per unit) ΔSC per year= £18,183</b></p> <p style="text-align: right;"><math>P_1 = -</math> <b>(ignoring the potential for displaced cost of current tests)</b></p>
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<sup>62</sup> The first year for which Unit cost of health and social care data is freely available online is 2004 (PSSRU 2004) (the 2002 version is not accessible). Although out of the time scale of this analysis, I sought data for this in order to gain a general impression of scale, but will not include this in the headroom analysis.



<p>Describe any potential costs/savings that you haven't quantified.</p>	<p>As indicated, I am ignoring for the purposes of this headroom analysis any potential cost savings that the CT3000 could stimulate by allowing urologists to conduct fewer of the current tests. However, this could be especially important if invasive cystometry procedures were reduced; a urodynamic investigation costs the NHS an average of £114 (Department of Health 2002) .</p> <p>Considering the approach taken, a potential for reduced service costs that is also being ignored is that, by reducing the number of unsuccessful prostatectomy procedures, the treatment costs for complications of prostatectomy would also be reduced, including urinary tract infection. The costs involved in patient follow-up for all men who undergo the prostatectomy would also be reduced.</p> <p>As mentioned in the text above, service costs for the provision of the CT3000 test have been ignored.</p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p>	<p>A QoL study conducted on a subsample of those involved in the U.S. Health Professionals Follow-up Study (HPFS) investigated the QoL implications of LUTS according to severity of symptoms (Welch, Weinger, &amp; Barry 2002). The most important health parameters affected by LUTS were (in order of impact): a) the impact of a patient's physical condition on his ability to carry out work or other usual activities, b) vitality or energy level, c) being depressed or anxious, d) general health perceptions and e) physical functioning.</p> <p>By taking the approach outlined above, we are assuming that the CT3000 results in an improvement in the success rate of prostatectomy procedures; this means that the same number of successful surgeries are undertaken, but that there are fewer <i>unsuccessful</i> ones. Although overall the <i>long term</i> health of patients would be the same before and after the introduction of CT3000, the disutility associated with the procedure itself would be avoided for those 6,667 patients who no longer undergo it. Whilst an important consideration for patients and those that manage their care, this would be difficult to translate into QALYs.</p> <p>As the cost saving impact of CT3000 is likely to represent sufficient reimbursement opportunity in itself, I will not spend the time trying to quantify this benefit.</p>
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<p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p style="text-align: right;"><b>ΔQALY= -</b> <b>(Av. per person) ΔQALY= -</b></p> <p><i>While this benefit to patients is left unquantified in this analysis, this would be an important consideration for patients and the clinicians that manage them.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[AMBER]</b> One of the key advantages of the CT3000 would be its non-invasive nature, and its ability to identify bladder obstruction more accurately than other current non-invasive methods. Although not used systematically at the moment, other non-invasive tests for bladder function include imaging techniques (Bluth et al. 2000; Grossfeld &amp; Coakley 2000).</li> <li>• <b>[GREEN]</b> The literature indicates that bladder function testing before prostatectomy is not carried out enough (Emberton et al. 1995; Lloyd &amp; Kirk 1991). If it proves to be as effective as anticipated, an easy non-invasive method by which this can be done could instil more systematic testing of patients into current practice.</li> <li>• <b>[GREEN]</b> Although rare, prostatectomy procedures (as with any form of surgery) carry with them the risk of operative complications and death (Lertakyamanee et al. 2002). Reducing the number of surgeries and ensuring they are undertaken only on those who stand to benefit, is important.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported</p>	<ul style="list-style-type: none"> <li>• The sensitivity and specificity of the CT3000 penile cuff test has been assumed to be such that the success rate of prostatectomy procedures is improved from 70% to 90%. Does this seem feasible? The appropriateness of this assumption should be tested during clinical investigations, by comparing the test to current means of investigation.</li> </ul>
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<p>above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and 'developments' section)?</p>	<ul style="list-style-type: none"> <li>• The analysis is based principally on the proposition that a large number of patients do not benefit from prostatectomy. This, and the specific number that was estimated, should be investigated further and verified by other studies if possible.</li> <li>• Would 550 units be sufficient to cover all patients for whom the test would be indicated?</li> <li>• The cost saving that may arise from disinvestment in other tests has been ignored. How exactly would the CT3000 be used in relation to current methods: alongside? Instead of? Where the test would replace other methods, there could be a significant saving for the health service.</li> <li>• Currently, it is thought that 50% of patients that undergo prostatectomy do not even have their flow rates measured (Emberton et al. 1995). Given the relatively straightforward nature of peak flow tests, why is this the case? Might the uptake of the CT3000 bladder function test be affected in the same way?</li> <li>• Does the introduction of the penile cuff test require any infrastructure or equipment in place that is not provided by Mediplus? If so, how much would this cost?</li> </ul>
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### Headroom Notes (Penile cuff test, CT3000)

The approach taken to estimate the headroom for reimbursement for this bladder function test was to estimate the overall cost saving to the health service that could be achieved, and to divide this by the number of machines required to service all patients (thought to be 550). This seems intuitive, given that:

- a) From a development perspective, it makes more sense to estimate the reimbursement opportunity per unit rather than per patient tested.
- b) It is not absolutely clear at this stage how the test would be employed and for how many patients.
- c) The main cost element of the CT3000 would be the piece of equipment itself, rather than the consumables associated with its use.

The headroom identified was **£18,183** per unit per year. I was unable to translate this into a 'development decision' as I have no information regarding how long each device will last. If there were no yearly service or maintenance costs, this headroom should simply be multiplied by the number of years it is thought that the CT3000 could work.

The CT3000 test requires around 15 minutes of preparation/operation time by a junior technician or health care assistant per day, and 5 minutes a day from a senior technician for calibration. Half a day of training would be required when the device is first introduced into a practice. These costs, as well as the disposable costs of the penile cuff (one required per test) will need to be considered, and need to fit within this headroom.

## Follow-up (Penile cuff test, CT3000)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The headroom estimated per device per year was £18,183, based on the total reduction in prostatectomy procedures that could result from better targeting, divided by the number of units required to service all relevant patients. Left out of this estimation were the potential cost savings in other types of urodynamic tests that might ensue from the uptake of CT3000. In order to inspire a positive development decision, this £18,183 needed to at least cover the cost of consumables, the equipment required to use the test, and service costs involved in carrying out each test.

The NHSC briefing indicates that the cost of the CT3000 system is £11,000. Single use disposables cost £5.50 per test. I have found no estimation of the NHS service costs (in terms of staff time), for providing the test, but these are likely to be quite modest given its simplicity and speed of use. The total yearly consumables cost per device clearly depends on its throughput. If throughput were 30,000 / 550, then this would be about 55 tests per year, indicating a consumables cost to the NHS of around £300 per year (55\*£5.50). The NHSC briefing indicates that the whole CT300 system, which apparently consists of PC, printer, trolley, flow meter, and CT300 'back box', costs £11,000. A CEP report published in 2007 for the Mediplus CT3000 (CEP 2007a), provides an evidence review for the device. Whilst an economic evaluation is not presented, the authors indicate that: 'the additional cost of specialised equipment associated with introducing the cuff method is estimated to be £5,000'. With no indication of what this refers to (no other prices or costs are provided at all) and whether this is on top of the CT3000 system price indicated above, it is difficult to know whether this should also be covered by the headroom.

Even with the inclusion of a potential extra £5,000, the headroom of £18,183 is likely to cover all equipment and consumable costs that have been identified since the device has come onto market. This, and the fact that this headroom should actually be multiplied by the number of years of service each CT3000 could provide, seems to provide sufficient potential for reimbursement, and thus is likely to have indicated a positive development decision<sup>63</sup>.

**Headroom would probably have indicated a positive development decision.**

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<sup>63</sup> An analysis of the development decision in terms of overall costs and allowable development costs could not be conducted without information regarding the longevity of the device.

### **Has there been a decision made on it by NICE? What was the outcome?**

NICE have not issued any guidance on the CT3000 penile cuff test.

### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

The CTP3000 received a CE mark and was launched in the UK in 2005, as the first non-invasive method of measuring bladder pressure in men (Mediplus 2005). Mediplus Ltd is a privately owned manufacturer of medical devices, based in the UK, which specialises principally in urology products but also for urogynaecology, gynaecology, gastroenterology, anaesthetics, and general surgery (Mediplus 2012a). On their website, Mediplus indicate that the first centres using the CT3000 are located in: Newcastle-Upon-Tyne, London, Bristol, Exeter, Leeds, Norfolk, Spain, Switzerland, USA, and Canada (Mediplus 2012c). I have found no further evidence of how widespread the use of CT3000 is. The CEP report published in 2007 indicates that the Mediplus CT3000 system shows significant potential for use in outpatient urology clinics (CEP 2007a). The outline of diagnostic tests employed to diagnose prostate enlargement on NHS Choices does not mention non-invasive bladder pressure tests.

### **Have there been investigations into its clinical / cost effectiveness?**

The principal assumption used to inform the headroom analysis was that the CT3000 cuff test would improve the success rate of prostatectomy from 70% to 90%. A study reported by Harding et al. showed that, using the CT3000 to target prostatectomy, there was a surgical success rate of 87% (Harding et al. 2007). This indicates that the estimate used for the headroom analysis was appropriate (though CEP note that it remains to be seen whether these findings can translate to the population beyond that of that particular study).

I found no economic evaluation. The CEP report deemed there to be too many unknowns.

