THE USE OF HEALTH ECONOMICS IN THE EARLY EVALUATION OF REGENERATIVE MEDICINE THERAPIES

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ABSTRACT

The aim of this thesis is to help the RM industry avoid misguidedly investing in technologies that are unlikely to be cost-effective and reimbursed by healthcare providers. Health economics provides the tools to demonstrate value for money. These tools are typically used by healthcare providers to drive demand side decisions. However, they can be used by manufacturers to inform the supply side. I propose a simple approach, termed the headroom method. This 'back of the envelope' calculation is based on estimates of effectiveness of the proposed treatment towards the upper end of the plausible range. The method can be used either to inform an intuitive decision to continue or abandon development, or as a screening test to decide if more elaborate models are justified. One problem I encountered was the development of technologies without clearly defining the clinical problem. In particular, the marginal gain in benefit over alternative treatments is frequently overlooked. A large part of this thesis is therefore concerned with the clinical epidemiology of the conditions at which treatment is targeted. In this way, it was found, for example, the headroom for health gain from new treatment for inguinal hernia was much smaller than that for incisional hernias.

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GLOSSARY

Unless otherwise stated, all definitions have been identified using the following online medical dictionaries: http://www.mondofacto.com/dictionary/, http://www.nlm.nih.gov/medlineplus/mplusdictionary.html, http://medical-dictionary.thefreedictionary.com.

Allogenic	Genetically different, although from the same species
Allograft	A graft of tissue obtained from a donor genetically different from, although of the same species as the recipient
Anastomose	To unite by openings
Anastomosis*	The surgical connection of separate or severed tubular hollow organs to form a continuous channel, as between two parts of the intestine
Angiogenesis	The process of vascularisation of a tissue involving the development of new capillary blood vessels
Antimesenteric	The part of the intestine that lies opposite the mesenteric attachment
Arthroplasty	The surgical repair of a joint
Atrophy	A decrease in the size of a cell, tissue, organ or part
Autograft	Tissue for transplantation that is taken from the patient
Autologous	Belonging to the same organism
Avascular	Without blood or lymphatic vessels
Bacteriuria	The presence of bacteria in the urine with or without consequent urinary tract infection
Bilharziasis	A parasite infection by a trematode worm acquired from infested water (also known as, *schistosomiasis)*. The species, which live in man, can produce liver, bladder, and gastrointestinal problems. The species which cannot live in man cause swimmer's itch
Bioreactor	A container in which living organisms carry out a biological reaction
Botulinum toxin	Neurotoxin produced by certain strains of Clostridium botulinum
Buccal mucosa	Mucous membrane lining the inner cheek
Cancellous Bone	Adult bone consisting of mineralised regularly ordered parallel collagen fibres and found in the end of long bones
Cardinal	Numbers that express an amount. Denotes quantity but not order
Cell therapy	The transplantation of human or animal cells to replace or repair damaged tissue and/or cells
Cells	Minute protoplasmic masses that make up organised tissue. Consist of a nucleus surrounded by a protoplasm containing various organelles. Cells are the fundamental, structural, and functional units of living organisms
Chondrocyte	Differentiated cell responsible for cartilage formation
Colon	This structure has 6 major divisions: caecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The total length is approximately 5 feet in the adult and it is responsible for forming, storing, and expelling waste matter. Also called the large intestine
Colostomy	A surgical procedure used to create an opening for urine and faeces to be released from the body
Condyle	A rounded articular surface at the extremity of a bone
Cortical Bone	The superficial thin layer of compact bone

* Definition taken from dictionary.com, http://dictionary.reference.com/

Crepitation	A dry, crackling sound or sensation, such as that produced by the grating of the ends of a fractured bone
Cystectomy*	Excision of a cyst or bladder, usually the urinary bladder
Cystoplasty	Any reconstructive operation on the urinary bladder
Decalcification	A loss of calcium from bone, causes weakening
Dehiscence	The parting of the sutured lips of a surgical wound resulting from infection
Dermis	connective tissue underlying the epithelium of the skin
Detrusor	A muscle that has the action of expelling a substance
Devitalised	Devoid of life
Diabetes Mellitus	A condition in which the pancreas no longer produces enough insulin, or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. Treatment includes changes in diet, oral medications, and in some cases, daily injections of insulin.
Diaphysis	The shaft of a long bone
Diverticulum	A small sac-like structure that sometimes forms in the walls of the intestines, diverticula can trap particles of food (e.g. small seeds and undigested grains) and become very inflamed and painful (a condition called diverticulitis)
Enteric	Relating to the small intestine
Enterocolitis	Inflammation of the small intestine and colon
Enterocutaneous	Pertaining to or communicating with the intestine and the skin, or surface of the body
Epispadias	A congenital defect resulting in the urethral opening on the dorsum of the penis
Epithelialised	To become covered with epithelial tissue
Epithelium	The cellular covering of internal and external body surfaces, including the lining of vessels and small cavities. It consists of cells joined by small amounts of cementing substances and is classified according to the number of layers and the shape of the cells
Extraperitoneal	Outside of the peritoneal cavity
Fascia	The flat layers of fibrous tissue that separate different layers of tissue
Fistula	A permanent abnormal passageway between two organs in the body or between an organ and the exterior of the body
Fournier's Gangrene	A type of necrotizing infection (gangrene) usually affecting the male genitals
Gangrene	The necrosis and subsequent decay of body tissues, usually the result of a critically insufficient blood supply. Caused by infection or thrombosis and sometimes injury and subsequent bacteria contamination.
Gastroesophageal	Relating to the stomach and the oesophagus
Gene therapy	The insertion of genetically altered genes into cells to replace defective genes
Growth factors	Proteins made by cells that cat on other cells to stimulate or inhibit their function. Growth factors are essential to the normal cell cycle, and are thus vital elements in the life of animals from conception to death.
Haematoma	A localised collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel
Health economics	The branch of economics concerned with issues related to scarcity in the allocation of health and health care.

* Definition taken from dictionary.com, http://dictionary.reference.com/

Hernia	Hernia is a general term used to describe a bulge or protrusion of an organ through the structure or muscle that usually contains it
Hernioplasty	see herniorrhaphy
Herniorrhaphy	The surgical repair of a hernia. This surgery can be done under local or general anaesthesia. May be performed using a conventional incision or using a laparoscope
Herniotomy	A cutting for the cure or relief of hernia
Homeostasis	Stability of the internal environment of an organism
Horizon Scanning*	The systematic examination of potential threats, opportunities and likely future developments, including (but not restricted to) those at the margins of current thinking and planning
Hyaline	Clear, transparent and granular free
Hydroxyapatite	A calcium phosphate complex and the primary mineral component of bone
Hyperchloraemic acidosis	A rare, sometimes familial, disorder of the renal tubule characterised by the inability to excrete urine of normal acidity
Hypertrophy	Enlargement or overgrowth of an organ due to an increase in size of its constituent cells
Hypospadias	A congenital defect in which the urethra opens on the ventral (bottom) surface of the penis rather than on the glans
Ileal conduit	An isolated segment of ileum serving as a replacement for another tubular organ; specifically, the use as a urinary conduit into which ureters can be implanted following total cystectomy or loss of normal bladder function
Ileocystoplasty	Surgical reconstruction of the bladder involving the use of an isolated intestinal segment to augment bladder capacity
Ileostomy	Surgical creation of an opening into the ileum, with a stoma on the abdominal wall
Ileus	A partial or complete non-mechanical blockage of the small and/or large intestine
Ileum	The last portion of the small intestine that communicates with the large intestine
Immunodeficiency	A group of disorders in which part of the immune system is missing or defective, therefore, the body's ability to fight infections is impaired. As a result, the person with an immunodeficiency disorder will have frequent infections that are generally more severe and last longer than usual.
Immunogenicity	Being able to evoke an immune response in an organism
In vitro	In an artificial environment outside the living organism
In vivo	Within a living organism
Incarcerated hernia	A hernia so occluded that it cannot be returned by manipulation; it may or may not be strangulated
Incisional hernia	A hernia through an old abdominal incision
Infertility	The failure of a couple to conceive a pregnancy after trying to do so for at least one full year
Inguinal hernia	Hernia located in the groin
Interstitial	Relating to or situated in the small, narrow spaces between tissues or parts of an organ
Interstitial cystitis	A chronic inflammatory condition of the bladder, cause is unknown, but occurs more commonly in females. Symptoms include difficulty urinating, pain on urination, urinary urgency and increased frequency of urination
Intraperitoneal	Within the peritoneal cavity, the area that contains the abdominal organs

* Definition taken from office of science and technology, http://www.foresight.gov.uk/HORIZON_SCANNING_CENTRE/FANclub/Index.html

Laparotomy	A surgical incision into the peritoneal cavity, usually performed under general or regional anaesthesia
Malabsorption	Impaired intestinal absorption of nutrients
Malnutrition	Malnutrition is the condition that develops when the body does not get the right amount of the vitamins, minerals, and other nutrients it needs to maintain healthy tissues and organ function
Meatus	A natural passage or canal; as, the external auditory meatus
Mesenchymal Cells	Derived from mesodermal layers and develop into tissue, muscle or blood
Mesenteric	A membranous fold attaching various organs to the body wall
Mesentery	The membranes, which connect the intestines and their appendages with the dorsal wall of the abdominal cavity.
Metaphysis	A conical section of bone between the epiphysis and diaphysis of long bones
Metaplasia	The change in the type of adult cells in a tissue to a form which is not normal for that tissue
Multiple sclerosis	A neurodegenerative disease characterised by the gradual accumulation of focal plaques of demyelination, onset is usually in 3rd or 4th decade with intermittent progression over an extended period. Cause uncertain
Myelodysplasia	Abnormal or defective formation of the bone marrow cells. Also known as ***myelodysplastic syndromes*** (MDS, formerly known as "preleukemia")
Myelomeningocele	A congenital defect in which the neural arches fail to close, so exposing the contents of the spinal canal, usually occurring in the lower back of the spine. Also known as ***Spina Bifida Cystica***
Myocutaneous	Vascularised autologous tissue, composed of, or supplying both muscles and skin
Necrosis	Cell death caused by the degenerative action of enzymes
Omphalocele	A congenital hernia in which a small portion of the foetal abdominal contents, covered by a membrane sac, protrudes into the base of the umbilical cord
Opportunity cost*	The cost of the benefits forgone from not using the resources on the next best alternative
Ordinal	Numbers that express position in a series or place in an ordered sequence
Ossification	The formation of bone
Osteoarthritis	Non-inflammatory degenerative joint disease accompanied by pain and stiffness
Osteoblasts	Bone cells that build new bone tissue
Osteocalcin	Polypeptide found in extracellular matrix of bone
Osteochondritis Dissecans	A type of osteochondritis in which articular cartilage and associated bone becomes partially or totally detached from the joint loose bodies
Osteoclasts	Bone cells that break down and remove bone tissue
Osteoconduction	Provision of a scaffold for the growth of new bone
Osteocytes	Bone cells that maintain bone tissue
Osteogenesis	Growth of new bone
Osteoinduction	Acceleration of new bone formation by chemical means
Osteopontin	A bone specific protein that links cells and hydroxyapatite of mineralised matrix. Found only in calcified bone, probably produced by osteoblasts
Ostomy	A surgical procedure creating an opening in the body for the discharge of body wastes
Osteomyelitis	Inflammation of bone, which may remain localised or may spread through the bone to involve the marrow, cortex, cancellous tissue and periosteum
Pancreatitis	Inflammation of the pancreas

* Definition taken from (Drummond et al., 2005)

Paraesthesia	An abnormal sensation, as burning, prickling, formication, etc
Parenteral	Taken into the body or administered in a manner other than through the digestive tract, as by intravenous or intramuscular injection
Parotid	Parotid gland, one of the salivary glands situated just in front of or below the ear. It is the largest of the salivary glands in man, and its duct opens into the interior of the mouth opposite the second molar of the upper jaw
Pericardium	A double membranous sac, which envelops and protects the heart. The layer in contact with the heart is referred to as the visceral layer; the outer layer in contact with surrounding organs is the parietal pericardium. In between the two layers is the pericardial space.
Perineum	The area between the opening of the vagina and the anus in a woman, or the area between the scrotum and the anus in a man
Periosteum	The membrane of fibrous connective tissue which closely invests all bones except at the articular surfaces
Peristomal	Pertaining to the area of skin surrounding a stoma in the abdominal wall
Peritoneal dialysis	The removal of soluble substances and water from the body by transfer across the peritoneum, utilizing a solution which is intermittently introduced into and removed from the peritoneal cavity
Peritonitis	Inflammation of the peritoneum
PEST analysis[*]	Analysis of the external macro-environment that affects all firms. P.E.S.T is an acronym for **P**olitical, **E**conomic, **S**ocial, and **T**echnological
Pharmacoeconomics	The scientific discipline that compares the value of one pharmaceutical drug or drug therapy to another. A sub-discipline of health economics
Porosity	Condition of having pores or open spaces
Prophylactically	Acting to defend against or prevent something, especially disease; protective
Prostatism	A symptom complex resulting from compression or obstruction of the urethra, due most commonly to nodular hyperplasia of the prostate
Pseudoarthrosis	A pathologic entity characterised by deossification of a weight-bearing long bone
Pyelonephritis	Inflammation of the kidney and its pelvis, beginning in the interstitium and rapidly extending to involve the tubules, glomeruli and blood vessels, due to bacterial infection
Radiopacity	The property of obstructing the passage of radiant energy, such as x-rays, the representative areas appearing light or white on the exposed film
Regenerative medicine[†]	Replaces or regenerates human cells, tissues or organs, to restore or establish normal function
Resection	Surgical removal of all or part of an organ, tissue, or structure
Revascularisation	The restoration of blood supply to a part or organ
Scaffold	A support, either natural or artificial, that maintains tissue contour.
Schistosomiasis	Disease caused by trematode worms of the genus Schistosoma, the adults of which live in the urinary or mesenteric blood vessels. *See Bilharziasis*
Seroma	A mass or swelling caused by the localized accumulation of serum within a tissue or organ
Serum	Blood plasma with the blood clotting proteins removed. It is prepared by removing blood from the subject, allowing blood to form a blood clot, and then using a centrifuge to remove the red blood cells and the blood clot
Small Bowel Obstruction	An obstruction of the small intestine that prevents the free passage of material; sometimes caused by postoperative adhesions

[*] Definition taken from dictionary.com, http://dictionary.reference.com/
[†] Definition taken from Mason and Dunhill (Mason et al., 2008)

Sphincter	A ring like band of muscle fibres that constricts a passage or closes a natural orifice, also called musculus sphincter
Spicules	A needle like structure or part
Spondylosyndesis	Spinal fusion surgery
Steatorrhea	Presence of excess fat in stools, caused by disease of the pancreas or intestine, and characterized by chronic diarrhoea and weight loss
Stem cells	Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialised and take the place of those that die or are lost
Stoma	A mouth like opening, particularly an incised opening which is kept open for drainage or other purposes
Strangulated hernia	So tightly constricted as to compromise the blood supply of the hernial sac, leading to gangrene of the sac and its contents
Strictures	A narrowing, especially of a tube or canal, due to scar tissue or tumour
Submucosa	A layer of tissue beneath a mucous membrane
SWOT analysis[*]	A strategic planning tool used to evaluate the **S**trengths, **W**eaknesses, **O**pportunities, and **T**hreats involved in a project or in a business venture. It involves specifying the objective of the business venture or project and identifying the internal and external factors that are favourable and unfavourable to achieving that objective
Syngenic	Genetically identical individuals
Tachyphylaxis	The rapidly decreasing response to a drug or physiologically active agent after administration of a few doses
Tissue engineering[†]	Tissue engineering is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physio-chemical factors to improve or replace biological functions
Trigone	A smooth triangular area on the inner surface of the bladder, limited by the apertures of the ureters and urethra
Tubercular	Of, pertaining to or resembling tubercles or nodules
Tuberculosis	An infection caused by a species of Mycobacterium, remains a major worldwide health problem.
Urease	An enzyme that breaks urea down into carbon dioxide and ammonia, its typically used to measure urea concentrations
Ureters	The tubes that carry urine from each kidney to the bladder
Urethroplasty	An operation for the repair of an injury or a defect in the walls of the urethra
Urinary obstruction	Urethral or ureteral obstruction often caused by lodgement of a urinary calculus in the narrow lumen.
Urogenital	Pertaining to the urinary and genital apparatus, genitourinary
Urothelium	A layer of transitional epithelium in the wall of the bladder, ureter, and renal pelvis
Vascular pedicle	The tissues containing arteries and veins of an organ
Viscera	The soft internal organs of the body, especially those contained within the abdominal and thoracic cavities
Xenogenic	Originating outside of the organism, or from a foreign substance that has been introduced into the organism
Xenograft	A tissue graft transplanted from one species to another (e.g. pig to human)

[*] Definition taken from dictionary.com, http://dictionary.reference.com/
[†] Definition taken from dictionary.com, http://dictionary.reference.com/

LIST OF ABBREVIATIONS

ACI	Autologous Chondrocyte Implantation
ACS	Abdominal Compartment Syndrome
ATS	Advanced Tissue Sciences
BMPs	Bone Morphogenic Proteins
CBA	Cost-Benefit Analysis
CCI	Characterised Chondrocyte Implantation
CEA	Cost-Effectiveness Analysis
CMA	Cost-Minimisation Analysis
CTS	Clinical Trial Simulation
CUA	Cost-Utility Analysis
DBM	Demineralised Bone Matrix
DDD	Degenerative Disc Disease
EBHC	Evidence-Based Healthcare
ERG	Evidence Review Group
GNP	Gross National Product
HADM	Human Acellular Dermal Matrix
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICRS	International Cartilage Repair Society
IDET	Intradiscal Electrothermal Therapy
IVD	Intervertebral Disc Degeneration
KOOS	Knee Injury and Osteoarthritis Outcome Score
MACI	Matrix-Induced Chondrocyte Implantation
MSCs	Mesenchymal Stem Cells
NICE	National Institute for Health and Clinical Excellence (UK)
NHS	National Health Service (UK)
OA	Osteoarthritis
QALY	Quality Adjusted Life Years
HRQL	Health-related quality of life
R&D	Research and Development
RCTs	Randomised Control Trials
RM	Regenerative Medicine
SG	Standard Gamble
SIS	Small Intestinal Submucosa
SMEs	Small and Medium enterprises
TAR	Technology Assessment Report
TE	Tissue Engineering
TKR	Total Knee Replacement
TTO	Time Trade-Off
VAS	Visual Analogue Scale
VOI	Value of Information
WHO	World Health Organisation
WTP	Willingness-to-Pay

PUBLICATIONS

As a result of the research conducted for this thesis, I have had articles published in peer-reviewed journals and given oral presentations at conferences.