An early study of the cuff test found that the device, when combined with information provided by flow rate, can classify more than two thirds of patients without the need for invasive testing; the system identified obstruction with 68% positive predictive value and 75% negative predictive value (Griffiths et al. 2005). One study published in the Journal of Urology assessed the usability of the cuff test by testing the variability in interpreting the results between experienced and novice users of the test (McArdle et al. 2009). The authors find good concordance of results, and conclude that introducing the penile cuff test into the routine assessment of men with LUTS would be straightforward. A study of repeatability found that diagnostic category repeatability (using the test on the test on the same man with a month's interval) was similar to that of conventional urodynamics (Clarkson et al. 2008). Another study tested pressure flow measurements (using the cuff test) before and after the removal of the obstruction (prostatectomy) (Sajeel et al. 2007). The study found that the test was sensitive to change following the removal of the obstruction. CEP provides details of further clinical investigations.

The extent of possible reductions in other tests is still unclear (CEP 2007a). Mediplus indicate that the test is not to be used as a replacement of other urodynamic tests, but as an adjunct (Mediplus 2012b). This supports the decision to leave this potential for cost saving out of the headroom

Retrospective case studies: 19. Penile cuff test, CT3000

estimates. Also, when using CT3000 to make a referral for surgery, a high proportion (87%) of patients had a good outcome from the TURP procedure (3). This ability to predict surgical outcome is equivalent to that offered by invasive urodynamic studies, though it remains to be proven whether this finding can be generalised beyond the population of that particular study.

The degree of accuracy offered by the Mediplus CT3000 system, in two clinical trials (144 and 193 patients), is greater than the accuracy achieved by flow rate measurement and symptomatic assessment (see refs in CEP report).

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

The gold standard in urodynamic assessment for patients with LUTS seems to still be cystometry. Peak flow rate still seems to be an important tool for urologists. Whilst it is clear that the CT3000 has been picked up, it is difficult to know how wide spread its application has become. On their website, Mediplus emphasise that the CT3000 is to be used *alongside* standard flow study, and not as a replacement to conventional urodynamic investigation, which remains the 'gold standard'. The penile cuff test provides useful extra information for urologists.

#### **Are there now many direct competitors?**

I have come across no other version of the penile cuff test in my internet and literature searches.

### **Conclusions: How useful might the headroom exercise have been?**

The headroom analysis indicated adequate room for development of the CT3000 bladder function test. The value estimation was drawn from the assumption that the CT3000 could improve the success rate of prostatectomy by more accurately targeting the procedure. Whilst some studies indicate that the system does indeed have the potential to improve the success rate of surgery, this remains to be tested on a large scale. There are no published economic evaluations for the product in order to test the assumptions made, but the system does seem to provide good value, and this is indicated by its uptake so far.

## 20. PFO Closure. *NMT Medical / St Jude Medical*

<p><b>1. Description</b></p> <p><i>Device;</i></p> <p><i>New indication;</i></p> <p><i>NICE IPG for follow-up</i></p> <p><i>Date of briefing: January 2006</i></p> <p><i>Time perspective of this report: 2005<sup>64</sup></i></p>	<p>Migraine is a common headache disorder, which is neurobiological in origin and manifests as recurrent attacks lasting anywhere between four and seventy-two hours. Migraine episodes are associated with headache pain and are sometimes accompanied by nausea, vomiting, and sensitivity to light or sound. The World Health Organisation estimate that migraine is 19<sup>th</sup> among the causes of years lived with disability (WHO 2004); social and work capacity can be significantly reduced.</p> <p>About 15% of people who have migraine have migraine with aura, which represents about 500,000 to 750,000 people in England and Wales. Those who have migraine with aura additionally experience visual (light flashes, clouded vision, etc) or other neurological disturbances (pins and needles, hearing, vertigo, sensitivity to touch, etc).</p> <p>A patent foramen ovale (PFO) is the presence of a hole in the wall between the two upper chambers of the heart. In the womb, a baby will have a small opening between the left and right atria (which allows blood to bypass the lungs); this hole should close by itself soon after the baby is born. PFO is present when this hole does not close fully and remains patent throughout a person's life. As many as one in four people have PFO, but for most this causes no complications.</p> <p>Although PFO is a well-established risk factor for ischaemic stroke (Del Sette et al. 1998), there is said to be an increased prevalence of PFO among those with migraine (especially with aura). Although a causal link has yet to be proven, various studies show there to be a relationship here. In one study, it was found that 47% of those with migraine with aura had PFO, and just 17% of the control subjects (Schwerzmann et al. 2005). Another study found that 41% of patients who had migraine with aura had PFO versus 16% of the controls (Del Sette et al. 1998). Yet another study that investigates this relationship is presented by Anzola et al. (Anzola et al. 1999), who found that PFO was present in 48% of patients with migraine w/aura, 23% of patients who had migraine without aura, and 20% in the age-matched non-migraine controls. We can deduce from these studies that people who have migraine with aura seem to be about two to three times more likely to have PFO than the general population.</p> <p>The patent foramen ovale (PFO) closure procedure is suggested for people who suffer from refractory migraine with aura, i.e. for those who do not respond to conservative treatment. This procedure is already established as a treatment option for patients with stroke or transient</p>
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<sup>64</sup> I have back-dated the perspective of this analysis from the publication of the NHSC briefing by just one year. The reason for this is that for this particular case, the device that is being proposed for this indication already exists and is used to treat patients but for a different clinical problem. Therefore, the question becomes whether this particular indication is worth pursuing not in terms of developing a device from scratch, but for investing in the research required to prove its worth clinically, and marketing the device toward this particular group of patients and their clinicians.

	<p>ischaemic attacks, and aims to prevent recurrent events. 379 PFO closure procedures took place in Britain in 2004.</p> <p>Percutaneous PFO closure involves placing an umbrella-like closure device to seal the PFO. <i>NMT Medical</i> (STARFlex septal repair implant) and <i>St Jude Medical</i> (Premere PFO closure device) have PFO closure devices that are already CE marked. NICE issued an interventional procedures guidance for PFO closure in the prevention of cerebral embolic stroke in January 2005 (NICE 2005a). NICE find that there are no major safety concerns and that the procedure is efficacious in achieving closure of the foramen. However, they are unable to confirm (due to insufficient evidence) that PFO closure prevents future strokes.</p> <p>PFO closure is suggested as a treatment option for patients whose symptoms do not respond to current medical management. It is thought that this could reduce the frequency and impact of migraine attacks.</p>
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<p><b>2. Comparator</b></p>	<p>There is no absolute cure for people who have a tendency to experience migraines. However, lifestyle modification and the use of medicines can reduce their frequency / impact. Pharmacological therapy includes that which is intended to alleviate symptoms (analgesics, anti-emetics, 5-HT<sub>1</sub> etc), and those that are designed to prevent future attacks (pizotifen, beta-blockers, sodium valproate, amitriptylline, topiramate, etc). Relaxation therapy and acupuncture are also considered beneficial.</p> <p>There are no other treatment options for migraine with aura patients who do not respond to any of these treatments.</p>
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<p><b>3. Market size</b></p>	<p>PFO closure would be indicated for refractory migraine with aura patients, whose symptoms are relatively severe. It is thought that 500-750,000 people have migraine with aura in England and Wales. Of these, at least 10-15% (50-75,000) have weekly attacks. The NHSC briefing indicates that this might represent the relevant patient population. However, it is difficult to know whether all of these patients would be relevant for PFO closure, given the uncertainty surrounding how many of these patients actually have PFO (under half of migraine with aura patients have PFO), and how many might respond adequately to current symptom-alleviating medication. Given the uncertainty in the number of relevant patients, as well as the presence of many existing competitors, I will consider this problem on a per unit basis rather than extrapolating any calculations by considering the likely number of procedures. Also, this parameter would be less crucial than it would be in a 'to develop or not to develop' decision (the PFO closure devices already exist).</p> <p style="text-align: right;"><b>Market size per year: -</b></p>
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<p><b>4. Health Service</b></p>	<p>Over 10 years ago, it was estimated that migraines cost the NHS about £23 million ([No authors listed])</p>
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<p>Changes in resource use. Any changes in service delivery costs to the NHS that will result from the application of the new technology, including the disinvestment in previous practice. This could include: Staff time, hospital bed days, GP visits, A&amp;E visits, etc. It should not include services for which the NHS (and personal social services) is not financially liable (e.g. lost productivity and [non-health] social care costs), but these should be noted in writing below to add to the verbal case for the product (NICE may incorporate social care costs into cost-effectiveness estimates in the near future).</p> <p>If relevant and not included in service cost impact above, search for price of the currently used product (P<sub>1</sub>).</p> <p>Use HCHS index to inflate estimates to current prices</p>	<p>1992) (probably worth nearly £40 million after inflating to today's prices).</p> <p>I have identified two economic evaluations conducted from the perspective of the NHS for migraines: one that investigates the cost-effectiveness of acupuncture (Vickers et al. 2004; Wonderling, Vickers, Grieve, &amp; McCarney 2004) and another that compares the cost-effectiveness of various management strategies for the acute treatment of migraine (Sculpher, Millson, Meddis, &amp; Poole 2002).</p> <p>Although the HTA on acupuncture is very comprehensive and offers a breakdown of NHS as well as personal costs of migraine, the patient population under investigation is that of 'chronic headache', which included tension-type headache, and the costs associated with medicines were not clear.</p> <p>The study comparing management strategies looks at the direct healthcare costs of the acute treatment of migraine using three approaches: stratified, and two stepped care approaches (across attacks and within attacks). Costs are provided in relation to total health service costs over six attacks, including rescue medications and adverse events (which included GP, A&amp;E or consultant neurologist costs where relevant). The highest cost strategy was stratified care, which was £28.25 for six attacks. I will use this, the highest estimate of migraine cost (as those serious migraines with aura patients who would be considered for PFO closure are likely to be the most costly patients). Assuming weekly attacks, this equates to a yearly cost of £245.</p> <p>Missing from the estimate above is the cost of preventative medicine that may be prescribed to patients. According to UK clinical guidelines, preventative treatment for migraines should be considered where migraine attacks cause significant disability, are regular (more than two or three per month), or where there is over-use of current medication (Prodigy 2005b). The severity of migraine patients that are likely to be indicated for PFO closure would fulfil these criteria. The guidelines recommend that first-line preventative treatment should be beta-blockers such as propranolol, metoprolol, timolol and atenolol (Prodigy 2005b). Information on the cost of these drugs in the UK has</p>
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	<p>been difficult to obtain. One appraisal of migraine drugs in the U.S. presented the wholesale cost for one month of preventative medicine according to type (Adelman et al. 1998). The average monthly cost of the four beta-blockers recommended by the PRODIGY guidelines was \$24.60- about £15. This equates to a yearly cost of about £180.</p> <p>However, the difficulty is knowing whether and to what extent the medicines for acute headache symptoms would be prescribed alongside these preventative drugs. Although it may be the case that both are used in some instances, I will simply take the medication cost associated with those severely affected by migraine with aura, which is £245 per year.</p> <p>It is thought that PFO closure could reduce the frequency and impact of migraines. Without having been given an estimate of the extent of this reduction, I will apply the assumption that the positive impact on migraines reduction will reduce health service costs by half each year: <b>£123</b>.</p> <p>In the NHSC briefing, it is proposed that implantation of the STARFlex by NMT Medical would use similar facilities and take a similar amount of time as an angiography; it would require access to echocardiography, (light) general anaesthetic, and could involve a hospital bed stay. NHS reference costs for 2003-2004 indicate that HRG Code E14 [Cardiac Catheterisation and Angiography without complications] has a national average unit cost of £1,221 (Department of Health 2005). The NHS reference cost database indicates that angiography is associated with a length of stay of two days. In order to approximate the procedural service costs associated with PFO closure, I will use the cost of angiography (£1,221) minus one day's worth of hospital costs, as according to the briefing it is likely to involve just one overnight hospital stay. The cost of an excess bed day for angiography is £255 (Department of Health 2005). The resultant service cost of providing the PFO closure would be approximately <b>£966</b>. This would be a one off cost.</p> <p>The net impact of PFO closure on service costs would depend on the time scale chosen; whilst the procedural costs associated with its closure would be</p>
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<p>Describe any potential costs/savings that you haven't quantified.</p>	<p>a one-off investment, the potential cost savings from reduced drug costs should last for the remainder of a patient's lifetime. In order to demonstrate the impact of the timescale taken, I will present the results according to a time horizon of: one year, five years, ten years and twenty years (see note (i) for workings).</p> <p style="text-align: right;"><b>TIME HORIZON: 1 Year</b> <b>(Av. Per person) ΔSC= £843</b></p> <p style="text-align: right;"><b>TIME HORIZON: 5 Years</b> <b>(Av. Per person) ΔSC= £391</b></p> <p style="text-align: right;"><b>TIME HORIZON: 10 Years</b> <b>(Av. Per person) ΔSC= -£93 (saving)</b></p> <p style="text-align: right;"><b>TIME HORIZON: 20 Years</b> <b>(Av. Per person) ΔSC= -£843 (saving)</b></p> <p><i>A major issue for sufferers of migraine is the impact of migraine episodes on productivity (ability to go to work and effectiveness whilst at work), and the knock-on effect this has on the economy. Some estimates value these productivity losses at around ten times that incurred by the NHS to treat migraines ([No authors listed] 1992). One study of the direct and indirect costs of migraine found that in the UK, the average total cost per migraine patient per year was €543; just €12 was accounted for by direct medical costs, and the remaining €520 by indirect costs (€156 for work absence and €375 for reduced productivity at work)(Berg &amp; Stovner 2005). Whilst not within the remit of an economic evaluation conducted from a health service perspective, this strong association with loss in productivity is likely to favour any treatment that can help those whose symptoms are not adequately controlled by current care options.</i></p> <p><i>One potential service cost that has not been considered is the investigation and clinical decision-making that would be involved pre- procedure, to decide whether the patient is suitable for PFO closure. This should be considered if it is thought that this may be significant.</i></p>
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<p><b>5. Patients</b></p> <p>Potential impact of the new device on</p>	<p>Migraine significantly affects a person's QoL and ability to work, as well as having a big impact on social and family life (Silberstein 2004). A means of</p>
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<p>patient health, as compared to current practice (preferred method of elicitation is from studies using the EQ-5D). Where NICE have not produced relevant economic analyses, search for cost-effectiveness studies or systematic reviews within the disease area (the CEA registry offers a useful platform to identify these studies).</p> <p><i>Describe any impact on patient health that you haven't quantified.</i></p>	<p>reducing the impact of migraines for those who suffer from them severely and who currently are not well managed by medicines and alternative therapies could have a significant positive impact on the HRQoL of those patients for the better.</p> <p>To estimate the QoL impact of a reduction in frequency and severity of migraines with no data on which to base these estimates would be highly speculative, given the uncertainty surrounding the current level of QoL of those patients, and how PFO closure might impact this.</p> <p>The HTA undertaken from an NHS perspective on acupuncture for migraine estimated the QALY impact of acupuncture on patients with chronic headache (Vickers et al. 2004; Wonderling, Vickers, Grieve, &amp; McCarney 2004). The patient characteristics are presented, which show that about 95% of participants were sufferers of migraine (Wonderling, Vickers, Grieve, &amp; McCarney 2004). The QALY impact of acupuncture on patients was found to be 0.021 over a 12 month time period (from 0.708 to 0.727). Given the paucity of information in the literature, I will use this QALY difference of 0.021 per year as an estimate of the impact that PFO closure might have on patient QoL. It should be noted though that this may well be an underestimate, considering the fact that those severe sufferers of migraine with aura that may be referred for PFO closure may well stand more to gain from symptom relief. Again, I will present this potential QALY impact over one, five, ten and twenty years (see note (ii) for calculations).</p> <p style="text-align: right;"><b>TIME HORIZON: 1 Year</b> <b>(Av. per person) ΔQALY= 0.021</b></p> <p style="text-align: right;"><b>TIME HORIZON: 5 Years</b> <b>(Av. per person) ΔQALY= 0.0981</b></p> <p style="text-align: right;"><b>TIME HORIZON: 10 Years</b> <b>(Av. per person) ΔQALY= 0.1808</b></p> <p style="text-align: right;"><b>TIME HORIZON: 20 Years</b> <b>(Av. per person) ΔQALY= 0.3089</b></p> <p><i>As mentioned previously, migraine has a big impact on a person's productivity, both inside and outside of the workplace. As well as the huge impact this can</i></p>
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	<p><i>have on the economy and a person's own finances, it can also interfere a great deal with non-work activities. More so than in many clinical areas, costs are often borne by patients. This is so much the case that some studies consider it more appropriate to value medicines by the willingness to pay of the patient rather than the health service. One particular study by Hamelsky and colleagues tries to assess the burden of migraine using a WTP model for migraine treatment (Hamelsky, Lipton, &amp; Stewart 2005). This highlights the fact that an economic evaluation undertaken from a health care perspective is likely to underestimate the true societal value of a treatment for migraine.</i></p>
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<p><b>6. Developments (clinical &amp; healthcare context)</b></p> <p>Consider the following questions to help you think about the space for your product within the market.</p> <p>Does the technology address any key national objectives for improving care in this area?</p> <p>How will the technology complement current practice? Is current practice likely to change?</p> <p>Are there any indications in the literature of potential effectiveness?</p> <p>Have you identified any direct competitors? (This could be another specific technology, or simply a different technique)</p> <p><b>RED:</b> Poses a significant threat to the opportunity identified in the market (i.e. works against current health service objectives, or there are other products being developed that are associated with better outcomes or are at a more advanced stage of development).</p> <p><b>AMBER:</b> Potential threat</p> <p><b>GREEN:</b> Further supports the case for the new technology</p>	<ul style="list-style-type: none"> <li>• <b>[GREEN]</b> A review of the available evidence by NICE has shown that PFO closure devices are successful in closing the PFO, and seem to be safe (NICE 2005a).</li> <li>• <b>[AMBER]</b> The literature has indicated that there is a true association between PFO and migraine (Anzola et al. 1999;Del Sette et al. 1998;Schwartzmann et al. 2005). <b>[RED]</b> However, whether there is an actual cause/effect relationship has yet to be proven. <b>[AMBER]</b> This will be crucial in predicting the effectiveness of PFO closure for migraine. This may be of some concern given the fact that in their interventional procedures guidance (NICE 2005a), NICE indicated that the evidence was not sufficient to say with certainty that PFO closure reduces the risk of stroke, even though intuitively the association between PFO and stroke would seem more logical than PFO and migraine.</li> <li>• <b>[AMBER]</b> Diffusion could be limited by the available number of neurologists and interventional cardiologists that would be required to screen patients with migraine for PFO, and for the suitability of PFO closure.</li> <li>• <b>[RED]</b> Presence of PFO is not information that is routinely collected. In order to integrate PFO closure into clinical practice for refractory migraine with aura patients, investigative screening would need to be incorporated into the clinical pathway for these patients. This may</li> </ul>
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	<p>substantially increase costs.</p> <ul style="list-style-type: none"> <li>• [RED] There are likely to be many competitors, as the intervention is already established.</li> <li>• [GREEN] Many economic evaluations in the area of migraine and headache include an estimation of productivity loss, which usually far outweighs any outlay by the NHS. The importance of patient-incurred costs in this area means that any treatments that can reduce this impact would be regarded favourably.</li> </ul>
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<p><b>7. Research questions</b></p> <p>This should be a list of the things that the developer needs to find out or monitor during the process of development, relating to the function of the device or how it fits into the market place.</p> <p>From the research undertaken and reported above, what are the most important questions or uncertainties that must be addressed / tested? What factors or assumptions have the calculations / economic or clinical case hinged upon? What potential benefits or threats have you ignored in the calculation (see italicised points in Qs 4&amp;5, and ‘developments’ section)?</p>	<ul style="list-style-type: none"> <li>• The most crucial assumption that has been made is that there is a cause effect relationship between PFO and migraine. Above all else, this direct causal link will need to be proven.</li> <li>• Selection is likely to be important. How will this be done? Would there be any extra service costs involved in this?</li> <li>• The potential market size should be investigated in more detail, as well as an investigation into the acceptability of the procedure for patients who suffer from migraine with aura.</li> <li>• To what extent will patients who have undergone the procedure still rely on medication for symptom relief? Is it appropriate to assume these costs will be halved, or does this over/underestimate its potential?</li> <li>• No cost analysis was found in the literature relating specifically to patients who suffer from migraine with aura. Is this significant, and has this resulted in the saved costs of patient management being underestimated?</li> <li>• Was it appropriate to assume similar costs as angiography? Were there any potential costs incurred that were missed?</li> <li>• Although the service costs used for the management of acute symptoms included the GP, A&amp;E and consultant costs that result from adverse events, does this cover any changes that might result from the decrease in general access to health services, such as routine appointments with a GP/clinic?</li> </ul>
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## Notes by AC