Chapter 3

1. Cosh, E., Girling, A., Lilford, R., McAteer H.L., & Young, T. 2007. Investing in New Medical Technologies: A decision framework *Journal of Commercial Biotechnology* **13:** 263-271

2. McAteer, H.L. & Lilford, R. 2nd July 2008. *"The Use of Health Economics in the Early Evaluation of Regenerative Medicine Applications"* in Annual Conference of the Tissue and Cell Engineering Society, University of Nottingham, UK. *European Cells and Materials* **16**:5

Chapter 4

3. McAteer, H. L., Cosh, E., Freeman, G., Pandit, A., Wood, P., & Lilford, R. 2007. Cost-effectiveness Analysis at the Development Phase of a Potential Health Technology: Examples based on Tissue Engineering of Bladder and Urethra. *Journal of Tissue Engineering and Regenerative Medicine* **1:** 343-349

Chapter 5

4. McAteer, H.L. & Lilford, R. 17th November 2009. *"Assessing the cost-effectiveness of tissue-engineered treatments"* in 2nd China-Europe Symposium on Biomaterials in Regenerative Medicine, Petit Palau, Palau de la Música, Barcelona, Spain.

PREFACE

This work was supported by the EPSRC REMEDI Grand Challenge (EP/C534247/1) and the EU FP-6 STEPS (FP6-500465) projects. The aim of this thesis is to help the regenerative medicine RM industry reduce the risk of investing in a new technology that once developed is unlikely to be reimbursed by the healthcare providers. The objectives of this thesis are:

i. To assess whether headroom method can be used, before the development process begins, to understand the scale of the market and clinical opportunity
ii. To develop a novel method using health economic principles that can be used early in healthcare technology development and that is simple enough to be used by Small and Medium enterprises (SME's)
iii. To demonstrate to the RM industry how this method can be used to assess the economic potential of their products at early stage product development

This thesis argues for the integration of the headroom method, which uses health economic principles, within healthcare technology development. Health economics provides the tools necessary to demonstrate value for money. These tools are typically used by healthcare providers to drive demand side decisions i.e. to select or reject treatment for reimbursement. However, these same tools can also be used by healthcare technology manufacturers and investors, to inform supply side decisions i.e. to determine whether the expected returns will outweigh the expected costs. The RM industry provides a good example to demonstrate the value of supply side analysis. Despite a rapid proliferation of start up companies in the 1990's very few RM products have been able to make the transition from laboratory bench to patient bedside. The failed attempts had been largely due to insufficient marginal effectiveness delivered for marginal costs incurred. In addition, the RM industry is heavily comprised of SME's all of which require large external investment to continue product development. Demonstrating value for money during the early stages of product development can be compelling evidence to attract further investment. However, conducting cost-effectiveness analysis when a product is yet to be developed is an extremely uncertain undertaking.

In order to conduct a cost-effectiveness analysis the question must be clearly defined. The proposed technology must be compared with the best existing treatment. I found that the industry had often not carried out this step and so a substantial part of my thesis has been concerned with defining the natural history and effectiveness of existing treatments with which a new proposed method will have to compete. Once this step is complete, the cost-effectiveness modelling can be carried out. There is an immediate difference here between traditional cost-effectiveness modelling versus the supply side modelling that I was doing. Supply side modelling involves estimating the effectiveness of a technology that does not yet exist, let alone one that has undergone head-to-head assessment. Two approaches were possible: i) full economic modelling across a Bayesian prior estimate and ii) modelling against the most optimistic plausible assumptions of effectiveness. I have called the latter the headroom method. The idea here is that if a technology is unlikely to be cost-effective under optimistic assumptions then the investment is unlikely to be repaid. Essentially a model is created at the optimistic end of a potential sensitivity analysis.

The thesis begins with a general introduction to the RM industry and health economics before going on to discuss the role of health economics within the RM industry. Chapter 2 reviews the current literature on the use of health economics during early stage product development within the wider healthcare industry. This chapter aims to identify the reasons for conducting early economic evaluation as well as the current tools and methods suggested for conducting early economic evaluation. Chapter 3 describes the research methodology used in this thesis. Chapter 4 describes the headroom method, and explains the key principles necessary to understand this method. In Chapters 5 through to 8, I illustrate the use of health economics at the supply side using real examples from the nascent industry of RM. In chapter 9, I describe the problems faced by SMEs associated with eliciting utilities and propose a new approach. Finally, in chapter 10 I will discuss the limitations of the headroom method and the implications of this work. I will close this thesis by means of a summary of this work and explanation of how it fits in the context of the current literature. I will review the unresolved issues and summarise the next steps for this work.

CHAPTER 1 GENERAL INTRODUCTION

1.1 The Regenerative Medicine Industry

1.1.1 What is Regenerative Medicine and Tissue Engineering?

Many definitions of RM exist. The world tissue-engineering centre defines RM as “an emerging multidisciplinary field of research and technology development focused on the repair, replacement or regeneration of cells, tissues, or organs, which has the potential to revolutionise medicine by changing the methods of health care treatment and improving health-related quality of life” (WTEC, 2002). More recently, Greenwood and colleagues offered a lengthier more detailed explanation: “Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement, or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging. It uses a combination of several technological approaches that moves it beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering, and the reprogramming of cell and tissue types” (Greenwood et al., 2006). In 2008, Mason and Dunnill offered a simpler, shorter explanation for regenerative medicine: “Regenerative medicine replaces or regenerates human cells, tissues or organs, to restore or establish normal function” (Mason et al, 2008). This was based on Greenwood and colleagues earlier definition but with the exclusion of ‘repair’, a word Mason and Dunnill felt did not encompass the full potential of RM, which is to return a patient to full health. They also excluded specific techniques, which they feel are likely to change over time and make the definition longer and more confusing.

Currently, RM approaches include tissue engineering (TE) (the use of cells, engineering and materials methods, and biochemical factors to improve or replace biological functions), cell therapy (the transplantation of human or animal cells to replace or repair damaged tissue and/or cells), and gene

therapy (the insertion of genetically altered genes into cells to replace defective genes). This thesis focuses primarily on the TE approach to RM. TE is defined, by the world tissue-engineering centre, as "the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues, and the development of biological substitutes to restore, maintain, or improve tissue function" (WTEC, 2002). However, the European commission has defined TE in narrower terms as "the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules" (Bock A.K et al., 2003).

Essentially, it is generally agreed that RM is a new multidisciplinary field of medicine with the potential to cause a step change in the delivery of healthcare and the main purpose of RM is to replace missing tissue and buttress the body's natural healing ability. A RM or TE product comprises of one or more of the following: growth factors (proteins made by the cells that act on other cells to stimulate or inhibit their function), cells (the fundamental, structural, and functional units of living organisms), or scaffolds (a support, either natural or artificial, that maintains tissue contour). Using growth factors independently is impractical because they will diffuse rapidly from the injected site and be enzymatically digested or deactivated. Likewise, cells delivered to a defect site may require some form of support to aid their growth and proliferation. Scaffolds alone will not usually work well unless the defect has the inherent potential to regenerate anyway (Tabata, 2005). However, the use of cells and/or growth factors can improve the performance of scaffolds. Therefore, practically speaking, these products are made up in one of the following three ways:

1. Scaffold and cells
2. Scaffold and growth factor
3. Scaffold, cells, and growth factors

A crucial technical aspect of these products is whether they are developed *in vitro* (in an artificial environment outside the living organism) or *in vivo* (within the living organism). In vitro tissue engineering occurs when the tissue, made in an artificial environment - usually a bioreactor (a container in which living organisms carry out a biological reaction), is implanted directly into the defect,

e.g. a tissue-engineered bladder is made outside the body and designed to replace the original bladder (see chapter 4). *In vivo* tissue engineering involves the implantation of a scaffold impregnated with growth factors and/or cells into the defect, e.g. bone morphogenic proteins impregnated on a collagen sponge for implantation into bony defects (see chapter 6). Finally, any cells used in these products may be autologous (belonging to the same organism), allogenic (being genetically different although belonging to the same species) or xenogenic (belonging to a different species). An allogenic or xenogenic cell is genetically and immunologically incompatible, and unlike an autologous cell can cause an immunological response in the patient. In addition to the manufacturing differences between *in vitro* an *in vivo* products there are also differences in costs. *In vitro* production incurs unavoidable costs compared to *in vivo* production stemming from the necessarily rigorous quality control as a well as from the logistics of co-ordinating laboratory and clinical activities.

1.1.2 The History of the Industry

Introduction

The field of TE has been developing since the early 1970s (although the term 'tissue engineering' was yet to be introduced) when the first attempts were made to generate cartilage, using chondrocytes seeded onto spicules (a needle-like structure) of bone and implanted into (immuno-suppressed) nude mice. Although unsuccessful it was concluded that with the advent of innovative biocompatible materials it would be possible to generate new tissue by seeding viable cells onto appropriately configured scaffolds (Vacanti, 2006). Over the coming decades research continued in this new discipline; by the mid-1980s, designs for an appropriate scaffold for cell delivery were emerging, and by the mid-1990s the TE field began to expand with a rapid proliferation of start-up companies (Vacanti, 2006). The worldwide investment in the industry between 1990 and 2000 rose to an estimated $3.5 billion (£2.1 billion, €2.4 billion)[*] (Lysaght et al., 2001), although 90% of funding was from the private sector.

[*] Currency conversion conducted using www.xe.com. Correct as of 04/11/10

Where it all went wrong

Organogenesis and Advanced Tissue Sciences (ATS) were the first companies to bring mass-produced TE skin products to market for the management of diabetic foot ulcers and venous leg ulcers. Their investors were promised a multi-billion dollar market for their product, based on the costs to treat chronic wounds at the time. However, this turned out to be a gross overestimation of the market for artificially engineered skin. Sales were poor and failed to cover operating costs; the two companies filed for bankruptcy in 2001 (Lysaght et al., 2004). The early failure of Organogenesis and ATS had a negative impact on interest and activity in the TE industry. Between 2000 and 2002 activity fell by 50% and the capital value of publicly traded TE corporations dropped by 90% (Lysaght et al, 2004). TE firms ran out of money and investors became increasingly reluctant to give more.

The demise of Organogenesis and ATS has been attributed to a poor business model. In reality, these artificial skin products were only appropriate for the small proportion of wounds that fell into the category between small, easy-to-heal wounds, and large, difficult to heal, gangrenous wounds. There was insufficient demand from clinicians for a high-tech solution for the treatment of wounds in this intermediate category and this quickly became a classic case of a technology looking for its application (Bouchie, 2002). The industry blames regulatory bodies for slow product and reimbursement approval. However, the lack of clinical and economic evidence supporting the cost-effectiveness of these products combined with the high production, maintenance, and transportation costs, limited demand and made regulators wary. In contrast, current more traditional therapies, such as collagen dressings and gels, had no restrictions placed upon them (Bouchie, 2002).

Despite many advances in the field of TE and RM, and although some products have made it to market, TE has had less of an impact in clinical practice than the enthusiasts predicted (Williams et al., 2005). The business side of the industry did not maintain the expectations of the scientists. The industry has had difficulty making the transition from development stage to commercial production (Lysaght et al, 2004;Mansbridge, 2006), due largely, I believe, to the insufficient marginal effectiveness delivered for the cost incurred. As with many new industries, the eventual success stories will be built on the foundations of numerous commercial failures.

A Brighter Future?

Investment in the industry is once again growing, with increasing interest from public investment, although the majority of investment remains private (Kemp, 2006). There are signs that the industry has learnt the lessons from the past. It has been observed that for the industry to achieve success it needs to marry a biologics operating model (which costs a lot to run) with a device-type business model (which typically yields small margins) (Kemp, 2006), and accept that potential applications must first be identified and the technology developed to meet the need.

Despite increases in investment many hurdles still face the industry, not only in the science, but also in the commercialisation of these products (Kemp, 2006). A recent report (Rowley et al., 2009) discusses, in depth, the barriers to commercialisation and utilisation of RM in the UK as viewed by 54 individuals from academic, industry, and clinical communities.

The barriers to commercialisation are viewed as:

- **Regulation** - a historically uncertain environment, which needs rapid clarification
- **Collaboration** – between sectors (academics, industry and clinicians) to share language and skills
- **Funding** - particularly in translational research,
- **Knowledge** – more needed at basic science level.

The barriers to utilisation are viewed as:

- **Collaboration** with clinicians - invention is no good without adoption,
- **Evidence** – an evidence base is demanded by clinicians, and increasingly by organisations that ration health care such as the National Institute for Health and Clinical Excellence (NICE) in England and Wales*,
- **Reimbursement** – currently, RM is expensive compared with current treatments, and the silo budgets (compartmentalised budgets) within the National Health Service (NHS) makes

* an independent organisation responsible for providing national guidance on promoting good health in England and Wales and preventing and treating ill health, further information at: www.nice.org.uk

economic arguments difficult when costs are incurred in one area while savings are realised in another

- **Organisational structure** – the NHS is a poor adopter of innovation, and many perceive the bureaucratic nature of the NHS as prohibitive
- **Clinical fit** - product design as well as distribution and storage.

It is the reimbursement challenge, which is addressed by this thesis. The aim is to help the RM industry reduce the risk of investing in a new technology that, once developed, is unlikely to be reimbursed by the healthcare providers.

1.2 Health Economics

1.2.1 What is Health Economics?

Health economics manages the scarcity of resources. It provides the tools necessary to assess the most efficient (best value for money) use of available resources in the allocation of health and health care. Economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (Drummond et al, 2005). Crucially it is concerned with the value of the opportunity cost – the cost of the benefits forgone from not using the resources on the next best alternative. It tries to identify where more benefit can be produced at the same cost, or a lower cost can be achieved for the same benefit. There are different types of economic evaluation. Most measure costs in a similar way but differ considerably in the way they measure consequences. A summary of each type is described below (Drummond et al, 2005).

- *Cost-minimisation analysis (CMA):* The consequences of two or more treatments are equivalent, so the difference between them reduces to a comparison of costs.
- *Cost-effectiveness analysis (CEA):* Consequences are common to both interventions but achieved to different degrees and measured in natural life units such as life years gained.

- *Cost-utility analysis (CUA):* a particular kind of CEA whose consequences are not common to both interventions. To make comparisons, treatments are compared by converting the outcomes to a common scale – a utility scale. Quality adjusted life years (QALYs) are such a scale.
- *Cost-benefit analysis (CBA):* Consequences not necessarily common to both interventions but instead of utility as a common scale all outcomes are measured in monetary units.

1.2.2 The Changing Face of Health Care Purchasing

Healthcare markets are increasingly competitive. CEA has become an important component of health technology assessments (HTA). Health services are using HTA to a greater extent to guide purchasing and reimbursement decisions. Assessments of whether a intervention is worthwhile have to be made by reference to an external standard (e.g. a specific budget constraint or a threshold cost-effectiveness ratio) (Drummond et al, 2005;Morris et al., 2007). In the UK, HTA reports are reviewed by NICE, who assess the evidence of clinical and cost-effectiveness of a particular technology, and gives recommendations to the NHS about whether and in what circumstances the technology should be used.

I will elaborate on the approach used by NICE to make reimbursement decisions, but first I will discuss a number of health economic concepts, which are appropriate and necessary to understanding the subsequent chapters of this thesis.

1.2.3 Health Utilities

Modern utility theory was first presented by von Neumann and Morgenstern in 1944 (von Neumann et al., 1944). This theory describes how individuals should make decisions in the face of uncertainty if they wish to act in a way that is defined as rational (Torrance, 1997). A health utility is a broader measure of health benefit. A utility is a cardinal value (measured from 0, death, to 1, perfect health) that represents the strength of an individual's preference for specific outcomes, under conditions of uncertainty (Petrou, 2001). A health utility is a preference for a specific health state or treatment. If

there is a greater preference for a particular health outcome there is also greater utility for that health outcome (Drummond et al, 2005).

Utility analysis, employed when conducting a CUA, is viewed as a particularly useful technique as it provides a generic outcome measure for comparison of costs and outcomes in different programmes (Drummond et al, 2005). This generic outcome is usually expressed as a quality adjusted life year (QALY).

Quality adjusted life years (QALYs)

Incremental health benefit is expressed in QALYs. A concept first introduced during 1968 by Herbert Klarman and colleagues (Drummond et al, 2005). A QALY allows comparisons to be made between illnesses and treatments. It provides a comparison of the relative value of one health state over another, which in turn can guide the setting of priorities to allow efficient distribution of healthcare resources for the general population (Hirskyj, 2007). A QALY is a measure that takes into account both the *quantity of life* and the *health-related quality of life* (HRQL) generated by healthcare. Quantity is expressed in years, in terms of survival or remaining life expectancy. Quality is measured by health utilities (a utility-based HRQL score).

Utilities can be used to calculate QALYs, unlike health-related quality of life scores, which directly measure the impact of a disease or treatment on people's ability to function in life and which cannot be used to calculate QALYs. QALYs, like utilities, are measured from 0, death, to 1, perfect health. One year of perfect health is worth 1 i.e. 1 QALY is equal to 1 year of perfect health.

Total incremental QALY (ΔQALY) for a new technology is calculated as in equation 1.1 - a function of the improvement in health utility (Δutility) between the new technology and the current gold standard treatment, and duration of improvement, when the new technology is compared to the current gold standard.

Equation 1.1: $\Delta QALY = \Delta Utility \times$ duration of time (years) with that health state

It should be noted that the concept of QALYs has been controversial since its conception. There is a great deal of debate in the literature surrounding the potential limitations of QALYS. The criticisms (to name a few) relate to difficulties in accommodating chronic disease, where HRQL is a major issue and survival less so; the high dependence on age and the inadequate weight attached to emotional and mental health problems (Phillips et al., 2003). Several alternatives to QALYs have been suggested such as healthy-life years (HYEs) and Disability adjusted life years (DALYs), but currently no alternative solves all the challenges (Drummond et al, 2005;Prieto et al., 2003). These methods are not used within the context of this work so are not explained here. However, a useful summary can be found in the book 'Economic Evaluation of Health Care Programmes' by Drummond et al (Drummond et al, 2005).