- (i) Discounting cost savings.  
 One-off procedural cost of PFO closure: £966  
 Yearly savings in healthcare resources (mainly medication): £123

In the first year, the net impact of PFO closure on costs to the NHS would be:  
 £966 - £123 = **£843**

Any costs incurred or saved in the future must be discounted in order to account for the time value of money. The rate that is used by NICE for this is 3.5%

### Time Horizon: 5 years

$$\Delta SC = £123 + \frac{£123}{1.035} + \frac{£123}{(1.035)^2} + \frac{£123}{(1.035)^3} + \frac{£123}{(1.035)^4} = £574.79$$

$$£966 - £575 = \mathbf{£391}$$

### Time horizon: 10 years

$$\Delta SC = £123 + \frac{£123}{1.035} + \frac{£123}{(1.035)^2} + \frac{£123}{(1.035)^3} + \frac{£123}{(1.035)^4} + \frac{£123}{(1.035)^5} + \frac{£123}{(1.035)^6} + \frac{£123}{(1.035)^7} + \frac{£123}{(1.035)^8} + \frac{£123}{(1.035)^9} = £1058.75$$

$$£966 - £1,059 = - \mathbf{£93 \text{ (saving)}}$$

### Time horizon: 20 years

$$\Delta SC = £123 + \frac{£123}{1.035} + \frac{£123}{(1.035)^2} + \frac{£123}{(1.035)^3} + \frac{£123}{(1.035)^4} + \frac{£123}{(1.035)^5} + \frac{£123}{(1.035)^6} + \frac{£123}{(1.035)^7} + \frac{£123}{(1.035)^8} + \frac{£123}{(1.035)^9} + \frac{£123}{(1.035)^{10}} + \frac{£123}{(1.035)^{11}} + \frac{£123}{(1.035)^{12}} + \frac{£123}{(1.035)^{13}} + \frac{£123}{(1.035)^{14}} + \frac{£123}{(1.035)^{15}} + \frac{£123}{(1.035)^{16}} + \frac{£123}{(1.035)^{17}} + \frac{£123}{(1.035)^{18}} + \frac{£123}{(1.035)^{19}} = £1809.31$$

$$= £966 - £1809 = - \mathbf{£843 \text{ (saving)}}$$

It can be observed that by applying the discount rate to calculate the value of savings a long way into the future has a big effect on the present value of those savings. Had we not applied a discount rate to the savings in medication costs, the net service cost impact for 20 years would have been calculated at (£966 – (20\*123)) = - £1,494 (saving).

- (ii) Discounting QALY benefit.  
 As well as costs, QALY benefit accrued in the future must also be discounted at a rate of 3.5%

### Time Horizon: 5 years

$$\Delta QALY = 0.021 + \frac{0.021}{1.035} + \frac{0.021}{(1.035)^2} + \frac{0.021}{(1.035)^3} + \frac{0.021}{(1.035)^4} = 0.0981 \text{ QALYs}$$

**Time horizon: 10 years**

$$\Delta QALY = 0.021 + \frac{0.021}{1.035} + \frac{0.021}{(1.035)^2} + \frac{0.021}{(1.035)^3} + \frac{0.021}{(1.035)^4} + \frac{0.021}{(1.035)^5} + \frac{0.021}{(1.035)^6} + \frac{0.021}{(1.035)^7} + \frac{0.021}{(1.035)^8} + \frac{0.021}{(1.035)^9} = 0.1808 \text{ QALYs}$$

**Time horizon: 20 years**

$$\Delta QALY = 0.021 + \frac{0.021}{1.035} + \frac{0.021}{(1.035)^2} + \frac{0.021}{(1.035)^3} + \frac{0.021}{(1.035)^4} + \frac{0.021}{(1.035)^5} + \frac{0.021}{(1.035)^6} + \frac{0.021}{(1.035)^7} + \frac{0.021}{(1.035)^8} + \frac{0.021}{(1.035)^9} + \frac{0.021}{(1.035)^{10}} + \frac{0.021}{(1.035)^{11}} + \frac{0.021}{(1.035)^{12}} + \frac{0.021}{(1.035)^{13}} + \frac{0.021}{(1.035)^{14}} + \frac{0.021}{(1.035)^{15}} + \frac{0.021}{(1.035)^{16}} + \frac{0.021}{(1.035)^{17}} + \frac{0.021}{(1.035)^{18}} + \frac{0.021}{(1.035)^{19}} = 0.3089 \text{ QALYs}$$

### Headroom Notes (PFO Closure)

In order to calculate the headroom for PFO closure, the main assumptions were:

- Half of current medication costs could be saved
- The procedural costs involved would be similar to that of a coronary angiography (minus one hospital bed day)
- The QALY benefit would be similar to that of acupuncture, giving rise to an extra 0.021 QALYs per year.

Under these assumptions, the maximum reimbursable price was calculated according to various time horizons:

	MRP	
	WTP: £20,000	WTP: £30,000
Time Horizon: 1 year	-£423	-£213
Time Horizon: 5 years	£1,571	£2,552
Time Horizon: 10 years	£3,709	£5,517
Time Horizon: 20 years	£7,021	£10,110

We can see from the above MRP figures that in the first year, the NHS would not be willing to spend any money on the PFO closure device; in fact, it would have to be *given* £213-£423 to even consider undertaking it. This means that the initial investment required to undertake the procedure more than outweighs the combined value of health benefit and saved medication costs that are seen in the first year. Considering a time horizon of 5 years renders a positive willingness to pay for the device, of £1,571 to £2,552. A time horizon of 10 years leads to an MRP of £3,709 to £5,517 and of 20 years: £7,021 to £10,110.

Clearly, the time perspective the health service is willing to adopt is very important here. The research questions should also be considered, including the appropriateness of assumptions made. One area of particular concern is the screening/ decision-making process, which has not been



considered in the health economic analysis. If deemed appropriate, this means that any investigational time / processes must be considered within the headroom calculated.

## Follow-up (PFO Closure)

### Headroom Outcome and Market success

#### **Does the MRP look realistic? Would it have indicated yes or no to development?**

The question relating to the feasibility of these devices must be posed slightly differently than it has done for previous examples. The headroom analysis would be used in this instance to indicate the potential value of PFO closure devices for this particular market. Although the calculation of headroom is exactly the same as it has been for other examples (except that we know that the device *does* work in closing the PFO), the way in which the resulting headroom and MRP should be considered is different. The devices for PFO closure (we have considered two specific ones here) have already been developed, and implanted into people with PFO – mainly in people at risk of stroke or TIA. By considering the value of the procedure for use in people who have refractory migraine with aura, the question becomes whether enough value could be generated to support the actual price of the device. This would inform the decision of whether to pursue this market (considering the costs involved in undertaking clinical trials, marketing, etc.).

The magnitude of costs that would have to fit into the estimated headroom would be much more tangible than if this were a development decision. At the time of analysis, the device would already have had a price, making the comparison between that price and the estimated headroom much more straightforward to conceptualise. The NHSC briefing indicated that the STARFlex (NMT Medical) and Premere (St Jude Medical) devices cost just over £4,000 (£3,500 + VAT). This did not include procedural costs (which is why procedural costs were incorporated into the headroom analysis).

Depending on the time horizon taken, the MRP of the PFO closure devices varied greatly. The relatively high procedural costs were incurred in year 1, whereas the health gain and treatment savings accumulated over time. In year one, PFO closure would be associated with a net health economic loss (WTP per QALY by the NHS would have to have been over £40,000 before you would see a net gain in year one). The MRP associated with a 5 year perspective for service costs and health gain would be £1,571 to £2,552; £3,709 to £5,517 for 10 years; and £7,021 to £10,110 for 20 years. This means that given the actual price of the PFO closure devices, a time horizon of at least 10 years would be required in order for the procedure to be reimbursable.

However, one important caveat is the question of how patients are identified and screened for the procedure. This was not mentioned in the NHSC briefing, but there is likely to be significant investment required for PFO investigation and organisational change required to incorporate this into routine clinical practice. Depending on how much this would cost the NHS, it is likely that an even longer time perspective would be required for the procedure to be cost-effective (i.e. over ten years). Unfortunately, I have identified no economic evaluations for the procedure that I can compare this with.

The favourability of headroom would depend on the time horizon that the reimbureser was willing to consider, and the magnitude of investment required for the developer to carry out clinical trials. The time perspective would need to be at least 10 years (which sounds feasible, given the effects of the procedure should last for the remaining life expectancy of the patient; the mean age of one migraine study that I considered was around 46 (Wonderling, Vickers, Grieve, & McCarney 2004)). However, this is without considering the investment required on the part of the NHS for screening, which may increase the cost per patient considerably. This is difficult to quantify, without understanding the scale of this upfront cost given the uncertainty of market size. Tentatively: if 50,000 people have migraine with aura symptoms that may warrant such invasive treatment (as suggested in the NHSC briefing), these patients would all need to be investigated for PFO, even though it is likely that under half will actually have PFO. NICE IPG guidance indicates that echocardiography is used to confirm PFO closure after a closure device is inserted (NICE 2010d); it may therefore be reasonable to assume that this type of investigation would also be used to diagnose PFO in the first place. According to a costing report by NICE (NICE 2011b), Echocardiography has a unit cost of £86. If this is used to investigate all 50,000 patients (total cost: £4,300,000), and around half of these go on to undertake the procedure as PFO was identified (Schwerzmann et al. 2005), then this would add £172 per patient treated. Whilst this seems reasonably modest, the structures that must be put in place to incorporate this front-line investigation into clinical practice may be significant and costly, and this large up-front cost may pose a barrier to uptake. This, in addition to the uncertain health benefit even if PFO closure did work (without consideration of which the procedure would *certainly* be extremely un cost-effective), presents significant potential barriers to the health economic case for PFO closure devices.

Although these barriers have been identified, I cannot say for sure whether the company would have perceived this assessment to be prohibitive. It should be noted, however, that even if the procedure works as well as hoped, its health economic case for uptake may be marginal.

**Headroom development decision result: uncertain.**

#### **Has there been a decision made on it by NICE? What was the outcome?**

NICE have issued guidance on the use of PFO closure for various indications: for the prevention of recurrent paradoxical embolism (NICE 2005a) in 2005, and now also for recurrent migraine (NICE 2010d) and for the prevention of recurrent paradoxical embolism in divers (NICE 2012), both issued in December 2010. NICE have indicated that the current evidence on the efficacy of PFO closure for recurrent migraine is not adequate, neither in quantity nor quality. Evidence of safety has shown a small incidence of serious adverse events, including device prolapse and embolism. NICE recommend that the procedure should only be undertaken with special arrangements for clinical governance, consent, and audit/research. Guidance for its use in divers is similar.

#### **Is it sold in the UK or the rest of the world?(Or has it in the past) If so, who is it bought by?**

The STARFlex device, produced by NMT Medical, was the first to be tested in a large RCT for PFO closure in Migraine patients (the MIST- Migraine Intervention with STARFlex technology- trial). The results were not favourable, and there was a lot of controversy surrounding their presentation

(allegations of bias and non-disclosure of important information, see section below). The company went into liquidation in 2011 (NMT Medical 2011;Wood 2011).

St Jude Medical, a medical technology company specialising in cardiac, neurological and chronic pain products, had at the time of the headroom analysis a device called Premere PFO Closure System. This product is still advertised on their website (St.Jude Medical 2012b). The information relating to the Premere device relates only to its design and use, rather than what/who it is used for. The website indicates that the product is available for use in select international markets, but not in the U.S. The company have another product for PFO closure—AMPLATZER PFO Occluder— for which there is more information (St.Jude Medical 2012a); it is assumed that this is the updated version of their previous model (though the device also seems to be associated with a company called AGA Medical Corp). The device is also said to be available to use in select international markets, but upon examination of its instructions for use, the device is intended for the closure of PFO in patients with a history of stroke or TIA. Migraine is not mentioned. The ESCAPE Migraine trial for the Premere PFO closure device, which started recruitment in 2005 and was due to complete in 2012 was terminated due to insufficient enrolment (ClinicalTrials.gov 2012).

#### **Have there been investigations into its clinical / cost effectiveness?**

The primary question for the whole headroom analysis was whether or not a causal link could be found between PFO and migraine / migraine with aura. Although the increased prevalence of PFO among migraine sufferers has been confirmed, the presence of a direct relationship between these and the proposed benefit of a PFO closure intervention are still controversial and unconfirmed, despite the intense investigation in the area (Sharma, Gheewala, & Silver 2011).

Clinical results seem to vary greatly from trial to trial. This is exemplified by two studies, one of which is a systematic review that concludes that patients who have migraine with aura are likely to represent a subset of patients in whom PFO closure has no impact (as opposed to other migraine patients who may benefit) (Butera et al. 2010), whereas another study finds that, after PFO closure, migraineurs with aura are 4.5 times more likely to experience migraine relief than those who had migraine without aura (despite residual shunt) (Jesurum et al. 2008).

The only RCT that has been completed for PFO closure in migraine patients is the MIST (Migraine Intervention With STARFlex Technology) trial, which randomly assigned patients who had migraine with aura to PFO closure, or a sham procedure (Dowson et al. 2008). The results of the trial indicated there to be no significant effect of PFO closure on migraine cessation or frequency/severity of migraine attacks. The results and how they have been presented by Dowson and colleagues (Dowson et al. 2008) have caused much controversy. One paper published later in 2008 discusses the allegations of misrepresentation of the effectiveness data (Tobis 2008). Tobis suggests that UK and U.S. governmental agencies should hold the company responsible for the publication of all data, and for providing an independent review of the data. Dr.Wilmshurst, the Co-PI of the MIST study and a cardiologist from Royal Shrewsbury hospital (a centre participating in the trial) alleged that NMT were withholding critical information that had been agreed in the trial design, and failing to disclose unfavourable data. For example, two patients with very unfavourable results were labelled as

'outliers' and omitted from the analysis with no real justification (Wood 2007). He also claimed that 30-40% of patients assigned to the intervention had large residual shunts (holes) following the procedure (Tobis 2008). NMT Medical subsequently denied that Wilmshurst was ever co-PI, threatened him with legal action for discussing the results of the trial with the press, and was dropped from the trial for 'committing protocol violations' (Wood 2007). In April 2011, after three and a half years of NMT Medical attempting to bring an expensive libel suit against Wilmshurst in the UK high court, the company went into liquidation (Boseley 2011;NMT Medical 2011;Wood 2011).

As mentioned above, the ESCAPE trial for St. Jude Medical's PFO closure device was terminated, many years into the study, due to insufficient enrolment, and information regarding the devices relate only to their use for stroke and TIA patients.

The fact that the MIST trial represents the only RCT in this area is indicative of the uncertainty around the procedure, as well as the relative difficulty in undertaking this sort of trial (which involves half of all the recruited patients having to undergo sham surgery). In their interventional procedure overview of PFO closure for recurrent migraine, NICE evaluate the current evidence for the procedure. The mixed results that are reported in the other studies (non-randomized comparative studies, comparative case series, studies of registry databases, and case reports of safety) do not provide sufficient evidence to support the efficacy of PFO closure for migraine patients, despite the fact that some non-randomised studies look favourable (NICE 2010d).

I found no health economic studies for PFO closure.

### **Has the landscape described changed significantly?**

#### **What is current gold standard clinical practice now? Has this changed?**

Given the lack of conclusive data for PFO closure, the intervention has not been recommended for the treatment of patients who have refractory migraine with aura. No interventional procedures are mentioned on patient-facing websites for migraine sufferers.

#### **Are there now many direct competitors?**

As indicated in the headroom analysis, various developers have produced PFO closure devices. Direct competitors include AGA Medical Corporation, Gore Medical and Applied Biometrics.

### **Conclusions: How useful might the headroom exercise have been?**

For this example, in which the health economic case for PFO closure was investigated in relation to Migraine with aura, the headroom that was calculated would not have been used to inform a development decision per se, but to support the decision of whether to pursue this market, and invest in clinical trials etc. The results of the headroom analysis indicated that the time perspective required to be taken by the reimbursers would need to be at least 10 years, but probably more considering the likely investment required to screen patients, that had not been incorporated into the analysis. Whether the results of the headroom analysis would have indicated a favourable decision to pursue this market or not is difficult to say, but the case for investment is certainly not an obvious one. Headroom calculations are based on a scenario in which the device *works as intended*.

The economic analysis brought up some interesting questions (and highlighted the importance of the timeframe considered). Unfortunately these could not be tested, as the clinical effectiveness of the procedure has not been proven, which is clearly a prerequisite for any reimbursement considerations! No health economic studies were found relating to PFO closure for migraine patients.