1.2.4 Measuring Preferences

There are different types of economic evaluation (described in section 1.2.1, page 30). It is cost-utility analysis (CUA), where benefit is measured using QALYs, that is advocated by NICE (NICE, 2008). As described, a QALY takes account of both the quantity, expressed in years, and the quality, measured by health utilities, of life generated by healthcare. It is usually straightforward estimating the duration of time in a particular health state, what is more difficult is estimating the utility-based HRQL associated with that health state.

There are three approaches to identifying a health utility:

i. Personal judgement (uncommon);
ii. Literature or in the database of utilities held by TUFTS (Tufts Medical Centre, 2009);
iii. Formal methods, using a primary survey

If a utility score is not given in the literature, it is necessary to elicit the utility directly from patients using formal methods. There are three key stages involved in measuring utilities using formal methods:

i. Define a set of health states of interest (e.g. side-effects of current treatment);
ii. Identify individuals to obtain utilities from (e.g. patients, clinicians, general public);

iii. Total across the individuals to determine average values for each health state

A number of formal methods exist for measuring preferences and eliciting utilities. Firstly, there are direct methods, those elicited from the general population by mapping preferences directly onto a utility scale via means of a rating scale or a trade off (standard gamble or time trade-off). The most common of which are the rating scale, time trade-off (TTO) and standard gamble (SG) (Drummond et al, 2005). Secondly, there are indirect methods. Elicited from patients using the treatment, these methods involve the mapping of preferences indirectly onto a utility scale via means of preference-based multi-attribute health status questionnaires such as EuroQoL (EQ-5D – www.EuroQoL.org) or SF-36 (www.sf-36.org/.). Finally, a method exists to estimate utility in monetary terms. This method is termed the contingent valuation method or willingness to pay (WTP). Individuals are asked to state a maximum WTP value to ensure welfare gain occurs.

i. Direct Methods

Rating Scale

This is the simplest of the direct methods. Subjects are first asked to rank health outcomes in order of preference, from most preferred to least preferred. Second they are asked to place the outcomes on a scale such that the spaces between placements corresponds to the differences in preferences perceived by the subject; i.e. outcomes almost equally desirable would be placed close together whilst those perceived as very different would be further apart (Drummond et al, 2005). There are many variations to the rating scale but the scale of numbers usually spans from 0 to 100. A common type of the rating scale is the visual analogue scale, which consists of a line often 10cm in length, with clearly defined end-points, and with or without other marks along the line. Although this may be the simplest method it is also the least favourable method as it is associated with a number of biases (Drummond et al, 2005). The most important biases are the end-of-scale bias in which subjects tend to shy away from using the ends of eh scale, and the context bias in which subjects tend to space out the outcomes over the scale regardless of how good or bad states are (Drummond et al, 2005).

Standard Gamble

Standard gamble (SG) is a classical method of measuring cardinal preferences based on a choice between the certainty of one outcome and a gamble with two possible outcomes. Subjects are offered two alternatives. Alternative 1 is a health state with certainty *(H_1)*, and alternative 2 is a gamble that has two possible outcomes, either the patient is returned to full health (*H_2)* with probability *P*, or has a risk of dying (H_3 = 1-*P*). The probability is varied until the subject is indifferent between the two alternatives, at which point, the preference score of H_1= *P* (assuming the time in that health states (H_1) is 1.o years) (Drummond et al, 2005;Morris et al, 2007).

Time Trade-Off

Time Trade-off (TTO) is a simpler alternative to standard gamble. Here, the subject is offered two alternatives: a) health outcome *i* for time *t* (life expectancy of an individual with chronic condition, e.g. 10 years) followed by death; b) healthy for time $x < t$ followed by death. Time *x* is varied until subject is indifferent between the two alternatives at which point the required preference score for health outcome *i* is given as $Hi = x/t$. The TTO values are converted into HRQL-based utility scores *(U)* using the following equation:

Equation 1.2: $U = x/t$

However, this method along with all direct measures can be time consuming and complex to administer.

ii. Indirect Methods

These are less time consuming and easier to administer alternative to direct measures. These questionnaires stratify data into a number of different dimensions. The questionnaire responses are converted to utilities by means of a tariff. These tariffs are available as a result of previous exercises in which various possible health states have been calibrated by means of a trade-off (for EQ-5D) or standard gamble (for SF-36) from a sample of the general population (Arnold et al., 2009). The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and

potential receivers of healthcare. The four most widely used indirect approaches are EQ-5D, Short Form-6D (SF-6D), Health Utilities Index (HUI), and the quality of well being scale (QWB).

EQ-5D

Devised by the EuroQoL group (EuroQol Group, 2008), a consortium in Western Europe, the EQ-5D is a health preference questionnaire, which addresses five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each attribute has three levels: no problem, some problems, and major problems. Therefore, this system results in 243 possible health states. The scoring function of the EQ-5D was devised by measuring the preferences of 3000 members of the UK adult population using TTO (described above). Further details on the EQ-5D can be found at: www.EuroQoL.org.

SF-6D

This is a utility instrument based on the HRQL questionnaire, the Short Form 36 (SF-36). The SF-6D was developed to convert the SF-36 into utilities and QALYs. It assesses six attributes: physical function, role limitations, social functioning, pain, mental health, and vitality (Brazier et al., 2002) and each attribute has four to six levels, resulting in a possible 18000 possible health states. To use this system, first the SF-36 questionnaire must be completed, then using the SF-6D scoring table the results can be translated into utilities (Drummond et al, 2005).

HUI

The Health Utility Index (HUI) consists of two systems, HUI2 and HUI3. HUI2 measures six attributes: sensation, mobility, emotion, cognition, self-care, pain, and fertility (can be deleted if not relevant). Each attribute has three to five levels (Torrance et al., 1996). HUI3 measures eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each attribute is measured by either five or six levels (Furlong et al., 2001). In both cases, the scoring formula is based on standard gamble utilities measured on the general public (Drummond et al, 2005). More information can be found at www.healthutilities.com.

QWB

The Quality Well Being (QWB) scale classifies patients according to four attributes: mobility, physical activity, social activity, and symptom-problem complex (Drummond et al, 2005). The scoring function is based on category scaling measurements previously taken on a random sample of the general public in San Diego, California. The disadvantage of the QWB system compared to the other indirect methods discussed above is that it is time consuming to administer (Drummond et al, 2005).

iii. Contingent Valuation

The final method I will discuss is known as contingent valuation or Willingness-to-Pay (WTP). The contingent valuation method is a survey based approach for eliciting consumer's monetary valuations for programme benefits for use in cost-benefit analysis (CBA) (Diener et al., 1998) (see section 1.2.1, page 30). CBA is based on the principles of welfare economic theory, which is defined as the 'systematic analysis of the social desirability of any set of arrangements, the state of the world or allocation of resources, solely in terms of the utility obtained by individuals' (Morris et al, 2007). Rather than measuring health utilities on a cardinal scale from 0 to 1, this approach estimates utility in monetary terms, therefore directly estimating the welfare gains/losses. Individuals are asked to state a maximum WTP or WTA (willingness-to-accept) value to ensure that the welfare gain occurs or to tolerate the welfare loss (depending on whether a programme is being introduced or removed) (Drummond et al, 2005).

There are a number of practical difficulties involved in measuring willingness-to-pay. The most important issue in order to obtain a precise and unbiased estimate of WTP is making sure the respondents understand the market scenarios presented to them and find them plausible and meaningful (Morris et al, 2007). There are two general formats a question can take: closed ended or open-ended. Closed ended questions are formed of three formats: payment scales, bidding games or discrete choice ('take-it-or-leave-it'). In the payment scale method the respondents are given a range of choices and asked to put a tick next to the amounts they are sure they would pay, a cross next to the amounts they are sure they would not pay and a circle around the maximum they would pay. The disadvantage is that respondents are given cues on the size of the WTP that is considered sensible

(Drummond et al, 2005;Morris et al, 2007). Bidding games can only really be conducted in an interview, respondents are given a price and asked if they would be willing to pay that price or not. The price is then raised or lowered, depending on the previous answer, this continues until the respondent can no longer choose. However this method leads to starting point bias (Drummond et al, 2005;Morris et al, 2007). In discrete choice format respondents are given a single value that they must choose to accept or reject. Different values are presented to different people in a sample and WTP values are estimated from the average responses (Drummond et al, 2005;Morris et al, 2007). Open-ended formats can be more difficult for respondents to understand, however, there is currently no consensus on which elicitation method should be used and all have associated biases.

iv. Practical Issues

Given the lack of a gold standard for utility elicitation, the person eliciting the utilities is required to decide between direct or indirect methods. On the grounds of efficiency, the indirect methods are preferable as they are far simpler to administer. However, it is well known that different methods of utility estimation yield systematically different values (Drummond et al, 2005;Hirskyj, 2007).

Arnold and colleagues (Arnold et al, 2009) compared direct and indirect methods for eliciting utility and found that the two methods yield different results. Direct methods produce significantly higher utility values compared to indirect methods across a wide range of diseases. Arnold and colleagues (Arnold et al, 2009) offer potential explanations for the observed differences. Firstly, indirect methods impose constraints; respondents are forced to encapsulate their potentially complex condition within just a few categories. In addition, the questionnaires do not allow respondents to report, for example, potentially positive aspects of their situations, which would give higher values of utility. Secondly, it is likely that the respondents who contribute trade off values for the tariffs used in indirect methods are systematically different from the patients that participate in direct methods. The general population used to obtain tariffs for indirect methods are spread across a wider age range than patient populations typically used in direct estimation.

It is important to note, however, that the utility score you get depends on how you do the measuring (Drummond et al, 2005;Hirskyj, 2007). Two key aspects can affect the outcome, firstly, how the question is framed, specifically whether the outcomes are certain or uncertain, and secondly, how the subject is asked to respond, specifically whether the subject is asked to perform a scaling task based on introspection or to make a choice (Drummond et al, 2005).

There is also debate in the literature regarding whose preferences should be measured; clinicians or healthcare professionals who are the caregivers and are knowledgeable about health states; patients who experience the impact of the disease and treatment; or the general public who may not have experienced the health state but who do represent public opinion (Hirskyj, 2007;Petrou, 2001). Some people think that utilities should be derived from patients because they really know what the condition is like. Whereas others think the citizen's perspective is more important. However, regardless of this debate, it is agreed that respondents should be representative of the relevant population required.

v. Conventional practice

The NICE guidance on methods of technology appraisal (NICE, 2008) state that as far as possible, for the valid analysis of clinical effectiveness, the principal outcome(s) will be clinically relevant; that is, they measure health benefits and adverse effects that are important to patients and/or their carers. The clinical outcome measures would usually be expected to have an impact on survival or HRQL and should be expressed in terms of QALYs for the evaluation of cost effectiveness. NICE states that the EQ-5D is the preferred method of measuring HRQL. As described earlier, different methods of measuring preferences produce different results, which cannot easily be compared. However, they acknowledge that access to EQ-5D data is not always possible. In these circumstances, they advise estimating EQ-5D utilities by mapping EQ-5D data from other HRQL measures. I have done this in chapter 5. Alternatively, direct methods can be used if this is seen as the most appropriate and EQ-5D utilities are not available, in which case the TTO approach is advocated. To maintain consistency with the methods of the EQ-5D it is specified that the TTO approach uses full health as the upper anchor (NICE, 2008).

1.2.5 Incremental cost effectiveness ratio (ICER)

CUA aims to quantify the incremental cost effectiveness ratio (ICER). This is the extra cost per unit of benefit when comparing one treatment, technology, or program against another. This is most commonly done on a cost per QALY basis i.e. using cost-utility analysis. The comparator should always be the current gold standard treatment for a specific condition, as only an improvement on this performance will support the reimbursement of a new technology.

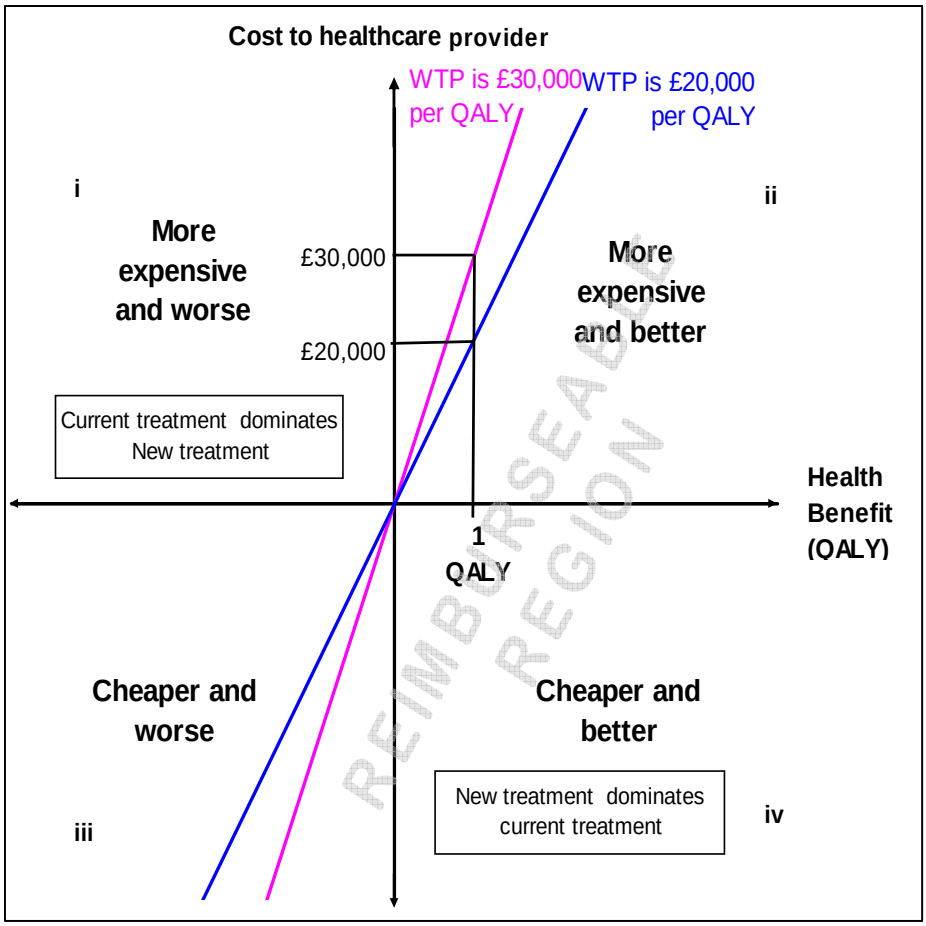
An ICER is calculated as in equation 1.3, using the incremental cost (change in cost from treatment A to treatment B (ΔC)) and the incremental effectiveness (change in effectiveness from treatment A to treatment B (ΔE)), resulting in a cost per additional unit of benefit. ΔE can be measured in different terms; in the UK, this is most frequently the QALY (discussed further below). ΔQALY becomes the measure of the change in effectiveness between the two treatment options thus, ICER = ΔC / ΔQALY. This gives a cost per additional unit of effectiveness, or an incremental cost per QALY. Estimates of cost per QALY can help to determine whether or not an intervention provides good value for money. The ICER determines whether an increase in cost is justified by a sufficient increase in effectiveness and reimbursement decisions are based on a threshold level for an ICER. This is done using the cost effectiveness plane.

Equation 1.3: ICER = ΔCost / ΔEffectiveness

1.2.6 The cost effectiveness plane

New technologies can be represented graphically according to their cost and effectiveness on a cost-effectiveness plane (figure 3.2). The origin represents zero additional costs and zero additional effects, respectively. The region above the horizontal axes represents higher costs and the region to the right of the vertical axes indicates increased effects (Morris et al, 2007). This plane shows those interventions, which are cost-effective, i.e. which are eligible for reimbursement by the healthcare system, and those that are not.

Figure 1.1: Cost effectiveness plane illustrating reimbursable region



Adapted from (Black, 1990)

In figure 3.2, a straight line passes through the origin, where cost is equal to benefit. The gradient of this line is dependent on the threshold limit of the ICER. This is the maximum cost a healthcare provider will pay for 1 QALY. It is also referred to as the maximum willingness to pay (WTP) threshold i.e. the maximum WTP for 1 QALY. This will vary from country to country. The line divides the plane into cost-effective (right half) and non-cost-effective (left half) sections. The ICER for the new technology can be plotted onto the plane. Depending on the position, the new technology may be accepted or rejected for reimbursement by the healthcare provider (Black, 1990). As stated in section 1.2.2 (page 31), assessment of cost-effectiveness needs to be compared to an external standard.

1.2.7 Decision Making in the UK

As described earlier, NICE is the body in the UK, which assesses HTA reports - the evidence of clinical and cost effectiveness of new technologies - and makes recommendations about whether and in what circumstances the technology should be used. NICE has to make decisions across different technologies and disease areas. It is therefore crucial that all analyses of clinical and cost-effectiveness adopt a consistent approach. NICE has defined a 'reference case' (table 1.1) that specifies the methods considered appropriate. The methods of HTA and appraisal by NICE are summarised in the *'Guide to the methods of technology appraisals'* (NICE, 2008).

In summary, the judgements on cost-effectiveness made by NICE are influenced by the following factors:

- The strength of the supporting clinical-effectiveness evidence
- The robustness and appropriateness of the structure of the economic models, in particular, whether the model reflects the decision problem at hand and the uncertainties around the assumptions on which the model is based
- The plausibility of the inputs into, and the assumptions made, in the economic models
- The preferred modelling approach is one that accounts for all of the economic evidence submitted
- The range and plausibility of the ICERs generated by the models reviewed
- The likelihood of decision error and its consequences

NICE decides if a technology is cost-effective based on a threshold range (NICE, 2008). Technologies with an ICER below £20,000 ($33,000, €23,000)[*] per QALY gained are recommended for reimbursement. Technologies with an ICER between £20,000 and £30,000 ($49,000, €34,000)[*] per QALY gained need other factors to be present to favour acceptance of the technology and technologies with an ICER above £30,000 per QALY gained need strong additional arguments favouring treatment.