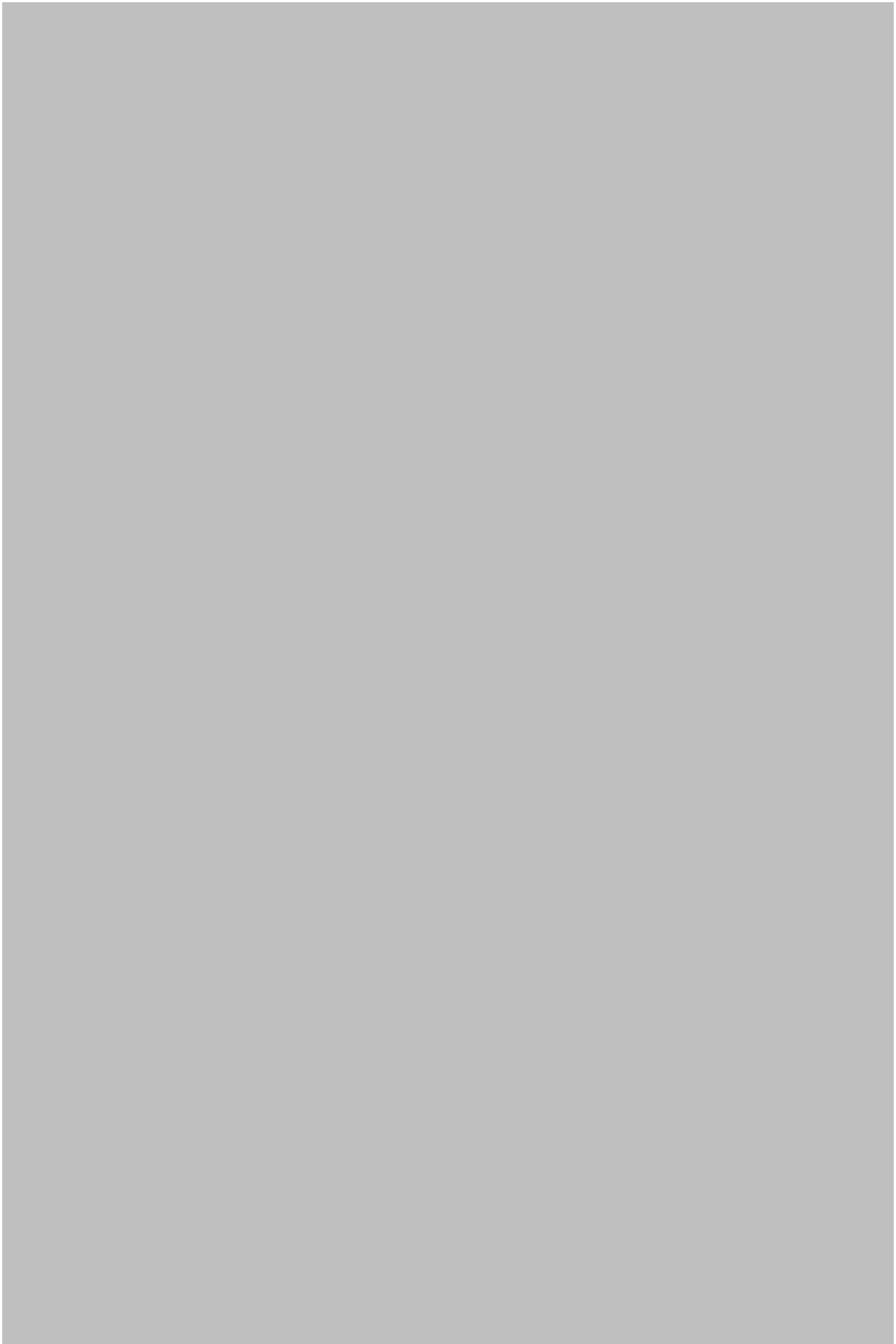
The literature has shown that the clinical efficacy of PFO closure for migraine has not been proven. During the headroom analysis, the question of efficacy and the causal link between PFO and migraine was highlighted as the crucial factor, and the non-recommendation of PFO closure for stroke patients offered a potential warning sign.

There may well have been some elements of the decision to pursue this market that would not have been addressed by the headroom analysis, such as strategic consideration relating to, for example, the free-riding of research (though in this case it may well have been that research by others worsened the prospects for other companies).

The headroom analysis (which in this case would principally have been used to explore the worth of investing in clinical trials) was uncertain, but this turned out not to matter as it was the clinical effectiveness that was its downfall. NMT performed an RCT which did not produce favourable results; the company has since gone bust. St. Jude Medical have a larger portfolio of products, so this was likely to have been less critical for them. They started a trial which was subsequently terminated due to insufficient enrolment (probably a results of other trials, as its status was only modified in 2011, and in 2008 the trial was still 'ongoing' (Wood 2008)).

The main research question identified was whether PFO closure would work in reducing the burden of migraine. This, as with any headroom analysis, of course turned out to be pertinent. The other questions related to the adequacy and appropriateness of the assumptions that were made. Unfortunately, these cannot be tested. Although the health economic case was uncertain, and the product is not currently widely used for migraine patients, these are not specifically related.

## Ethical Approval



## Appendix 8: Participant Information Sheet and Consent Form

**Project Title:** The Headroom Method of early economic evaluation of medical devices

Dear Participant,

You are being asked to take part in some interview research, the aim of which is to compliment and further explore the usefulness of the Headroom Method of early economic evaluation of medical devices. The Headroom Method is intended to aid early decision making in the development of new devices, by exploring the potential health economic value of a new product. The main aim of the study is to apply the method to specific medical devices. These interviews are being undertaken in order to gain a deeper insight into the aptness and feasibility of applying the method, by discussing the process with its intended user: the developer. The study has received ethical approval from the University's Science, Technology, Engineering and Mathematics Ethical Review Committee.

### What will be involved in the interview?

After having discussed with you some of the theory behind the headroom method and talked through some worked examples, you will be asked a series of general questions which will relate to the method itself and its application (rather than any specific medical device). The interview will last no longer than 20-30 minutes, and will be tape recorded.

### How will the interview be used?

Where relevant, your anonymity will be conserved in the recording of findings within the research project (in which case, you will be referred to by job title e.g. clinician, medical device company, etc).

Your participation is voluntary and you have the right to withdraw at any time, in which case any data collected will be destroyed, and will not be used in the project.

### Where can I get more information?

If at any time you have questions about the study or about how the information / views you provide will be used, then please contact the primary researcher (Amanda Chapman) at any time. Details of the lead project supervisor are also provided below, whom you may also contact.

[Redacted contact information]

## The Headroom Method of early economic evaluation of medical devices

### *Consent for participation in Interview Research*

**Name of Researcher: Amanda Chapman, PhD Student, University of Birmingham**

1. I confirm that I have discussed what will be involved in the interview and read the participant information sheet. I understand the intent and purpose of the research.
2. I am happy with how the information discussed will be used and presented as part of an academic piece of work (to be published within the researcher's thesis). Where relevant, this will include anonymity of views offered. I have had the opportunity to discuss any questions I might have and these have been answered to my satisfaction.
3. I have the right to request to be shown the format in which the research will be presented.
4. I understand that my interview will be audio recorded, and that this recording will be stored securely.
5. I understand that my participation is voluntary, and I have the right to decline to answer any question or terminate the interview at any time (without having to offer an explanation). I also have the right to withdraw from the study at any time during or after the interview, in which case my data will not be used.

I have read and understood the explanation provided to me, and I consent to participate in today's interview.

Name of Participant

Date

Signature

.....

.....

.....

Name of Researcher

Date

Signature

.....

.....

.....



## Appendix 9: Semi-structured Interviews: Question Topics

### What you do at the moment

- What are the main drivers in your decision to develop (/advise clients to develop) a new medical device? What gets you excited about a new idea?
- To what extent and at what stage do you formally consider the value that the product could provide for the NHS?
- To what extent were you familiar with health economics before? Did you / how did you explore the reimbursement prospects?

### Thoughts on the headroom method

- As an approach, do you *understand* the headroom method?
- Do you agree with its suggested application (e.g. early)?
- Does it involve an oversimplification of the situation (clinical or reimbursement)?
- I've shown you that I've put together a guide to go about identifying headroom. Do you think you could apply the method yourself / incorporate it into your approach?
- What would the barriers be?

### The headroom method in practice



- Is the output useful? (MRP).. i.e. can costs be conceptualized at such an early stage?
- Is it very different to the sorts of things you think about already? (Did you learn anything new?)
- Do you think it is a good use of time?
- Would you let the results influence your perception of viability of the product?
- What has been left out? Do you think there are more important factors that should prevail at an early stage?
- Scope: is it too UK focused? To what extent is your market focus a global one?
- Who do you think this would be most useful for?

Any other comments, or concerns about the headroom method, how it might be used, difficulties that may arise?

## Appendix 10: Presentation slides for interview sessions

The **Headroom Method** of early economic evaluation for medical devices

*A tool for early investment decisions*



### The Headroom Method...

- **What is it?** A simple health economic decision making tool, to identify the innovations that have the potential to represent *value* for the end buyer, and so a *good investment* for you
- **When should it be applied?** At 'concept' stage of a new device. i.e. Before decision to develop
- **Why is it valuable?** To avoid wasting resources on devices that will never be cost-effective

### Early Expectations / Lack of data

- At this stage, what we DON'T have is:
  - Probability data
  - Comprehensive idea of spectrum of outcomes
  - Sensitivity analysis
  - Exact costs of production
- What we DO have is an idea of what we hope the device will achieve for patients and for the health service.