[*] Currency conversion conducted using www.xe.com. Correct as of 04/11/10

Table 1.1 NICE Reference Case for estimating clinical and cost-effectiveness

Element of HTA	Reference case	Position statement
Defining the decision problem	The scope developed by NICE	Estimating clinical and cost effectiveness should begin with a clear statement of the decision problem. This will require a definition and justification of the technologies being compared and the relevant patient group(s) to be treated. These characteristics should be consistent with the Institute's scope for the appraisal.
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	
Perspective on costs	NHS and PSS	The perspective on outcomes should be all direct health effects, whether for patients or, when relevant, other people (principally carers). The perspective adopted on costs should be that of the NHS and PSS. Technologies for which a substantial proportion of the costs (or cost savings) are expected to be incurred outside of the NHS and PSS, or which are associated with significant non-resource effects other than health, should be identified during the scoping stage of an appraisal. In these exceptional circumstances, information on costs to other government bodies, when these are not reflected in HRQL measures, may be reported separately from the reference-case analysis. The intention to include such data will normally be agreed with the DoH before finalisation of the remit.
Perspective on outcomes	All health effects	
Type of economic evaluation	Cost-effectiveness analysis	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.
Synthesis of evidence on outcomes	Based on a systematic review	The objective of the analysis of clinical effectiveness is the production of an unbiased estimate of the mean clinical effectiveness of the technologies being compared. The analysis of clinical effectiveness should be based on data from all relevant studies of the best available quality and should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes, comparison with relevant comparators, and measures of both relative and absolute effectiveness with appropriate measures of uncertainty.
Measure of health effects	QALYs	For cost-effectiveness analysis, the value of health effects should be expressed in terms of QALYs for the appropriate time horizon. The measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.
Source of data for measure of HRQL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. An annual discount rate of 3.5% should be used for both costs and benefits. When results are potentially sensitive to the discount rate used, consideration should be given to sensitivity analyses that use differential rates for costs and outcomes and/or that vary the rate between 0% and 6%.
Equity weighting	An additional QALY always has the same weight	An additional QALY should receive the same weight regardless of any other characteristics of the people receiving the health benefit.

Source: (NICE, 2008)

1.2.8 Uncertainty in Economic Evaluations

In addition to the reference case, it is also necessary for the HTA report to provide evidence of the uncertainty and limitations associated with the clinical and cost effectiveness evidence. Uncertainty may arise from missing data, imprecise estimates, or methodological controversy. Consideration of any uncertainties and consideration of the possible consequences of an uncertain decision for the NHS, is essential prior to any recommendations on the use of the technology (NICE, 2008).

Uncertainty in economic evaluation can exist around a number of areas:

1. Structural uncertainty – when constructing a model there is potential for selection bias in the inputs to the model, for example, the representation of different pathways of care.
2. The choice of data sources to inform key parameters, i.e. the sources of estimates for costs and benefits.
3. The precision of the key parameters, i.e. the uncertainty associated with the mean parameter values.

To appreciate the uncertainties and limitations of the economic evaluation the evidence and rationale of any assumptions made in the model, along with the data sources used, must be clearly documented (NICE, 2008). It is recommended that mean values are reported along with the distribution around the mean and sensitivity analysis is used to reflect the implications of any uncertainties around parameter estimates (NICE, 2008).

Sensitivity analysis is a way of exploring uncertainty in the results of economic evaluations. Sensitivity analysis examines the effect on the result of using different assumptions around the parameter estimates. There are different types of sensitivity analysis, these are summarised below.

1. Univariate analysis - one way simple sensitivity analysis – each parameter is varied individually to isolate the consequences of each parameter
2. Scenario analysis – Multi-way simple sensitivity analysis - two or more parameters are varied at the same time and overall effect on the results is evaluated

3. Threshold sensitivity analysis – the critical value of parameters above or below which conditions of the study will change are identified
4. Probabilistic sensitivity analysis – probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation). NICE recommend this method as the preferred approach when it is necessary to provide distributions around the mean.

1.2.9 Limitations of economic evaluation

In some circumstances, the identity of the recipient group, (for example, the elderly) may be an important factor in assessing the social desirability of a service or programme. Although it has been suggested whether differential weights be attached to the value of outcomes accruing to special recipient groups, this is not normal procedure. Rather, an equitable distribution of costs and consequences across social groups is viewed as a competing dimension upon which decisions are made. Finally it is important to remember that an evaluation of any sort is itself a costly activity i.e. it is worth considering whether economic evaluations should be subject to economic evaluations (Drummond et al, 2005).

1.3 Using Health Economics at the Supply Side

The aim of this thesis is to help the RM industry reduce the risk of investing in a new technology that once developed is unlikely to be reimbursed by the healthcare providers. As I have already stated the RM industry has had difficulties translating RM products from laboratory bench to patient bedside and the failed attempts have been largely due to insufficient marginal effectiveness delivered for marginal costs incurred.

The adoption of new technologies is determined (at least in part) by its cost-effectiveness. CEA is typically conducted from the demand side i.e. after the product has been developed, using parameter estimates made available from direct studies. At this stage if the product is deemed not to be cost-

effective and thus not appropriate for reimbursement it can lead to commercial failure, as was seen with the first TE products that reached the market.

This thesis is inspired by the idea that health economics could reduce the risk of commercial failure by helping to inform investment decisions and indicate which products have the greatest potential. By conducting CEA at the supply side i.e. early stage development, when effectiveness is unknown, at key stages throughout product development, predictions about the probability of the product being sufficiently affordable can be established and could prove significant in persuading third party payers, patients and investors of its value (Archer et al., 2005;Williams et al, 2005). However, unlike conventional CEA, in the case of a technology yet to be developed, or in early stages of development, the very nature of the product is uncertain and no effectiveness studies have been conducted. I propose a simple approach, which I term the headroom method, to the challenge of conducting supply side analysis. The headroom method is designed to help healthcare manufacturers avoid misguidedly investing in those technologies that are very unlikely to be cost-effective. The headroom method is described in further detail in chapter 3 (page 65).

This thesis concerns the application of health economics in decision making at the supply side and hence builds on the premise that there is a need for such an approach. The underlying idea is that adoption of new technologies is determined (at least in part) by its cost-effectiveness and manufacturers and investors would be well advised to take a view on how their projects are likely to be assessed in the procurement of healthcare. Clearly, this only applies as far as health economics really does enter the frame when such procurement decisions are made. This differs around the world but I discern a trend of increased use of explicit cost effective models to inform health procurement decisions while recognising that this methodology is perhaps most influential in England and Wales, through the operations of NICE. However, I also discern a growing tendency to follow this pathway in many other jurisdictions. Likewise, there is an increasing tendency for journals to publish CEA (see chapter 2, section 2.5.1, page 51) and they presumably do this because or in response to growing recognition throughout the world, of the concept of opportunity cost and hence the need to inform decisions through health economics.

The Headroom Method in this thesis has been applied using reimbursement thresholds applicable to a UK setting. These values were selected as the UK, through NICE, has been more transparent than most other countries in clarifying the range where the threshold limit lies. However, any threshold value deemed to be appropriate by the manufacturer and investor can be applied. Although, it should be noted that the value of applying these methods at the supply side is dependent on the planned technologies being aimed at the third party (an organisation other than the patient (first party) or healthcare provider (second party)).

In the next chapter I review the literature to ascertain the purpose of conducting early economic evaluation and, what, if any, methodologies exist for conducting health economic analysis at the supply side before going on to outline my own approach to the problem of conducting CEA when effectiveness is unknown.

CHAPTER 2 HEALTH ECONOMICS AT THE DEVELOPMENT STAGE: A LITERATURE REVIEW

2.1 Introduction

Health economic evaluation, the assessment of healthcare technologies based on costs and effectiveness, has rapidly grown in popularity since the 1990's (Shemer et al., 2005). This has been driven by a worldwide increase in the demand for healthcare coupled with limited healthcare resources in relation to supply. As cost-effectiveness of a new technology demonstrates value for money, economic evaluation plays an increasing role in reimbursement decisions.

Investing in healthcare innovation is risky business with the potential for large gains but also substantial losses. The financial viability of the innovative activities is dependent not only on scientific and medical progress, but is also critically reliant on the costs and returns of new drug development. With high R&D costs, good choices make the difference between success and failure so it is worth spending resources, time, and effort in establishing a reasonable way of choosing successful projects (Senn, 1996). In essence, health economics can not only help inform on the future economic viability of the product but can also help rationalise product development decisions (DiMasi et al., 2001).

2.2 Objectives

In this chapter, I examine the literature to identify the following:

i. The origins of economic evaluation of healthcare technologies;
ii. The purpose of early economic evaluation in the healthcare industry;
iii. The methodologies proposed to conduct early economic evaluation of new healthcare technologies.

I did not expect to identify literature relating to early economic evaluation within the RM industry, as this is a new healthcare industry. Instead, I included literature relating to early economic evaluation in the more mature pharmaceutical or medical device industries. Finally, I discussed whether the reasons and methodologies identified relate to the RM industry.

2.3 Search Strategy

I conducted a review of the literature using the search strategy shown in table 2.1. I identified literature through a search of the electronic database PubMed *(*www.ncbi.nlm.nih.gov/pubmed/), Google Scholar, and the Cochrane Library. All papers found in the search were assessed on their abstract content, and where there appeared to be relevant information, the full paper was scrutinised and relevant references sourced. Any articles not available online were sourced through the University of Birmingham's libraries or the British library, when necessary. My search uncovered a recent review article by Hartz and colleagues (Hartz et al., 2008), which reviews the contribution of economic evaluation to decision making in early phases of product development. I have used this as a basis for my review, updating Hartz's review where applicable.

Table 2.1: **Search Strings**

Search	Term	Yield
1	Economic evaluation AND new technolog* AND Invest*	75
2	Investing AND new technolog*	20
3	Economic evaluation AND emerging Medical Technolog*	5
4	Economic evaluation AND investing in medical technology	3
5	Emerging Medical Technolog* AND cost effectiveness analysis	3
6	Economic evaluation AND product development	491
7	Economic evaluation AND early product development	36
8	health economics AND product development	849
9	health economics AND early product development	53
10	regenerative medicine AND economic evaluation	16
11	regenerative medicine AND cost effectiveness analysis	8
12	tissue engineering AND cost effectiveness analysis	15

2.4 Summary of Findings

Health technology assessment (HTA) has been around since the 1970's but has rapidly grown in popularity over the last two decades due to concerns about unproven technologies, rising costs of new technologies and a rise in consumer expectations and demands. These drivers have put healthcare purchasers under increasing pressure to provide value for money over alternative clinical practice. As a result, the healthcare industry now considers cost-effectiveness as the fourth hurdle to market, after safety, efficacy, and quality (Shemer et al, 2005).

Traditionally, new technologies have been evaluated at the demand side, as a one off exercise by decision makers to decide whether to purchase the technology. As the health service decision makers think this way, the manufacturers have started to respond by looking at the technologies in the same way and providing the necessary evidence required by the decision makers, which, if in favour of cost-effectiveness can be also be used as a marketing tool. The demand side has driven the supply side. The timely application of economic evaluation in the product development process can provide the manufacturer with a vast amount of useful information, not just on the future economic viability of the new product (Pietzsch et al., 2008;Shemer et al, 2005). A search of the literature identifies six potential benefits of early economic evaluation, along with five methodologies for conducting such an evaluation. However, the manufacturers may not have the resources to conduct such complex health economic modelling. Based on the findings of this review I found that there is a need for a simple approach to the problem of conducting CEA, when the availability of clinical and economic data is limited, for use by SME's.

2.5 Main Results

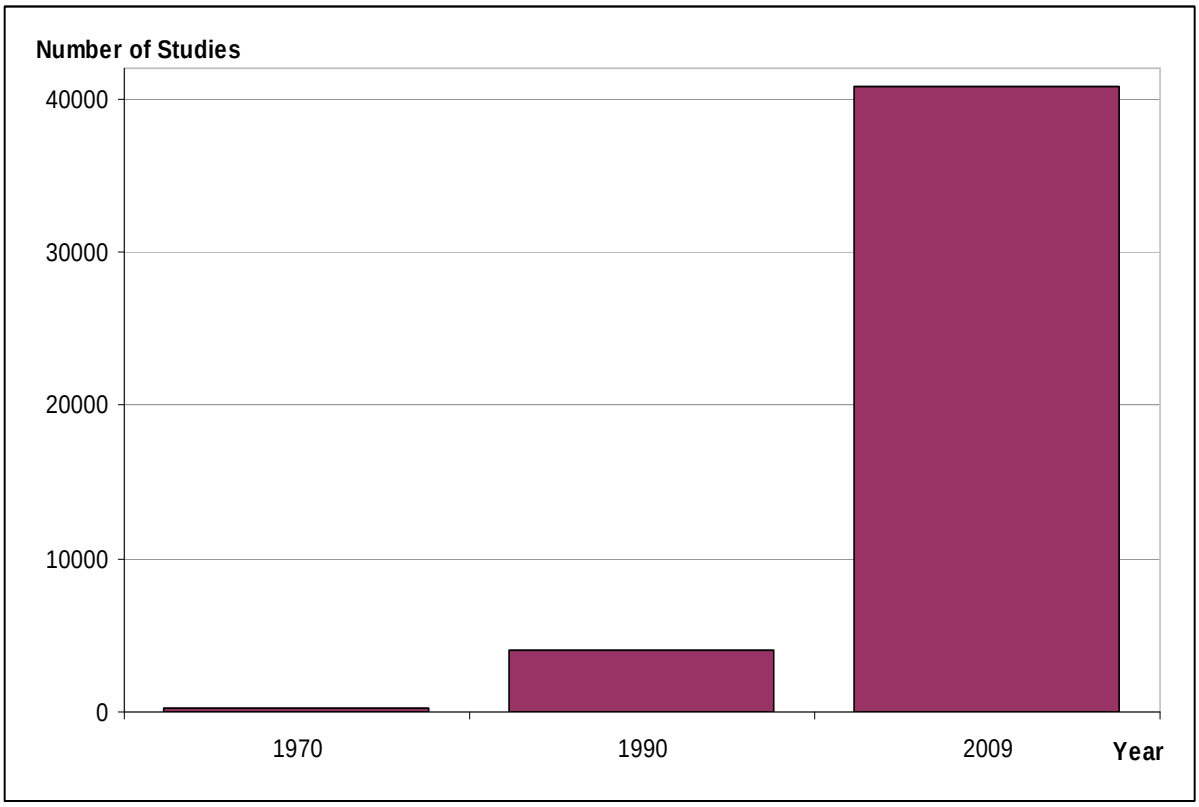
2.5.1 Health Technology Assessment at the Demand Side

Background

The term HTA was first used in the US in 1967, and in 1972 the congressional office of technology assessment was established (Banta, 2003). At this time, the definition of technology assessment was "a comprehensive form of policy research that examines the short- and long- term social consequences of the application or use of technology" (Banta, 2003). Also in 1972, a landmark in the development of HTA came in the form of a book published by Cochrane (Banta, 2003), "*Effectiveness and Efficiency: random reflections on health services'*" (Cochrane, 1972), this became a milestone in the effectiveness revolution. Cochrane identified the scarcity of evidence of effectiveness in health care and strongly advocated the randomised control trial (RCT) as the solution (Stevens et al., 2003). In 1992, the first Cochrane centre opened in the UK with the aim of developing a database of evidence on which to base decisions. Since then the collaboration has grown to include 15 centres in 12 countries (Banta, 2003). The Cochrane collaboration has had a big impact in the development of evidence-based health care (EBHC) – the process of linking evidence to healthcare practice, with the aim of improving quality and effectiveness of patient care.

The healthcare field has become one of the principal applications of CEA and the number of studies conducted continues to increase. This was illustrated by Eisenburg (Eisenberg, 1992). Using only the search terms "drug " and "economics", he found that in 1970 there were 68 published cost-effectiveness studies but by 1990 this had grown to 687 (Pausjenssen et al., 1998). Since the 1990's, the growth in cost-effectiveness studies has been ever more rapid. Using the PubMed database I conducted the same search as Eisenburg and found that in 2009 there were 40776 published studies (however, using PubMed, I found that there were 219 published articles in 1970 and 4067 in 1990) (figure 2.1). This simple search demonstrates the rapid growth of CEA in the last two decades as well as its importance today in the assessment of healthcare technologies.

Figure 2.1: A graph to demonstrate the increase in the number of cost-effectiveness studies over the last four decades



Number of published articles found when using only the search terms "drug" and "economics".

The Case for HTA

HTA works to influence health policy. It is closely linked to EBHC and CEA. It can be defined as the provision, to healthcare decision makers, of high quality research information on the cost, effectiveness and broader impact of health technologies, where health technologies are all interventions offered to patients (Stevens et al, 2003). Similarly to EBHC and CEA, HTA has also grown in popularity over the last two decades and three main forces have driven these developments (Stevens et al, 2003):

1. Concern about the adoption of unproven technologies – many interventions were seen to be under-researched and not based on robust science
2. Concern about cost-containment - there are increasing numbers of new technologies and the unit costs of these new technologies are much higher than those they replace
3. Inexorable rise in consumer expectations and demand

HTA in Practice

Currently, new technologies are evaluated at the demand side, as a one off exercise by decision makers who decide whether to purchase the technology. Traditionally, market access for manufacturers was ensured once the product passed three regulatory hurdles – safety, efficacy, and quality. However, the three drivers discussed above have put health care purchasers and budget holders under extreme pressure to provide value for money over alternative clinical practice (Paul et al., 2001).

Many countries have now established national technology assessment centres that use HTA to make purchasing and reimbursement decisions. In the UK, this agency is NICE. The NHS HTA programme provides the scientific information on clinical and cost-effectiveness that NICE requires to determine whether technologies should be encouraged into, or discouraged from, routine clinical practice. Although not the first – Australia and Canada were the pioneers of this process - NICE is one of the most influential of all healthcare technology assessment agencies around the world, and in contrast to other agencies NICE are much more open in their review process (Paul et al, 2001).