- Will the NHS buy it?
- What will they pay for it?

### Why is early economic evaluation important?

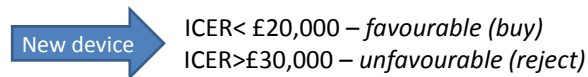
- To check the **commercial viability** of a new technology
- To **avoid wasting resources** on devices that will never be cost effective and so never make it to market
- To be a '**predictor**' of later coverage decisions
  - Decision-makers use 'economic evaluation' to determine whether a new healthcare product represents *value* to the NHS, by comparing it to current practice in terms of:
    - Impact on healthcare resources ( $\Delta$ cost) and...
    - Impact on patient health ( $\Delta$  effectiveness)
  - *The **Headroom Method** is a way to incorporate this demand-side reimbursement process (decision to buy) into supply-side investment decisions (decision to develop).*

### How do we do this?

- A manipulation of the 'ICER' equation

$$\text{ICER} = \frac{\Delta \text{Cost}}{\Delta \text{QALY}}$$

- NICE 'threshold' ICER: £20,000 - £30,000



- Therefore...  $\text{Max WTP} = £20,000 = \frac{\Delta \text{Cost}}{\Delta \text{QALY}}$
- **Max  $\Delta \text{Cost} = £20,000 \times \Delta \text{QALY}$**

*Headroom: An estimate of the maximum additional cost (to the health service) over the comparator, at which the technology is considered cost-effective*

$$\text{Max } \Delta \text{Cost} = £20,000 \times \Delta \text{QALY}$$

*Headroom: An estimate of the maximum additional cost (to the health service) over the comparator, at which the technology is considered cost-effective*

**The Decision:** Does the manufacturer deem it feasible to produce the new device at a price which will keep costs to the NHS within this threshold?

 **Develop**

 **Abandon**

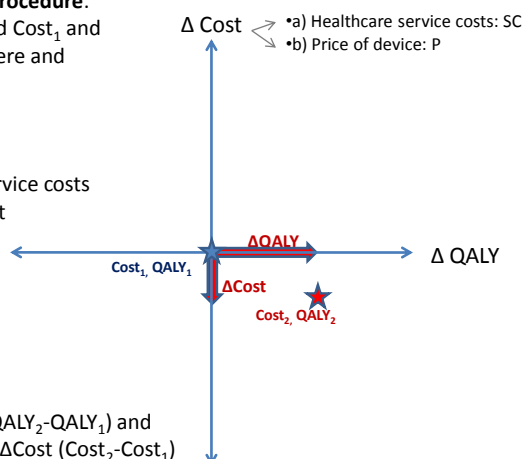
### The headroom method in graphs

- Isolating maximum reimbursable price (MRP): 'Commercial Headroom'
- Examples
  1. Device that saves service costs *and* improves health
  2. Device that costs more but improves health
  3. Device that reduces costs, with no impact on outcome

#### 1. Device that saves service costs *and* improves health

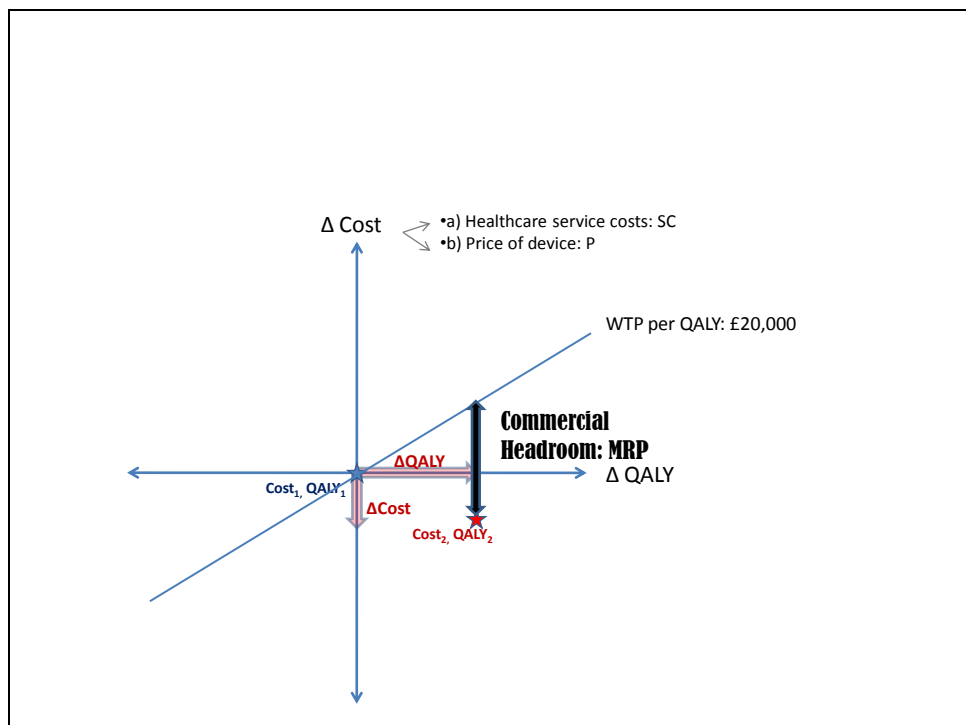
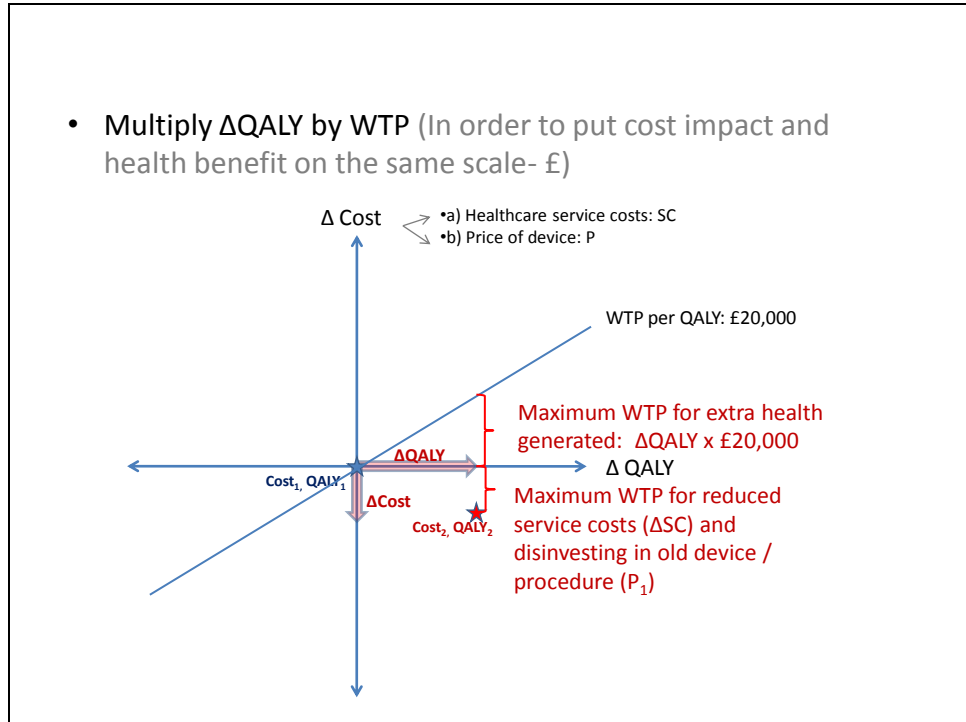
★ **Comparator device / procedure:**  
Has a known associated  $Cost_1$  and  $QALY_1$ , that places it here and becomes our 'baseline'

★ **New device:**  
No set  $P_2$  *But..*  
✓ Potential impact on service costs  
✓ Potential health benefit



We use these to plot...  
1. Impact on health  $\Delta QALY (QALY_2 - QALY_1)$  and  
2. Impact on cost to the NHS  $\Delta Cost (Cost_2 - Cost_1)$

- Multiply  $\Delta QALY$  by WTP (In order to put cost impact and health benefit on the same scale- £)



- Thus, the Headroom quantifies the maximum the NHS will pay for the new device ( $P_2$ ), i.e. The *value* it creates for the health service.