HTA (and CEA) will continue to be important as the need to contain costs and reduce unjustified variations in clinical practice and health service provision mean future decision makers need more, not less, high quality information on treatment impact (Stevens et al, 2003). Next, I investigate the growing interest in early HTA.

2.5.2 Health Technology Assessment at the Supply Side

As discussed previously, currently, the HTA process is applied at the demand side, to existing technologies i.e. licensed technologies. However, evaluating new technologies earlier in the development cycle has started to attract attention (Hartz et al, 2008). Manufacturers have started to look at their technologies in the same way as the decision makers in order to make better investment decisions. Since the final commercial success of a proposed product will be largely determined by a cost-effectiveness analysis, it is sensible to conduct such an analysis at the outset. The dilemma when it comes to the assessment of innovative medical technologies in the early stages is that the available

evidence of clinical and cost-effectiveness is still lacking or only available to a very limited extent. A full assessment can only be undertaken when enough relevant data is available, but at that point of time, the technology is often already in a stage that can no longer be considered experimental or emerging (Hartz et al., 2009). Pietzsch and colleagues provide a useful summary of the similarities and differences of a classical HTA, conducted after a technology has been developed, versus an early HTA, conducted during technology development (table 2.2).

Table 2.2: Similarities and differences between classical HTA and early HTA

	Classical HTA	Early HTA
Aim	Assess safety, effectiveness and cost-effectiveness profiles of a new technology	Assess (likely) safety, effectiveness and cost-effectiveness profiles of a new technology
Decision Support	Decision-support for **regulators, payers, and patients,** about market clearance, payment, and usage of a technology	Decision-support for **manufacturers and investors** about design and management of a technology, as well as regulatory and reimbursement strategy
Available Evidence	Usually evidence from clinical studies performed with the new technology	Evidence from early bench and animal testing, and from previous generations of the technology
Influence on technology performance	Limited or no influence on clinical performance of a new technology	Potentially significant influence on (future) clinical performance of a new technology

Adapted from Pietzsch et al, 2008

i. Early Economic Evaluation

Introduction

In 1997, Sculpher (Sculpher et al., 1997) advocated that economic evaluation should not be a one off activity during late phase development but should begin with an early developmental stage and progress through development as the innovation matures and moves into routine clinical practice. This was later corroborated by Langley (Langley, 2004) who advocated that health economic activities should be linked directly to each phase of technology development.

Early economic evaluation can be defined by the limited availability of clinical and economic data (Vallejo-Torres et al., 2008). Sculpher (Sculpher et al, 1997) proposes it should take place once the basic science has been investigated. It should focus on the systemic review of costs and effectiveness

of the current practice, which the new technology seeks to replace. An estimate of the likely range of the differences in cost and effectiveness between innovation and cost of practice can be calculated. The aim of early economic evaluation is to assess the extent to which current practice is less than effective and estimate an 'effectiveness gap'. If the existing practice is highly effective, there is limited scope for the new technology to be cost effective, unless it can offer a clear cost advantage. If the current practice is ineffective for a large proportion of patients, or if it is associated with significant side effects, there will be potential for the innovation to represent good value for money, even if it is more costly.

Langley (Langley, 2004) refers to early economic evaluation as "the foundation health economic assessment". He suggests this should involve defining the disease state, providing an epidemiological profile, reviewing the health economics literature, undertaking a preliminary treatment pattern analysis to identify principal pathways, providing pooled clinical analysis of comparator therapies to identify end-points, evaluating treatment guidelines, undertaking preliminary assessment of treatment costs, pricing options, and developing a preliminary business opportunity.

The Case for Early Economic Evaluation

1. Strategic Research and Development (R&D) Decision Making

Most healthcare technology R&D is a long, costly, and risky undertaking. The cost of development increases as a technology progresses through development phases. In the pharmaceutical industry, it is common for a number of drugs to be in development at any one time. Many will be unsuccessful, but the few that may be successful must pay for the rest (Senn, 1996). Therefore, it is important to determine early in the product development whether the expected returns on their successful products will outweigh their expected R&D costs. The pharmaceutical industry has also reported that early economic evaluations can be used to guide the selection of promising compounds and identify potentially safe and effective doses and dosing regimens (DiMasi et al, 2001;Miller et al., 2005).

2. Pre-clinical preliminary market assessment

This assessment includes the investigation of disease state, target population and epidemiological factors as well as associated costs and current treatments to picture disease impact (Hartz et al, 2008). Costs and effectiveness of available therapies have to be assessed, the less effective the current treatments are, the higher the potential for a new therapy to be cost-effective (Sculpher et al, 1997). This can be achieved through a review of the literature. The results of this assessment provide a benchmark for the minimum performance required and a forecast of market potential that can be used in a business opportunity assessment (Hartz et al, 2008;Langley, 2004).

3. Go/no-go decisions, identification of potentially successful projects

As previously discussed, the pharmaceutical industry often receives their profits from a small number of products, and it depends on these blockbusters to subsidise the unsuccessful products. Data from phase I and phase II clinical trials can be fed into the business opportunity assessment and serve as a basis for R&D priority setting and "go/no-go decisions" (Hartz et al, 2008;Langley, 2004). This will help to determine whether development should continue into the more expensive phase III trials (Drummond, 1994). It is important to identify successful and unsuccessful projects as early as possible; the later a drug fails the more expensive that failure becomes. DiMasi (DiMasi, 2002) reported that 8% reductions in costs can be achieved if the decision to abandon is shifted from phase II to phase I and more if the decision to terminate is shifted from phase III to phase II or I.

<u>The Methods for Early Economic Evaluation</u>

1. Simple Deterministic Economic Modelling

Based on the work by Sculpher and Langley (described above), this type of modelling serves three functions, firstly, to synthesise the available clinical and economic evidence, secondly, to provide a useful framework to analyse various scenarios, and thirdly, as an interface to external decision makers (Hartz et al, 2008). However, this early modelling has its drawbacks, primarily the scarcity and uncertainty of data. Here, data is sought from the literature, expert opinion, or early clinical evidence. However, this data is often from studies with small sample sizes, short follow-up times, and unrepresentative participants and study settings, which do not reflect routine practice.

An example of this method has been demonstrated by Craven and Colleagues (Craven et al., 2009), who have devised a simple Excel spreadsheet tool based on a basic decision tree model. This tool is designed as a decision aid for estimating the cost-effectiveness of specific medical device innovations in the early stages of product development, and for use by the non-expert health economist. The tool is provided in a spreadsheet package consisting of instructions, data input sheet, interactive decision tree, cost-effectiveness plane chart and financials (a breakeven analysis sheet, which includes selling price, predicted market share, unit manufacturing cost and non-recoverable expense). The user enters data onto the data input sheet. Each parameter requires a value as well as a range of minimum and maximum possible values, which automatically populate the decision tree and produce a resulting ICER. The tool can also assist with sensitivity analysis on the ICER. The authors provide three example applications of this tool but acknowledge that further work is required, noting the difficultly between balancing the generalisability of the decision tree and the need to keep the model simple.

2. Probabilistic Economic Modelling

Bayesian methods can be defined as the explicit quantitative use of external evidence in the design, monitoring, analysis, interpretation, and reporting of HTA (Spiegelhalter et al., 2000). These methods are based on Bayes' theorem of:

i. A prior distribution or belief about the value of a quantity of interest (for example, a treatment effect) based on evidence not derived from the study under analysis, with;
ii. A summary of the information concerning the same quantity available from the data collected in the study (known as the likelihood), to yield;
iii. An updated or posterior distribution of the quantity of interest (Spiegelhalter et al, 2000).

Bayesian methods allow for existing evidence, knowledge or beliefs about a parameter, formally expressed as a probability distribution, to be updated by new information as it becomes available from further studies, making explicit and quantitative use of all information available at that point (Vallejo-Torres et al, 2008). These methods directly address the question of how new evidence should change what we currently believe (Spiegelhalter et al, 2000). As the Bayesian framework provides an updated

knowledge valuable to decision makers it has been recommended for use in R&D, in particular to help inform phase II trial design and to support go/no-go decisions (Hartz et al, 2008).

More recently, Vallejo-Torres and colleagues (Vallejo-Torres et al, 2008) have argued for a commercial application of a Bayesian approach for medical devices. Medical devices, unlike pharmaceuticals, are fast changing technologies with short life cycles. The authors recommend that a Bayesian approach could support medical device development in three ways:

i. By allowing the estimation of potential cost-effectiveness to be part of the investment decision process and to avoid investing in a technology that could never be cost-effective;
ii. By supporting companies to prioritise between several competing possibly cost-effective concepts or prototypes;
iii. By identifying from early stages of development, those parameters that have the largest influence on the likely cost-effectiveness of the product to direct scarce research resources.

Vallejo-Torres and colleagues (Vallejo-Torres et al, 2008) suggest that Bayesian methods are used, following initial early economic evaluation (similar to that described earlier by Sculpher and Langley), as a means of combining new, but limited data with the beliefs previously identified. This allows for expert opinion based on extensive experience to influence the estimated outcome, which is of interest when the only available evidence is from small and uncontrolled trials (Vallejo-Torres et al, 2008). However, the cost in terms of time and resources of collecting this extra information is typically high, and companies will need to decide whether they should fund this additional research to reduce uncertainty.

Early Economic Evaluation in Practice

In 2001, DiMasi and colleagues (DiMasi et al, 2001) conducted a study to assess the emerging role of pharmacoeconomics in R&D decision making. Almost half (42%) of the thirty-one pharmaceutical companies questioned indicated that it is company policy to subject all products to pharmacoeconomic evaluation *at some point* during the development process (although, this also indicates that almost half have *no* policy to conduct economic evaluation on their products at any stage of development).

However, DiMasi found that over the past decade, pharmacoeconomic staff sizes had grown rapidly and this was expected to increase further as reimbursement approval becomes more dependent on such evidence. DiMasi and colleagues concluded that those companies that recognise the strategic value of pharmacoeconomic analysis and effectively integrate pharmacoeconomics into R&D decision-making processes would acquire important competitive advantages over those who do not.

This study was conducted back in 2001 and could now be assumed out-of-date. It would be interesting to see how things have changed in pharmaceutical companies. I expect that as pharmaceutical companies have grown, so have the health economics teams and as a result I would expect that economic evaluation per se, including early economic evaluation plays a larger role in R&D of new drugs. In addition, the size of many pharmaceutical companies would suggest that they have the resources to tap into the ever-expanding health economist consultancies.

However, the same cannot be said for the medical device industry. Recently, Vallejo-Torres (Vallejo 2008) and colleagues have reported that conducting health economic evaluations is not a core activity of most medical device companies, especially, not the smaller ones, such an evaluation, if undertaken is usually done as a one-off exercise at the late stage of development of new technologies. Most medical device companies operate some form of staged decision making development process that is regularly reviewed as the route to commercialisation is complicated by regulatory and reimbursement approval requirements (Vallejo-Torres et al, 2008). This has been supported recently by Craven and Colleagues (Craven et al, 2009) who conducted 12 detailed industry interviews as part of a wider programme of research (EPSRC MATCH programme) and found that few medical device companies, and no SME's, had used heath economics during product development.

ii. Modelling to Inform Clinical Trials

Introduction

As discussed in the previous section, early economic evaluation has a role in informing early strategic decisions, in selecting potentially successful products and assessing the potential market. This analysis is conducted during the pre-clinical stages of technology development i.e. before the

technology reaches humans. The next stage of development is the clinical trial. Economic evaluation can also be used to inform the development of future trial design and improve R&D resource allocation (Hartz et al, 2008).

The Case for Informing Clinical Trials

Economic evaluation can be used in clinical trial study design, particularly from phase II onwards (Hartz et al, 2008). Economic modelling in early stages can identify parameters such as choice of comparator, outcome parameters, endpoints, and health-related quality of life measures, to which cost-effectiveness is particularly sensitive. These crucial parameters can then be prioritised to ensure that appropriate data are collected for late-stage cost-effectiveness studies (Annemans et al., 2000;Chilcott et al., 2003;DiMasi et al, 2001;Sculpher et al, 1997).

The Methods used to Inform Clinical Trials

1. Value of Information (VOI) analysis

Founded on statistical decision theory, the underlying principal of VoI is to determine the value of obtaining additional information to support a decision. It can also provide insights into the variables in the model for which additional information would be most valuable (Hartz et al, 2008;Vallejo-Torres et al, 2008). VoI is based on the idea that information is valuable because it reduces costs of uncertainty surrounding a decision (Vallejo-Torres et al, 2008). VoI can be combined and updated with the Bayesian methodology to help identify the decision problems where the cost of uncertainty are highest, so that additionally gained information will be most valuable which can support R&D prioritisation decisions (Hartz et al, 2008).

Whether or not a company should fund additional research to reduce uncertainty relating to the reimbursement decision can be informed by means of VoI analysis, but this needs to be adapted to inform the value of that further information to the company, rather than the standard value to society of reducing uncertainty (Vallejo-Torres et al, 2008).

2. Clinical Trial Simulation (CTS)

Computer simulation of clinical trials uses mathematical synthesis to integrate simultaneously models of pharmacokinetic and pharmacodynamic drug action, disease progression, placebo effects, and patient variability (Hartz et al, 2008). The main objective is to increase drug development efficiency by improving trial protocols, maximising the probability to meet trial targets and enhancing quality of data gained. Different assumptions about parameters and intended trial design can be tested to detect weaknesses and limitations. CTS can help prevent trial failures and uninformative or unnecessary studies and can supply information otherwise unavailable for economic evaluation (Hartz et al, 2008).

How often are these methods used in practice?

There is a great deal of literature on VoI and this methodology has been demonstrated in an early assessment of second generation left ventricular assist devices (Girling et al., 2007) and in two UK pilot studies to establish the feasibility and requirements of using VoI analysis in health policy decisions (Claxton et al., 2004;Claxton et al., 2006). However, it is yet to be adopted by the healthcare purchasers.

iii. Modelling to Determine Price

Introduction

Price determination with regard to the assessment of future reimbursement and pricing schemes can help manufacturers and investors decide whether to continue with investment. It is assumed that a company will only develop a new medical technology if it has evidence that it will provide returns that are greater than the investment required to develop that technology and bring it to the market (Brown et al., 2007). The price that can be commanded and the volumes sold determine the returns that will be made on the initial investment (Brown et al, 2007). Pricing of a new technology should start early in development and is necessary for two reasons: firstly, to understand the customers value perceptions and secondly, to ensure a product yields a sufficient return on investment (Hartz et al, 2008).

The case for Early determination of Price

1. Assessment of Future Reimbursement

An economic evaluation can help manufacturers gain reimbursement (Drummond, 1994). Some suggest this is of most importance as third party payers have replaced the solo physician as the major purchaser in the healthcare market and they demand proof of value for money, to which the manufacturers must respond (Pausjenssen et al, 1998). However, an assessment of future reimbursement can also be used as a marketing tool for physicians and patients (Drummond, 1994).

2. Price Determination

The price of a new technology must match its clinical value to avoid an unfavourable reimbursement scenario (Hartz et al, 2008). An economic model can also help find suitable price ranges for products (Drummond, 1994). A preliminary evaluation of the cost-effectiveness in key market segments at different pricing scenarios, patient populations, and indications can be modelled, which can help identify gaps in the evidence needed for reimbursement (Hartz et al, 2008). It can also determine which clinical profile has to be attained for a given price to make a product cost-effective, or for given clinical and economic outcomes, to calculate the cost-effectiveness under different pricing scenarios (Hartz et al, 2008).

How often are these methods used in practice?

Current published articles on price determination are few and simplistic. Later in chapter 6, I discuss further, how supply side analysis can be used to determine future pricing strategies. Recently, a more sophisticated model on pricing has been produced by my colleague Alan Girling (Girling et al., 2010) .

2.6 Discussion and Conclusion

2.6.1 Industry Differences

The literature reviewed here is from the pharmaceutical and medical device industries. However, the market structure of these industries differs, and different still is the RM industry.

Medical device innovation is characterised more often by small, incremental steps than by large, technological leaps. The innovation process is sensitive to a variety of forces, including the availability of funds, the reactions of users and regulators, as well as market trends (Littell, 1994). Three-quarters of the medical device industry is comprised of SMEs and venture capital funding is critical for continued R&D innovation of smaller start-up companies (Littell, 1994). These small firms do not possess the resources or expertise to manage the uncertainty and resistance associated with innovation (Littell, 1994). This is a stark contrast to the large companies that make up the pharmaceutical industry, which have the resources to employ pharmacoeconomic teams. However, the time to market of a medical device can be as short as 18-24 months – very different to the 15-20 years of a pharmaceutical product.

A RM technology is more likely to be like a pharmaceutical product than a medical device product in terms of time to market. However, the RM industry is more comparable with the medical device industry in that it is comprised almost entirely of SMEs. SMEs have small staff numbers, therefore are unlikely to have designated health economists. In addition, they have limited funds, particular during early development stages, so have no capacity to employ healthcare consultants. It is necessary for SMEs to attract investment for further R&D but this is increasingly difficult if the company cannot provide evidence that their product is a sound investment.

Littell (Littell, 1994) wrote about the challenges for innovation in the medical device industry 16 years ago, however, this has relevance to the current state of the RM industry. The RM industry is comprised of SMEs and reliant on investment from venture capitalists but unlike the medical device industry, has the added challenges from the regulatory bodies, which is likely to add to the already high production costs of RM technologies. Biotech firms have already found that the costs of manufacturer for biologics are higher than for generic drugs. Like RM, these too are mainly developmental stage companies, most are not profitable, and the variance of such financial statistics is greater than for the pharmaceutical industry (Grabowski et al., 2006). If RM companies do not begin to conduct early economic evaluation, as the pharmaceutical industry has done, then those that manage

to reach market could find their product is not reimbursable, but many will find they are unable to attract further investment to pursue product development altogether.

2.6.2 Limitations with the Methodologies

Problems with early economic data stem from the fact that they cover only a relatively short period of time and are likely to be different in real-world practice, so that the conclusions drawn cannot be taken as “hard facts” (Hartz et al, 2009). This uncertainty has to be accounted for in the decision (Hartz et al, 2009) and there are various methods which can reduce this uncertainty. However, Bayesian methods are a controversial topic as they may involve the explicit use of subjective judgements in what is conventionally supposed to be a rigorous scientific exercise (Spiegelhalter et al, 2000). The main disadvantage of Bayesian methods and VoI analysis is that these approaches are complex to apply for those with no prior knowledge. The pilot studies have shown that it is not just the manufacturers that are unfamiliar with these methods but also the decision makers who are reluctant to base their decisions on such evidence (Hartz et al, 2008).

2.6.3 Conclusion

To date, it appears that across the worldwide healthcare industry, as a whole, most economic evaluations are conducted on products already launched. However, the interest in conducting early CEA is growing and gradually more CEA are being conducted prior to registration for marketing approval. As we have seen, if applied timely in the product development process, economic evaluation can provide the manufacturer with useful information on the future economic viability of the new product (Pietzsch et al, 2008;Shemer et al, 2005). The integration of health economics into the various stages of product development is essential to identifying, achieving, and maintaining an acceptable return on investment. Bringing in health economics at the last minute to try to achieve reimbursement is a recipe for disaster (Langley, 2004).

However, it is all very well stating that the RM industry should start conducting economic evaluations but how does a SME conduct such analysis when they have no pharmacoeconomics department. I foresee two options; firstly, they could employ the services of a consultancy firm to conduct such

economic evaluations, but with limited resources, this may not be possible; secondly, they conduct a crude economic evaluation themselves, to give insight to potential market and demonstrate in early stage product development whether such a venture is worth pursuing.

The following chapter describes my approach to the problem of conducting cost-effectiveness analysis at the supply side. Similar to the early economic modelling methodology described above, I will describe an approach that was published by myself and colleagues which has been termed the headroom method (Cosh et al., 2007). The headroom method is intended to help the healthcare industries reduce the risk of investing in a technology that, once developed, is unlikely to be cost-effective, and reimbursed by the healthcare providers. As an alternative to a full cost-effectiveness analysis, at least in the first instance, the headroom method estimates the maximum cost that a technology can be brought to market and still be considered cost-effective. This is a necessary step to attracting further investment and this approach is designed to be simple enough to be targeted for use by SMEs within the RM industry so, at least in the first instance, early economic analysis can be conducted without employing an expensive consultant. As development progresses and the company grows a consultant could be used to conduct the more complex further economic modelling as described in this chapter, or investment could be sought to employ a health economist.

CHAPTER 3 METHODOLOGY

3.1 Introduction

In a finite resource healthcare system, the cost-effectiveness of a technology can be compelling evidence for its adoption. It makes sense for a company developing a new technology to assess its potential cost effectiveness as early as possible in the development cycle, particularly when the new technology is likely to be high in cost, such as a RM technology.

Chapter 2 showed that cost-effectiveness is an important hurdle for a new healthcare technology to reach the market. Early economic evaluation has been advocated in the pharmaceutical industry for the last 10 years. The potential benefits of early economic evaluation were highlighted in chapter 2, and although the literature was in the context of the pharmaceutical or medical device industries, these remain applicable to the RM industry. It makes sense to select potentially successful candidates as early as possible and a number of tools have been investigated for this purpose. Unfortunately, many of these tools require extensive knowledge of health economics and modelling. Thus, I believe there is a gap for a method directed towards manufacturers to guide them through the process of conducting their own very early-stage cost-effectiveness analysis.

In this chapter, I describe the headroom method (Cosh et al, 2007), an approach to the problem of conducting health economic analysis at the supply side, under circumstances where effectiveness is uncertain or even unknown. I then describe the research methodology used in the thesis to apply the headroom method to real examples from the nascent RM industry, all of which are under active consideration for development.

3.2 The Headroom Method

3.2.1 The Origins of the Headroom Method

The Headroom Method arose from work on the use of economics to inform supply side decisions. The Headroom Method had an intellectual and practical provenance. From the practical point of view, the task prescribed by the sponsors of this research (EPSRC REMEDI Grand Challenge (EP/C534247/1) and the EU FP-6 STEPS (FP6-500465)) was to develop a suite of methods to assist manufacturers and investors to assess the health economic value of proposed healthcare technology developments. From the intellectual point of view, the task proposed the challenge of performing a CEA in the absence of effectiveness parameter values.

The formal approach to this challenge would be to construct a Bayesian prior and determine a distribution of cost effectiveness values over this prior in a standard manner. However, from a practical point of view, such an exercise represents a considerable undertaking and given the likely vague prior probability estimates, is bound to yield commensurately vague posteriors. Furthermore, a full implementation of such a model would have to take account of decision gates in the development pathway and hence calculation of option values. Thus, a pragmatic solution is required both to justify such an elaborated decision analytic model and to provide a methodology for industrial decision makers who are either unwilling or unable to commission a fully specified CEA.

It was discerned that both the practical and intellectual problem could be addressed by reversing the question that usually motivates a CEA, thus instead of asking the question;

"*What are the probabilities that a new proposed treatment will achieve different levels of cost effectiveness?*"

We ask instead the question;

"*How cost effective would the technology have to be to represent value for money in the health service?*"

To put this another way, the approach consists of establishing the cost effectiveness gap, or the "headroom", within which the technology could prove cost-effective. This methodology recognises that

the limiting case is defined by the epidemiology of the condition, most notably the effectiveness of the current best treatment and an optimistic assumption concerning the effectiveness of the new technology.

Specifying the above properties of effectiveness of existing treatments and the upper plausible limit of the effectiveness of the new treatment is not entirely straightforward. This thesis is concerned with this problem. Crucial to the understanding of the headroom method, however, is that this is a rapid method to provide insight that would otherwise not exist. Such insights include the possibility that there is no point proceeding further and that even a full CEA would not represent good use of resources. The method acts as some mitigation against the risk that new technology might be developed based on its technical merits rather than the human need it can address.

The headroom method is akin to a “back of the envelope” calculation and the counterfactual against which it should be judged is not a fully elaborated CEA over Bayesian prior probabilities but rather intuitive or ad hoc decisions that characterises the supply side of much of the device industry (Hartz et al, 2008).

3.2.2 The Headroom Method as a Framework for Investment Decisions

The headroom method, as previously described, is an approach to help industry avoid misguidedly investing in technologies that are unlikely to be cost-effective and reimbursed by the healthcare providers. It consists of a series of processes that should be conducted before substantial investments are made.

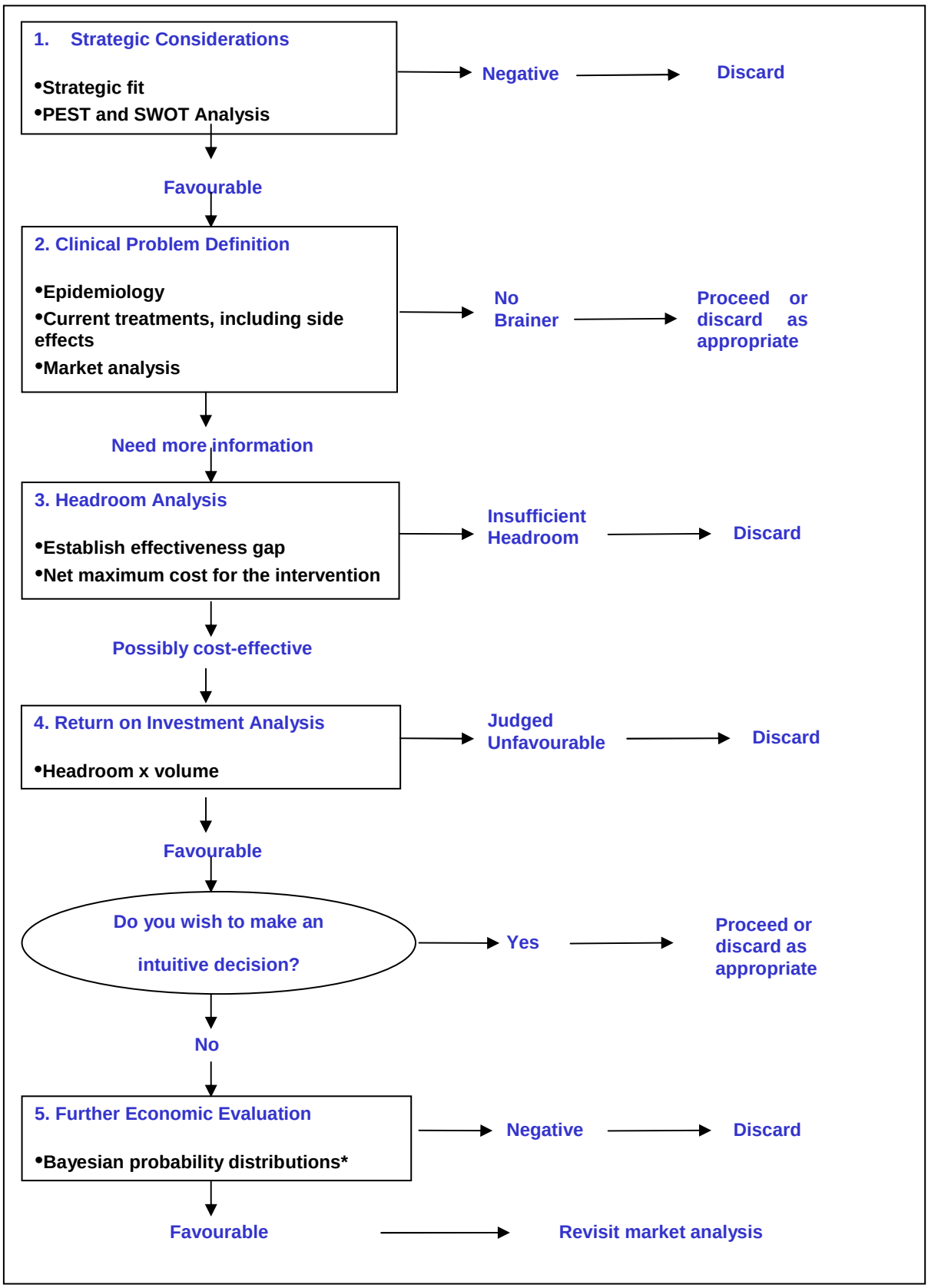
The headroom method is based on the principles of cost-effectiveness analysis and is conducted towards the upper end of the sensitivity analysis with particular reference to the effectiveness of the technology. In other words, it simply looks at the potential of a clinically defined market and can be used to estimate the maximum potential cost of the new treatment (including development costs and factoring in any health service savings). If this cost is too low i.e. if the incremental cost of the product could not realistically be held below this level, then investment funds should be channelled elsewhere.

Of course, the reverse is not true; the new technology might still fail despite adequate headroom. For example, it might turn out to be less effective or more expensive than hoped or better alternatives may emerge while the technology is being developed. The headroom method is designed to reduce the risk of embarking on an investment that is doomed from the outset.

This method fits into a broader decision framework, illustrated in Figure 3.1, which illuminates a situation that may otherwise be hard to fathom. In the remainder of this chapter, I discuss the steps of the decision-making framework in further detail and focus on the health economic concepts necessary to understand the key stages of the headroom method – stages 2 and 3 – defining the clinical problem and the headroom analysis itself.

I have produced a user guide of this methodology to enable SMEs to conduct this preliminary assessment themselves. This guide is shown in appendix 1 and is available for download from (http://www.haps.bham.ac.uk/publichealth/methodology/hes/).

Figure 3.1: Framework for investment decisions for new technologies



** discussed elsewhere (Vallejo-Torres et al, 2008)*

3.2.3 Strategic Considerations

An organisation needs to begin by addressing strategic fit issues and asking questions such as:

- *Does this technology fit with our skills and strategy?*
- *Who are our competitors?*
- *How will our decision influence competitor behaviour?*
- *What changes to the regulations are in the pipeline?*
- *Are similar/competing technologies about to be launched?*

Management tools, such as PEST (political, economic, social, technology) and SWOT (strength, weaknesses, opportunities, threats) analysis, exist for structuring and defining a business problem situation. This process may do no more than formalise existing knowledge. It will however provide rigour to the decision and exclude obviously futile schemes. At the very least, it reduces the risk of accidentally omitting important considerations from the deliberations.

With respect to regenerative medicine, however, there is an additional important question:

- *"What changes to the regulations are in the pipeline?"*

If the problem is not ruled out by strategic considerations, then the investigation should move to the next stage with a study of the clinical problem and an analysis of how the technology may help.

3.2.4 Clinical Problem Definition

In some circumstances, the decision to invest in a technology can be made without recourse to any formal method of evaluation. If an unmet clinical need can be identified and resolved, such as curing a common, chronic disease at low cost, then the decision makes itself. In 1895, when Roentgen's wife was persuaded to interpose her hand between his x-ray source and a photographic plate, he did not need a health economist to tell him he was onto a winner. These blockbuster discoveries come along only seldom. The cost effectiveness of most proposed new technologies is much more difficult to

predict. In such cases, it is important not to be carried away by enthusiasm for the technology per se or to over estimate the size of the potential market.

There is always a limit on how cost effective a new technology may be. The epidemiology and clinical features of the condition in question limit the potential benefit. All the conditions where a new technology may have an application should be examined in turn, at least to the point where it is clear there is a material clinical problem to be solved. It is important to be as specific as possible about the clinical problem. A clearly defined clinical need based on a clear understanding of the strengths and weaknesses of current treatment is crucial to the uptake of any new technology. It is essential to complete this prior to conducting the headroom analysis. This defines the effectiveness gap – the room for improvement in effectiveness between the current best treatment and that which the new technology might plausibly achieve. This issue was addressed in chapter 2. It was reported that a preliminary assessment of the market could be beneficial for forecasting market potential and providing a benchmark of minimum performance. In fact, in 1997, Sculpher (Sculpher et al, 1997) referred to the aim of early economic evaluation as the identification of the effectiveness gap.

This point may sound obvious but, in my experience, investors and even inventors typically have a very vague, even naïve, understanding of the clinical problem. Enthusiastic supporters of a new technology may fall into the trap of superficial epidemiological analysis, leading to an overestimation of market size and value. Table 3.1 below outlines the questions that will help establish a clear definition of the clinical problem. The majority of this information can be sought through a systematic search of the literature (further details can be found in section 3.3.1 at the end of this chapter, page 81).

Table 3.1: Defining the clinical problem

Questions	Definition
What is the technology?	Give a precise description of new technology being considered, including a description of any uncertainties. For example, in the field of regenerative medicine it is uncertain whether a tissue-engineered bladder will become re-innervated with nerves.
What is the disease/condition?	Give a precise description of disease and natural history. This includes analysis of disease sub-groups where the new technology may be more or less applicable. For example, there may be a greater need for tissue-engineered bone for fracture nonunion repair than for spinal fusion surgery to treat degenerative disc disease.
What is the prevalence and incidence of the disease/condition?	This information can be obtained through a literature search of published studies. Hospital episode statistics (www.**hes**online.nhs.uk/) can be a useful source of data on incidence. This data will need to be broken down by relevant sub-groups, since the effectiveness gap may vary widely by sub-group, as it does, for example in hernia repair.
What are the current treatments?	The current gold standard is the comparator for the new technology. However, new developments must also be reviewed as this may change the shape of the market. For example, the availability of bone morphogenic proteins is replacing the need for complicated bone scaffolds, especially those populated by living cells in vitro.
What is the effectiveness of current treatments?	The effectiveness, including any side effects and complications of the current gold standard treatment must be clearly described. Any side effects or complications, which could potentially be avoided by the new treatment, must be identified. For example, a tissue-engineered solution to repair complex hernias would avoid adhesions and infections, which result from current treatment.

3.2.5 Headroom Analysis

The headroom method simply looks at the potential of a clinically defined market. Instead of asking the conventional cost-effectiveness analysis question:

"*How cost-effective will the technology be?"*

I ask,

"Would it be cost-effective if it works as well as one would hope?"

In other words, optimistic assumptions are made about the incremental effectiveness of the proposed treatment over the best alternative. I then ask:

"At what cost would this new technology be cost-effective?"

The headroom method involves two key aspects:

1. **Establish the 'headroom' in effectiveness –** *the effectiveness gap*. This is the room for improvement in effectiveness between the current and the new treatment. This is essential but not always straightforward. The comparator should always be the current gold standard treatment for a specific condition, as only an improvement on this performance will support the reimbursement of a new technology. The current gold standard treatment should have been identified during stage 2 - defining the clinical problem.

2. **Calculate the headroom -** the *maximum incremental cost* (maximum additional cost compared to the current best treatment) of the new technology which could still be considered cost effective. This is based on optimistic but plausible estimates of effectiveness of the technology being assessed.

Estimating the effectiveness gap

The headroom is based on optimistic but plausible estimates of effectiveness of the technology being assessed. Of course, a developer will always have optimistic hopes for their product, but rather than blind faith, this method aims to concentrate the mind on a realistic upper limit. The degree of formality

used in eliciting these values is a matter for the decision maker(s) and dependent on the information and expertise available.

Having defined the clinical problem and its epidemiology (as described in stage 2) the simplest situation is to assume the outcome of the prospective treatment will be as good as the current treatment, and that there is no difference in mortality. In this case, the utility of the new treatment is assumed the same as the current treatment and only the period of time during which the utility values of the two treatments differ need be considered.

In other circumstances, when current treatment is suboptimal, an "effectiveness gap" (Sculpher et al, 1997), can be estimated. That is, for those conditions with treatments, which are ineffective for large proportions of patients, or have significant side effects, the maximum potential increase in effectiveness over current treatment may be used as the optimistic assumption. Here I calculate the effectiveness gap by subtracting the utility value associated with the current treatment from a utility value of 1 (perfect health). Since the true effectiveness of our new technology is unknown, the most optimistic scenario for the new treatment is assumed.

There are two steps required to calculate the effectiveness gap (maxΔQALY):

1. **Establish health utility associated with current best treatment -** At one extreme, they [the decision makers] may simply use personal judgement (uncommon). Alternatively health utilities can be identified in the literature or in the database of utilities held by TUFTS (Tufts Medical Centre, 2009). If not, the utility values will have to be established by conducting a primary survey using formal methods. Health utilities are described in further detail in section 1.2.3 (page 31).

2. **Estimate duration of improvement -** Once the improvement in health utility has been established the next step is to identify the maximum potential duration of the clinical benefit expected from the new treatment. If there is no difference in life expectancy, it is necessary only

to consider the period of time during which the health utility values differ. If there is likely to be a difference in life expectancy then this must be included in the calculation.