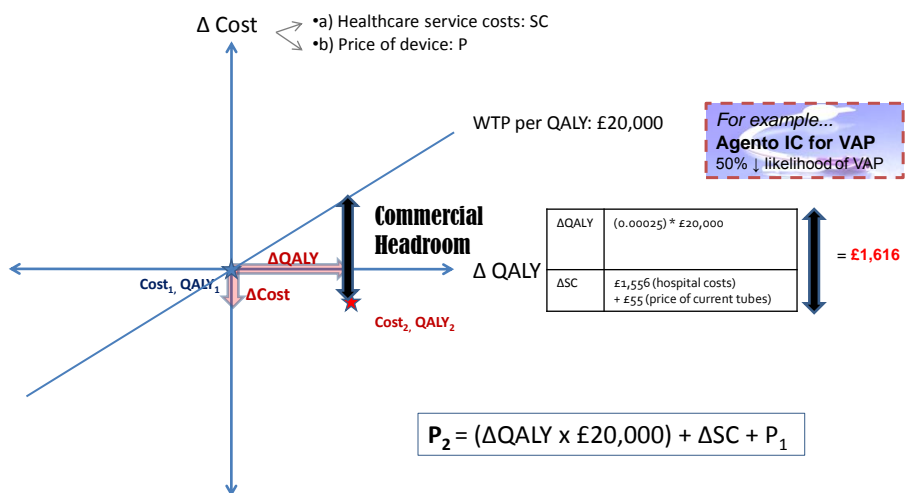
$$P_2 = (\Delta QALY \times \text{£}20,000) + \Delta SC + P_1$$

MRP  
'Commercial Headroom'

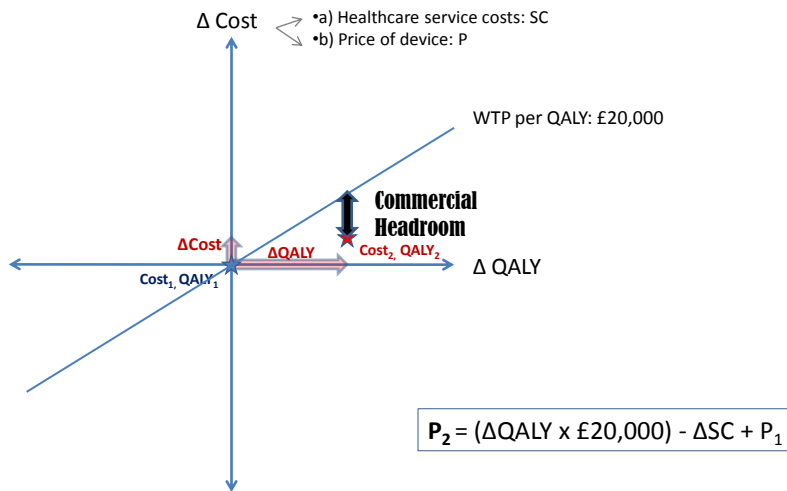
Cost saving for services  
 Adds to headroom, because represents a disinvestment

$\Delta Cost$

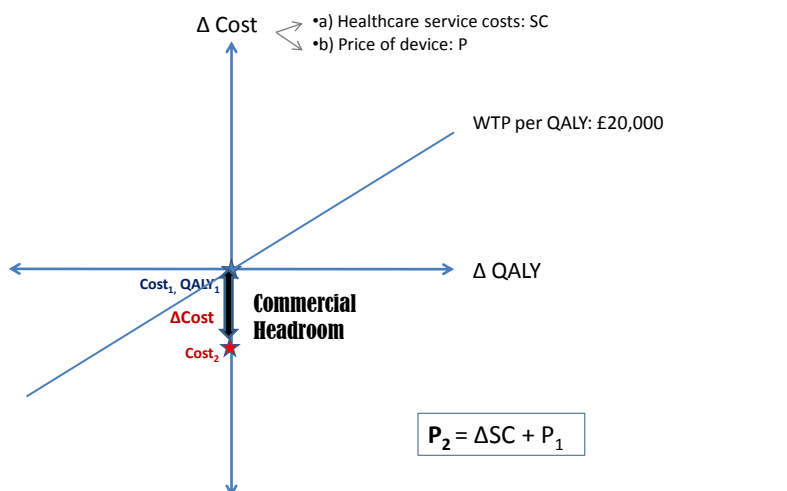
### 1. Device that saves service costs *and* improves health (summary)



## 2. Device that costs more but improves health



## 3. Device that reduces costs, with no impact on outcome





- Does the MRP represent a feasible price for your product, when considering the costs of production, profit, selling costs, and also the need to recover 'sunk' development costs?
- By asking this question early on, investment decisions can be as *informed* as possible at this early stage
- The headroom method offers a framework for assessing the commercial viability of a new device idea

### The Headroom Method Summary

An early warning signal for industry

Stops manufacturers wasting resources on devices that will never be cost effective so never make it to market

**DANGER**  
Maximum Headroom  
£ £ £

The Headroom method allows us to estimate the *height* of the future reimbursement opportunity...

## Appendix 11: Thematic analysis codes

The following table provides a summary and description of all codes used for the coding of data (interview scripts), organised into themes.

<b>GUIDING PRINCIPLES / MOTIVATION</b>	<b>BD</b>	<b>Burden of Disease</b>	<i>The importance of how many people the problem affects</i>
	<b>IDHS</b>	<b>Impact of disease on health service</b>	<i>Consideration of the impact on NHS services or service organization</i>
	<b>DCP</b>	<b>Deficiencies in current practice</b>	<i>What's wrong with how things work at the moment (thereby justifying the space for the new device)</i>
	<b>Costly</b>	<b>The clinical problem is costly to the health service</b>	<i>An account of how much the problem costs the health service</i>
	<b>IPC</b>	<b>A focus on improving patient care</b>	<i>An account of how patient care or the patient pathway could be improved</i>
	<b>SOP</b>	<b>Statement of own perspective</b>	<i>Bringing in own perspective, in terms of experience, outlook, past, etc.</i>
	<b>CV</b>	<b>Concept of value</b>	<i>An example of the interviewee's concept of value</i>
	<b>BIP</b>	<b>Belief in product</b>	<i>Demonstration of interviewee's belief in their own product</i>
	<b>BS</b>	<b>Business sense</b>	<i>Reference to business opportunity/profit</i>
	<b>CFC</b>	<b>Current feasibility check</b>	<i>Procedures or ways they make decisions at the moment</i>
	<b>IDM</b>	<b>Influencing Decision-Making</b>	<i>Ability to influence decisions</i>
	<b>FUNC</b>	<b>Function of Product</b>	<i>Focus on the product functionality</i>
<b>Headroom PRACTICALITIES</b>	<b>-UND</b>	<b>Understanding (negative)</b>	<i>Difficulty understanding method</i>
	<b>+UND</b>	<b>Understanding (positive)</b>	<i>Good understanding of method</i>
	<b>WF</b>	<b>Where do I find the figures?</b>	<i>Articulating difficulty or uncertainty surrounding the finding of figures to furnish headroom assumptions/calculations</i>
	<b>HA</b>	<b>How do I make the assumptions?</b>	<i>Uncertainty re appropriate assumptions</i>
	<b>ASS</b>	<b>Appropriateness of assumptions</b>	<i>Whether or not the assumptions made in the headroom analysis were appropriate</i>
	<b>INAD</b>	<b>Information is readily available now-a-days</b>	<i>A recognition that information / numbers are easier to find now</i>
	<b>F</b>	<b>Figures</b>	<i>Reference to the figures used in headroom (outside: 'where do I find them?')</i>
	<b>TM</b>	<b>Target market</b>	<i>Target market reference. Stratification of the potential patient population</i>
	<b>COST</b>	<b>Understanding of own costs</b>	<i>Ability to weigh up future costs with the headroom presented</i>
	<b>PRAC</b>	<b>Practicality of doing it yourself</b>	<i>How practical / feasible the method would be to carry out without me</i>

Headroom SCOPE	<b>SIMPL</b>	<b>Simplifying</b>	<i>Reference to the simplifications process of headroom</i>
	<b>COMPL</b>	<b>'Completeness' of the headroom analysis</b>	<i>The fullness of the headroom message. To what extent the benefits were captured.</i>
	<b>NS</b>	<b>Narrow scope of headroom method</b>	<i>Scope too narrow. Not enough considered. Factors left out (e.g. global, other buyers)</i>
	<b>AR</b>	<b>Actual reimbursement</b>	<i>How the reimbursement scene actually works!</i>
	<b>UNDER</b>	<b>Underestimate of problem/potential impact</b>	<i>A belief that the headroom analysis may (have) underestimate(d) the true benefit of the product</i>
	<b>DD</b>	<b>Devices are different</b>	<i>An appreciation of devices being different to evaluate / considers (e.g comparison with pharmaceuticals)</i>
	<b>IHE</b>	<b>Importance of health economics</b>	<i>The relative importance of the health economic case to the interviewee</i>
	<b>COMP</b>	<b>Competitors</b>	<i>Consideration of competitors</i>
	<b>PvsA</b>	<b>Product vs. Application</b>	<i>Reference to these not being the same. E.g. multiple applications, product then application etc.</i>
	<b>TIM</b>	<b>Timing</b>	<i>When these ideas (economic evaluation) should be considered</i>
	<b>SI</b>	<b>Suggested Improvements</b>	<i>Things to change about / to add to the tool</i>
	<b>ES</b>	<b>Extra Scope</b>	<i>Wider scope of headroom method outside of specified application</i>
Headroom IMPACT	<b>MOTH</b>	<b>Motivation for conducting h/room</b>	<i>The reason health economic 'value' is being considered</i>
	<b>WUF</b>	<b>Who useful for</b>	<i>Who would benefit most from the method</i>
	<b>SUB</b>	<b>Subconscious use of same principles</b>	<i>Basic elements of headroom considered pre-headroom education'..although you might not know that you're doing that'</i>
	<b>KHE</b>	<b>Knowledge of health economics (before)</b>	<i>How new are the principles?</i>
	<b>ART</b>	<b>Articulating a general notion into something concrete</b>	<i>A tool to hone in on the value</i>
	<b>PS</b>	<b>Price setting</b>	<i>How the price will actually be set</i>
	<b>IFI</b>	<b>Informing future investigation</b>	<i>Use to shape future research</i>
	<b>LEARN</b>	<b>A learning experience</b>	<i>Having learnt from the headroom method (e.g. about NICE)</i>
	<b>COMM</b>	<b>A tool to help communicate value</b>	<i>Use of output as a communication tool with the relevant stakeholders</i>
	<b>ACT</b>	<b>Action</b>	<i>What the method has / will be used for specifically. What it has / will helped to achieve</i>

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