Using equation 1.1 (page 32) the max∆QALY can be calculated, which in turn can be used to calculate the maximum potential headroom associated with the proposed new treatment (see next section).

Calculating the Headroom

Quantifying the benefit of a treatment is an inherently uncertain process; even when the product is finalised, effects will vary from one population to another and there are limits to the precision with which effectiveness can be measured. These problems are much greater for a treatment that does not yet exist. At this stage, there are no head-to-head comparisons of the technology against an alternative and so effectiveness estimates rely on conjecture.

As previously discussed, there is always a prior limit to how cost effective a new technology may be – the epidemiology and clinical features of the condition in question limit the potential benefit. The headroom calculation is based on the most optimistic assumptions in the plausible range. If the new technology does not show cost-effectiveness under the most optimistic scenario then it would not show cost-effectiveness under less optimistic assumptions, such as reduced effectiveness or lower threshold.

The headroom is the maximum incremental cost for which the technology would still be considered cost-effective; this is calculated by rearranging equation 1.3 (page 40) into equation 3.1 below. You may notice that in this equation, 'ICER' is substituted by 'WTP threshold' this is for appropriateness.

Equation 3.1: max ∆Cost = WTP threshold x max ∆QALY

Where, ***max∆cost*** is the *headroom* – the maximum additional cost of new treatment over the comparator (current gold standard) for the new treatment to be deemed cost-effective. It is important to note that max∆Cost is the net difference in cost [to the health service] of the proposed new technology.

It includes any net savings or costs to the health service along with the costs of the product itself; ***WTP threshold*** *is the maximum threshold for the incremental cost effectiveness ratio*. As the headroom method is based on optimistic assumptions, I assume the most optimistic WTP threshold for the UK NHS of £30,000 ($49,000, €34,000). Equation 3.1 can also be expressed as max ΔCost = £30,000 x max ΔQALY; ***maxΔQALY*** is the *effectiveness gap* - the maximum additional benefit that could be obtained from the new treatment, this must be estimated before I calculate the headroom (see next section).

If there is little or no chance that the technology could be marketed at a price that would keep the headroom (maxΔCost) below the cost effectiveness threshold, then the technology should not attract further investment. Since the ICER is calculated at the most optimistic end of the probability distribution for effectiveness, the headroom method is a CEA at the optimistic end of a conventional sensitivity analysis.

However, it is important to revisit economic analysis with new information regarding the likely effectiveness of the technology as it becomes available. A headroom analysis is primarily useful as a barrier to misguidedly investing in those technologies, which are unlikely to be cost effective. As research progresses, estimates of costs and effectiveness can be updated, the headroom recalculated or further economic analysis conducted. Continual economic assessment at various stages of the development cycle will enable more accurate predictions of a product's cost-effectiveness and hence of its market potential (Archer et al, 2005;Williams et al, 2005).

3.2.6 Return on Investment

For those technologies that appear to have headroom, continuing development and investment would appear to be justified. However, a viable new business requires substantial volumes to repay the return on investment. At this stage, our interest is focussed on whether or not this technology has the potential to succeed once it has been brought to market. Return on investment may be affected by the rarity of a condition or because it occurs, only in economies unable to support high cost remedies.

Although future development costs will contribute to the decision to continue or abandon, these will largely be based on factors internal to the organisation rather than the technology itself and, as such, are not discussed here.

The revenue that can be generated is a function of headroom, the likely cost, and volumes, represented by equation 3.2.

Equation 3.2: $R = (\max\Delta \text{ Cost} - C') \times V$

Here, R = revenue, Δ Cost = Headroom, C' = expected cost of production and V = cases per year. The expected profit however, must be discounted over a time horizon chosen to reflect the company strategy.

3.2.7 Further Economic Evaluation: Bayesian Probability Distributions

The steps outlined in this chapter may show that a technology could be profitable. It is a necessary but not sufficient basis on which to proceed. Two further possibilities exist.

1. The investor can make an intuitive decision to invest based on the outcome of the headroom method.
2. The investor can perform more formal value of investment analysis (Bayesian probability distributions, see below for more details).

This latter option was discussed earlier in section 2.5.2, page 53 and involves testing a more 'realistic' prior probability than that taken from the most optimistic end of the plausible range. In the case of bladder cancer, for example, it would not be assumed that the RM solution would work as well as hoped in all cases – some may undergo contracture, or leak and hence require further surgery, for example. In that case, the calculation of 'headroom' can be repeated over a range of probability estimates for effectiveness and a threshold determined where the technology would not be cost-

effective at its likely cost. To put another way, the probability that the technology would come into routine use would be derived. Next, 'expected' effectiveness contingent on this scenario would be calculated. The expected 'headroom' under the assumption is then calculated along with the consequent revenue streams in a 'Value of Investment' decision.

This methodology has been illustrated elsewhere (Girling, 2007) using left ventricular assist devices (LVADs), particularly second-generation LVADs used as a destination therapy in end stage heart failure. Early cost-effectiveness assessments, based on first-generation devices, were not encouraging. A Bayesian model was used to assess the future cost-effectiveness of second-generation LVAD therapy. Here, it was clear that the cost-effectiveness of the therapy depends on substantial improvements in survival being achieved. However, the lack of RCTs meant there was great uncertainty surrounding the survival benefits of second-generation LVAD therapy. A way forward was found by exploring the expert opinions of those best able to assess the likely effectiveness of the current generation of devices; in this case cardiac specialists with experience of this form of treatment. This assessment was done by eliciting Bayesian prior distributions for the survival parameters (using the elicitation procedure described by Garthwatie (Garthwaite et al., 2005)). The priors were used in two ways: first to estimate the probability that second-generation LVADs will turn out to be cost-effective when their full benefits are known, and second in a Bayesian value-of-information analysis to address the secondary question of whether further trials in this area should be conducted. The results found that second-generation LVAD therapy is unlikely to be cost-effective at current UK QALY valuations of around £30,000 ($49,000, €34,000) if the device costs as much as the £60,000 ($97,000, €68,000) previously reported. Nevertheless, the figures were not inconsistent with an ultimately favourable assessment of second-generation LVAD therapy if the cost of the device were to fall in the future. Therefore, assuming a plausible device-cost of around £40,000, a future trial would represent value for money in a UK setting. Value of information is used here as a form of sensitivity analysis to explore the decision-value of parameter uncertainties in a cost-effectiveness model.

From my perspective, there are two main differences between a Bayesian exercise (supply side analysis) and the HTA (demand side analysis):

i. The decision the model is designed to inform is not a dichotomous decision. In standard HTA the decision is dichotomised: to adopt or not to adopt the technology. However, at the design stage the decision is three way: develop, abandon, or develop to the next decision gate.

ii. Often there is no direct evidence of effectiveness. The effectiveness parameter must therefore be captured by expert opinion through a Bayesian prior. This Bayesian prior can then be used in Value of Investment analysis, as for Value of Information.

The use of further economic evaluation and Bayesian probability distributions goes beyond the scope of this thesis, but I feel it is worth mentioning that there are subsequent steps, as outlined in the framework (figure 3.1, page 70), that can be followed in order to build up a more comprehensive picture regarding the probability of reimbursement. The headroom method is designed to be the first step from which a crude estimate of likely cost-effectiveness can be obtained. It is the investor's decision whether to continue to conduct economic analysis with more formal models. This work is currently ongoing under the EPSRC MATCH (multidisciplinary assessment of technology centre for health) programme led in Birmingham by Richard Lilford and Alan Girling.

3.3 Research Methodology

In the following chapters, I demonstrate the headroom method with real examples from the nascent industry of RM. The technologies I discuss have passed the strategic consideration stage and are all under active consideration for development.

In chapter 4, I will investigate the potential for a TE technology for use in the repair of urethral strictures and bladder resection following cancer. In chapter 5, I will investigate the application with the greatest potential for a TE solution for the repair of abdominal wall defects. In chapter 6, I demonstrate supply side analysis using an example based on a RM alternative to bone for use in bony defects. Finally, in chapter 7, I conduct supply side analysis on RM treatments for articular cartilage defects of the knee.

The selection of the clinical applications to evaluate in this thesis was two-fold. Firstly, the research teams (EPSRC REMEDI GRAND Challenge (EP/C534247/1) and EU FP6 STEPS (FP6-500465)) had particular applications for which they sought an economic perspective. For example, bone defects were an interest in both the REMEDI and STEPS projects. Secondly, requests were received from SMEs, who had an interest in a particular area, for example, cartilage defects. In most cases there were overlapping academic and commercial interest.

3.3.1 Literature Searches

My first task for each application was to define the clinical problem. This distinguishes conditions with small headroom for improvement from those where headroom is larger. For each application, I review the clinical epidemiology of the potential conditions where a RM solution may be considered and document the strengths and weaknesses of the current treatment options. This is essential risk assessment for anyone considering investing their time or money in a particular RM method.

The majority of this information can be sought through a systematic search of the literature. I begin by obtaining basic clinical and epidemiological information from textbooks. Then I attempt to seek a recent systematic review of the topic. Where no review was available, a search of primary literature is performed. I identify literature through the search of electronic databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.co.uk/), and the Cochrane Library (http://www.cochrane.org/). All papers found in the search are assessed on their abstract content, and where there appeared to be relevant information, the full paper and its references are scrutinised. Any articles not available online are sourced through the University of Birmingham's libraries or the British library, when necessary. In addition, I conducted a search of NICE guidance (http://www.nice.org.uk/guidance/index.jsp) to obtain information on cost and effectiveness of current treatment and to identify whether there are any other potential treatments for the clinical condition in question.

My second task is to identify the most propitious applications for a RM technology and compare clinical effectiveness (with special emphasis on HRQoL and utility) and costs of current treatment.

Clinical effectiveness is ascertained from the review of the literature. Costs are ascertained, where available, from the literature, the Department of Health national schedule of reference costs (Department of Health, 2006b;Department of Health, 2007) and National tariff (Department of Health, 2006a). All cost data is given in pounds sterling, US dollars, and Euros (currency conversions were conducted on 04/11/10 using www.xe.com). Finally, I conduct cost-effectiveness analysis and apply the headroom method.

3.3.2 Measuring Preferences

Having defined the clinical problem, the next step is to calculate the 'headroom' for improvement in effectiveness (the effectiveness gap) between the current best treatment and that which the new technology might plausibly achieve. In the headroom method, effectiveness is measured in terms of QALYs, as advocated by NICE (NICE, 2008). As previously described (section 1.2.3, page 31), a QALY takes account of both the *quantity* and *quality* of life years that might be gained through a new technology.

Estimating the duration of time spent in a particular health state is usually straightforward. However estimating the utility based-HRQL of the health state is more difficult. A health utility can be identified in the literature or in the database of utilities held by TUFTS (Tufts Medical Centre, 2009) as in chapters 6 and 7. However, when these sources are exhausted it is necessary to elicit utilities by means of primary studies, as in chapters 4 and 5. A number of formal methods have been developed for this purpose and these are described in chapter 1 (section 1.2.4, page 33).

In the case of urogenital defects (chapter 4) and abdominal wall defects (chapter 5), I elicited the utility values were elicited using formal methods, as there were no utility values reported in the literature. For the purposes of this thesis, I decided to use direct methods, where practically and logistically possible, to elicit the required utility values (based on the findings from Arnold & colleagues (Arnold et al, 2009)). Time trade-off (TTO) was the direct method selected (advocated by NICE (NICE, 2008)), in conjunction with the WTP approach. I designed a questionnaire based on the TTO and WTP approaches. For the TTO question, each interviewee was asked what amount of time they would be

willing to sacrifice, from 10 years of remaining life, to avoid the negative side effects of the condition described to them. In WTP, participants were asked how much they would be willing to pay for a treatment that would relieve them of the described health state. Combining the response from both WTP and TTO questions allowed me to calculate each individual's WTP per QALY.

Next, it was necessary for me to decide whom to ask. Ideally, with regard to this thesis, I would have preferred to elicit the utility values directly from patients. However, due to logistic, time and ethical constraints this was not possible. Instead, I used a proxy for the patients, for example, general population, and clinicians. I asked the proxy what they personally would trade to avoid a health state that has been described to them. It has been reported that there is a risk of discrepancy between the HRQL estimates from patients and the general population (Ubel et al., 2003) and this might exaggerate the impact of disease on the HRQL, as patients tend to rate their health states higher than the general population, leading to a lower estimate of these benefits of health care than would have been estimated by a proxy.

In chapter 4 and 5, I used three questionnaires, two of the three questionnaires were completed by clinicians of relevant speciality to the condition in question, and the final one was completed by a sample of the general public. Further details describing how these questionnaires were completed, are included in the relevant corresponding chapters.

3.3.3 Clinical Engagement

A considerable proportion of this thesis is concerned with defining the clinical problem. Although, as previously described, this information was primarily sought from the literature, it was necessary and appropriate to expand on this by seeking expert opinion. Expert opinion was sought from clinicians specialising in an area relevant to the clinical application under consideration. Clinicians were found through Professor Lilford's existing local network of clinicians, via recommendation from members of the EPSRC REMEDI and EU-FP6 STEPS projects, or through attendance at conferences. Clinicians were used to seek additional information, or clarification of the clinical problem, used to help describe the health state when writing the questionnaires, and, as described, to elicit utility values by

completing the questionnaires. Clinicians were engaged through email, teleconference, face-to-face meetings, and conferences. In addition, at the invitation of an orthopaedic surgeon with whom I had been in contact, I also had the opportunity of observing a spinal fusion operation.

3.3.4 Industry Engagement

Another necessary part of defining the clinical problem is engaging with the RM industry to ensure the information on the current state-of-the-art in RM technology is up-to-date. There were a number of industry partners (mostly SMEs) involved in both of the projects, which sponsored this work. In some cases, the industry partners were a substantial member of the consortium and were influential in steering, which clinical applications were to be assessed. For example, for the abdominal wall defects work I worked closely with the French TE firm, Sofradim - an industrial partner for the EU-FP6 STEPS project. In addition to these industry partners, I also established several other industry links, external to the projects, although contact was made through networks established in the projects. The industry partners were engaged through face-to-face meetings, teleconference, and conferences/meetings.

In the following four chapters, the headroom method is demonstrated using real examples from the nascent industry of RM; urogenital defects, abdominal wall defects, bone, and cartilage.

CHAPTER 4 COST EFFECTIVENESS ANALYSIS AT THE DEVELOPMENT PHASE OF TISSUE ENGINEERED BLADDER AND URETHRA

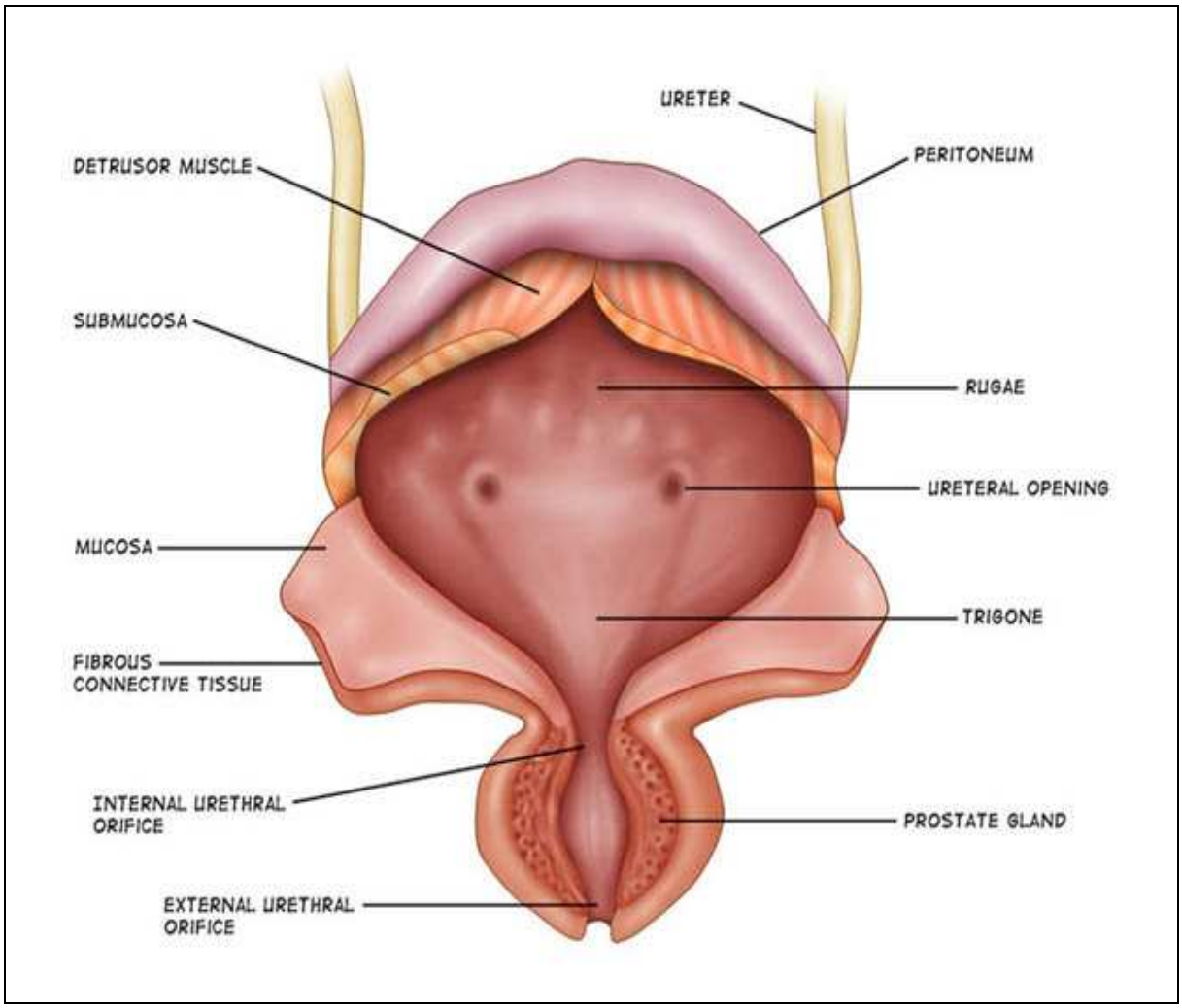
4.1 Introduction

In this chapter, I evaluate TE products designed for use in the field of urogenital medicine. Firstly, I consider a TE bladder, inspired by Atala's work (Atala et al., 2006) and research at the French firm, Sofradim. Secondly, I consider a relatively simple application to bridge urethral gaps using a TE solution. The aim of this chapter is to investigate whether a TE solution to bladder and urethra defects may provide a higher patient HRQL and whether this approach may be cost-effective.

The bladder and urethra are components of the urinary system (illustrations of the structures of the bladder and urethra are shown in figure 4.1). The bladder, also known as the urinary bladder, is a hollow muscular organ that serves to collect urine excreted by the kidneys prior to disposal by urination, a result of bladder contraction. A number of conditions can cause damage to the bladder, resulting in decreased bladder capacity. Currently, bladder capacity is increased via a bladder cystoplasty. This operation increases bladder capacity by directly increasing the volume of the bladder through the stitching of a section of detubularised ileum (small intestine) into the bladder. A TE solution aims to replace the use of ileum in this procedure.

The urethra is the tube that conveys urine from the bladder to be discharged from the body. Medical problems associated with the urethra result from birth defects or physical damage later in life. Defects of the urethra are currently repaired via an urethroplasty, an operation to repair the urethra wall using tissue grafts and genital flaps to restore function. A TE solution aims to replace the use of tissue grafts in this procedure.

Figure 4.1: Structure of a bladder and urethra in males and females



Source: http://www.mdaillustration.com/charts.html

4.2 Methods

4.2.1 Overview

The clinical conditions where TE urethral tissue could have potential are identified and the strengths and weaknesses of the current best treatment documented. The extent to which it was plausible that a TE solution may offset the problems associated with the current treatment, without introducing new hazards was ascertained. This enables the identification of the precise clinical problem that a TE solution is supposed to solve before applying the headroom method.

4.2.2 Defining the Clinical Problem

A former colleague from within my Public Health team* conducted the initial literature review in 2006. I conducted subsequent searches to update the review where applicable in 2009. Literature was sourced using the search strings shown in appendix 3 and the search strategy outlined in section 3.3.1 (page 81). Additional online articles were sourced, when necessary, from e-Medicine (http://emedicine.medscape.com/), the world health organisation (WHO) website (http://www.who.int/en/), and Urology Today (http://www.urotoday.com/). The literature was supplemented by discussions with tissue engineers from Sofradim and FAB (two European TE companies known to us through the European Union Framework Package 6 STEPS (a systems approach to tissue engineering) project), and Tengion (an American company seeking to exploit Atala and colleagues breakthrough research) (Atala et al., 1993;Atala et al, 2006;Oberpenning et al., 1999)).

Analysis of the clinical problem revealed two potential indications for TE urogenital tissue: cystoplasty for bladder carcinoma and urethroplasty for urethral strictures. The duration and severity of the clinical effects were documented along with the costs of the current treatment. As previously described in chapter 3, to conduct the headroom analysis it is necessary to obtain a utility-based HRQL score associated with the clinical effects of the current treatment. Following a comprehensive literature

* The project grants, which subsequently funded my PhD, commenced before the start of my PhD and a former research associate conducted this work prior to the start of my PhD.

search, no existing utility-based HRQL scores associated with a cystoplasty or urethroplasty procedure were found so a questionnaire was devised to elicit the utility scores associated with each. The methods are described below.

Eliciting Health Utility

The utilities were elicited using TTO and WTP methods (section 3.3, page 80). In TTO, each interviewee was asked what amount of time they would sacrifice from a 10-year life expectancy, to avoid the negative side effects of the procedure in question, and have perfect health for the remainder of their life. The TTO values were converted into utility scores using equation 4.1.

Equation 4.1: HRQL = TTO ÷ t

In WTP, each participant was asked how much they would pay for a treatment that would relieve them of the described health state rather than them having to endure it for six months. Combining these responses with those from the TTO question made it possible to calculate each individual's WTP per QALY.

The questionnaire design, data collection, and data entry were all conducted by a former colleague Guy Freeman, assisted by two medical students doing work experience. More details on the questionnaire design are described in appendix 2 and a copy of the questionnaires is provided in appendix 4.

It was not possible to obtain the health utility directly from patients due to insufficient time to get ethics approval and the logistics and time required to arrange face-to-face interviews. In addition, due to time and cost constraints, it was not possible to obtain a fully randomised sample of a national or international population. Instead, the utility scores for cystoplasty and urethroplasty were elicited from a sample of urologists and the general public, respectively. The urethroplasty questionnaire was completed by a sample of the general public, selected, at random, from within the public health building at the University of Birmingham (unknown to those collecting the data) and from Birmingham

city centre (outside Birmingham Central Library and New Street Station). The cystoplasty questionnaire was completed by a sample of specialist urologists. Sixteen urologists from within the Birmingham and Black Country area were identified by using the NHS website to identify hospitals and the individual hospital websites to identify the urologists. The reason for the geographical restriction was that face-to-face interviews were planned. However, this became difficult to organise, clinicians were not willing to give up their time, or their availability was very limited. This would have delayed the completion of the analysis. Instead, it was decided that a questionnaire would be emailed to each urologist and those who did not respond within two weeks were followed up by a phone call.

I conducted data analysis using Excel. The key results (those necessary to complete the headroom analysis) are presented in the relevant sections within this chapter and the supplementary results are presented following the corresponding questionnaire in appendix 4. The supplementary analysis includes the analysis of potential covariates such as, familiarity with buccal mucosa donations, familiarity with the time-trade off method and cost-benefit method, and the location where the interview took place.

4.2.3 Cost-Effectiveness Analysis

Using the data collected by Guy Freeman, I calculated a utility-based HRQL score associated with the clinical effects of cystoplasty and urethroplasty. Using these utility scores, I populated equation 4.2 and calculated the headroom - the maximum cost for which a TE solution for cystoplasty and urethroplasty would be considered cost effective.

Equation 4.2: $\max\Delta Cost = \max\Delta QALY \times$ willingness-to-pay threshold

Where, $\Delta Cost$ is the maximum headroom, $\Delta QALY$ is the maximum change in benefit measured in QALYs and willingness-to-pay threshold is the reimbursement threshold of £30,000 ($49,000, €34,000).

4.3 Treatment

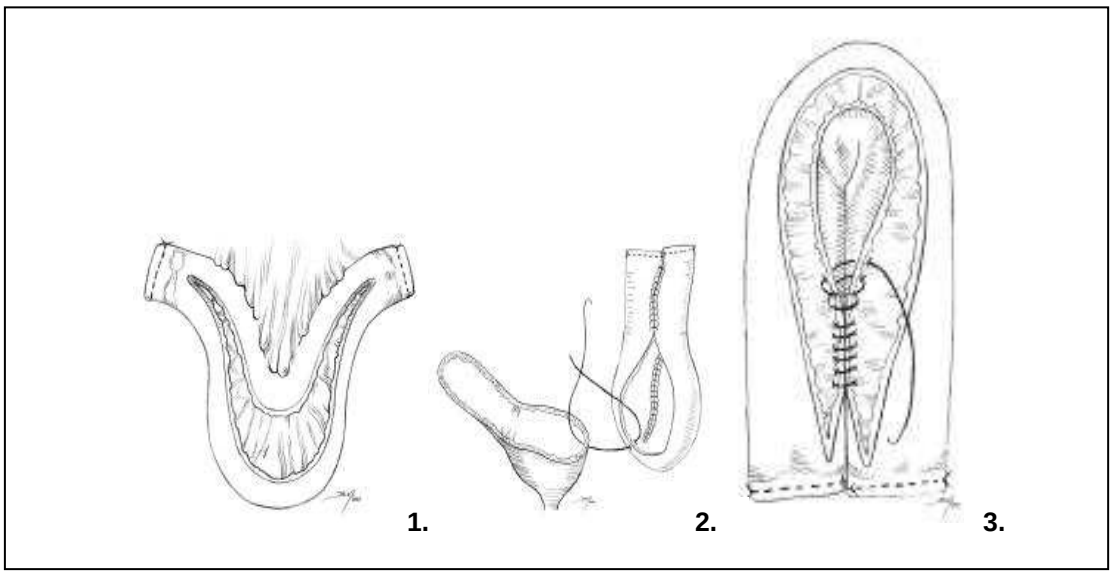
4.3.1 Current Treatment

Bladder Cystoplasty

When bladder capacity or function has been substantially reduced current surgical intervention is by means of a cystoplasty procedure. Complete bladder excision (radial cystectomy) is usually accompanied by urinary diversion, a procedure necessary to maintain the flow of urine via a reroute from the normal pathway through an opening in the abdominal wall. Substitution cystoplasty entails the creation of a new reservoir from bowel segments (ileum or colon), and has been advocated following radial cystectomy, provided the urethral sphincter (ring of muscle) and its innervation can be preserved. In such cases the urethras are implanted directly into the bladder substitute and voiding is achieved by the application of abdominal pressure (Venn et al., 2000). Currently, the vast majority of instances of substitution cystoplasty follow a radical cystectomy for invasive cancer (Venn et al., 1998).

Partial excision (partial cystectomy) of the bladder, where the trigone (a triangular region of the internal bladder sensitive to expansion of the bladder, (figure 4.1)) is spared, is usually accompanied by augmentation cystoplasty (operation to increase size of bladder). Augmentation cystoplasty involves material being stitched into the bladder, with the conventional patch being a section of detubularised ileum (small intestine) on a vascular pedicle (a tissue containing arteries and veins) (Duel et al., 1998;Greenwell et al., 2001). This procedure is often termed an ileocystoplasty and is illustrated in figure 4.2.

Figure 4.2: Cystoplasty procedure



1: *The segment of ileum chosen for augmentation is isolated on an adequate mesentery (membrane which connects intestine with the dorsal wall of the abdominal cavity) and re-establishes intestinal continuity. Close the ends of the segment with suture, and open the antimesenteric surface (the part of the intestine that lies opposite the mesenteric attachment).* ***2:*** *Fold the segment of ileum and sew it upon itself. This detubularises the segment, reduces enteric (intestine) contractions, and maximizes the volume that the segment contributes to urinary storage.* ***3:*** *Anastomose (communicate or connect) the augmenting segment to the prepared bladder. Perform a wide-mouthed anastomosis (surgical connection of two normally separate hollow organs) to ensure that the augmentation is spherical. If this is not carried out properly, the augmenting segment can exist only as a poorly draining diverticulum (sac-like structure) that is prone to complications.*
Image reprinted with permission from eMedicine.com, 2009.
Available at: http://emedicine.medscape.com/article/443916-overview

Urethroplasty

Urethral surgery is required for strictures (narrowing of urethra) and other urethral abnormalities such as epispadias (congenital defect resulting in urethral opening on the upper side of the penis) and hypospadias (congenital defect resulting in urethral opening on the bottom of the penis).

In a substitution urethroplasty, a section of the urethra is surgically opened or removed, and the urethra is repaired with a tissue graft or flap. Historically, skin graft has been the most widely used substitute for urethroplasty, but since the early 1990's this has being largely superseded by buccal mucosa, the tissue making up the inner lining of the cheek (Bhargava et al., 2004). The impression that buccal mucosa is becoming the gold standard as a urethra substitute was gleaned from the literature and confirmed following discussion with urologists. Buccal Mucosa, like urethral tissue, is a

mucous membrane, with similar physical and immunologic properties (Fichtner et al., 2004). It has high elasticity (Barbagli et al., 2003), compatibility with a wet environment, and is non-hair bearing (Bhargava et al, 2004). However, the use of buccal mucosa has disadvantages relating to the donor site.

4.3.2 State of the Art in Tissue Engineering

TE solutions for bladder and urethra are aimed at improving the quality rather than the quantity of life. They offer an alternative to the use of bowel for cystoplasty following partial or (more rarely) radial cystectomy and to the use of skin grafts for urethroplasty.

TE material should be “amenable to surgical manipulation and reconfiguration, able to distend at low pressure with no spontaneous pressure generation, of low malignant potential, have no role in absorption or secretion of urinary constituents and should not produce mucus” (Duel et al, 1998;Greenwell et al, 2001). In addition, the need for functional innervation should be added to this list.

TE grafts can be one of two types *in vivo* or *in vitro* (Schultheiss et al., 2000). *In vivo* grafts are based on a natural but acellular matrix, which harnesses the bladder’s natural regenerative abilities by providing a structural platform for cells to migrate and proliferate, resulting in the ingrowth of smooth muscle tissue and mucosa (Shokeir, 2002). Urogenital grafts need to replicate bladder or urethral elasticity. Current acellular matrices include porcine SIS (Pig Small Intestine Submucosa) and BAMA (Bladder Acellular Matrix Allograft). These acellular grafts have been investigated in a variety of mammalian models (Kropp et al., 1995;Kropp et al., 1996;Nuininga et al., 2004;Piechota et al., 1998a;Piechota et al., 1998b;Probst et al., 1997;Probst et al., 2000;Sutherland et al., 1996;Vaught et al., 1996) where the graft was found to acquire microscopic and macroscopic properties of bladder vestibule. Unfortunately, not all the cited studies agree on the ability of the graft to acquire normal function and innervation.

The *in vitro* approach creates an entirely artificial bladder or urethra graft and uses both urothelial and smooth muscle cell types in a scaffold. Bladder grafts using this approach have been cited in a number of animal models (Atala et al, 1993;Oberpenning et al, 1999;Wang et al., 2006) demonstrating successful formation of tissue-specific architecture comparable with natural bladder (Atala et al, 1993;Oberpenning et al, 1999;Wang et al, 2006) as well as increased bladder capacity (Oberpenning et al, 1999). The implantation of TE bladders into dogs (Oberpenning et al, 1999) has demonstrated that the bladder did become innervated and was able to void normally, but this possibility remains untested in humans. Atala et al (Atala et al, 2006) reported that seven patients with upper motor neurone bladder lesions treated with a TE bladder had improved symptoms with fewer infections, reduced immunogenic reaction and no electrolyte disturbance. However, the patients were not able to void spontaneously, which the authors ascribe to the underlying neurological condition. However, TE regeneration of the complicated trigone area of the bladder is not currently on the horizon and thus remains but a distant hope.

Both acellular and cellular grafts are promising solutions to the problem of finding the ideal urogenital tissue replacement. However, the question remains whether the advantages of cellular grafts would be enough to offset the significantly higher costs incurred by using an *in vitro* option. The acellular approach, if successful, may provide the economic “off the shelf” solution. Although, the resultant bladders following an *in vivo* approach are smaller than those obtained by *in vitro* approach. TE approaches for bladder cancer follow excision of substantial amounts of normal bladder tissue. Since a procedure is needed to make good large defects, it could be assumed that *in vitro* techniques would be necessary. In the case of urethra, however, a smaller defect has to be bridged and here both *in vivo* and *in vitro* solutions for this application are considered.

4.4 Potential Indications for a TE solution

Four types of indication for a urogenital TE intervention were discerned following the literature review. These were:

i. Dysfunctional bladder (e.g. neurological disease and detrusor instability)
ii. Small contracted bladders (e.g. bilharziasis)
iii. Bladder carcinoma
iv. Urethral strictures

The first three are potential indications for bladder augmentation and the last for urethroplasty. Now I consider the above four indications in turn to define the potential value for TE.

4.4.1 Dysfunctional Bladders

The dysfunctional bladder reduces the functional capacity of the bladder and can create a strong urge to urinate. It can be diagnosed as either idiopathic detrusor instability (spontaneous and uninhibited contraction of the detrusor muscle during bladder filling) or neuropathic bladder dysfunction (malfunctioning urinary bladder due to neurologic dysfunction), depending on whether or not a known underlying neurological condition is present. Detrusor instability has a number of synonyms and closely related conditions, including overactive bladder, urge incontinence, detrusor hyperreflexia, irritable bladder, spasmodic bladder, and unstable bladder. Detrusor instability is the more common condition with a prevalence rate of 17% among Europeans aged 40 and over (Milsom et al., 2001). This condition is controlled by drug or behaviour therapy, where this fails bladder augmentation can be used. The operation deactivates the “unstable” muscle by cutting through the detrusor close to the urethral meatus (Ivil et al., 2002). Cystoplasty then restores capacity to the now-stabilised bladder.

Neurological conditions (such as Myelodysplasia (myelodysplastic syndromes (MDS), Myelomeningocele (Spina bifida), or multiple sclerosis (MS)) often affect bladder function causing either incontinence or inability to void (Jamison et al., 2004;Mingin et al., 2003). This is the case in 95% of ambulatory Spina bifida sufferers (Mingin et al, 2003) and 80% of MS patients (Henze, 2005);

amounting to 211,000 and 65,000 patients in the USA and UK, respectively**.** A surgical intervention for neurogenic bladder is only considered if the patient does not respond to any form of medical therapy and if bladder symptoms are extremely incapacitating. This is the case in less than 10% of Myelodysplasia sufferers (Mingin et al, 2003).

The niche for a TE solution for dysfunctional bladders is likely to be very small, for the following three reasons:

1. Many patients with intractable over-activity are either unsuitable or unwilling to undergo a major operative procedure involving incision into “normal” bladder tissue for a functional lesion that is not life-threatening (Harper et al., 2004). If the bladder is not excised, lesions may re-grow with recurrent symptoms. Furthermore, if re-innervation occurs in TE bladder then symptoms are likely to recur even if bladder is excised.
2. Patients with idiopathic detrusor instability have been documented to respond poorly to surgical interventions (see section 4.5, page 100).
3. The advent of a new intervention, botulinum toxin (or botox), is likely to further curtail the role of adventurous surgical solutions, both for detrusor instability and for neurological lesions. Botulinum toxin targets the neuromuscular junction of the detrusor where it interferes with synaptic function. As a result, the detrusor enters a state of flaccid paralysis and bladder overactivity is significantly reduced. Treatment can then be carried out via minimally invasive surgery. The majority of studies into this treatment were in an outpatient setting and reported good results with no tachyphylaxis (decrease in response to drugs) (Harper et al., 2003;Radziszewski et al., 2002;Reitz et al., 2004;Schurch et al., 2000).

4.4.2 Small Contracted and Inflammatory Bladders

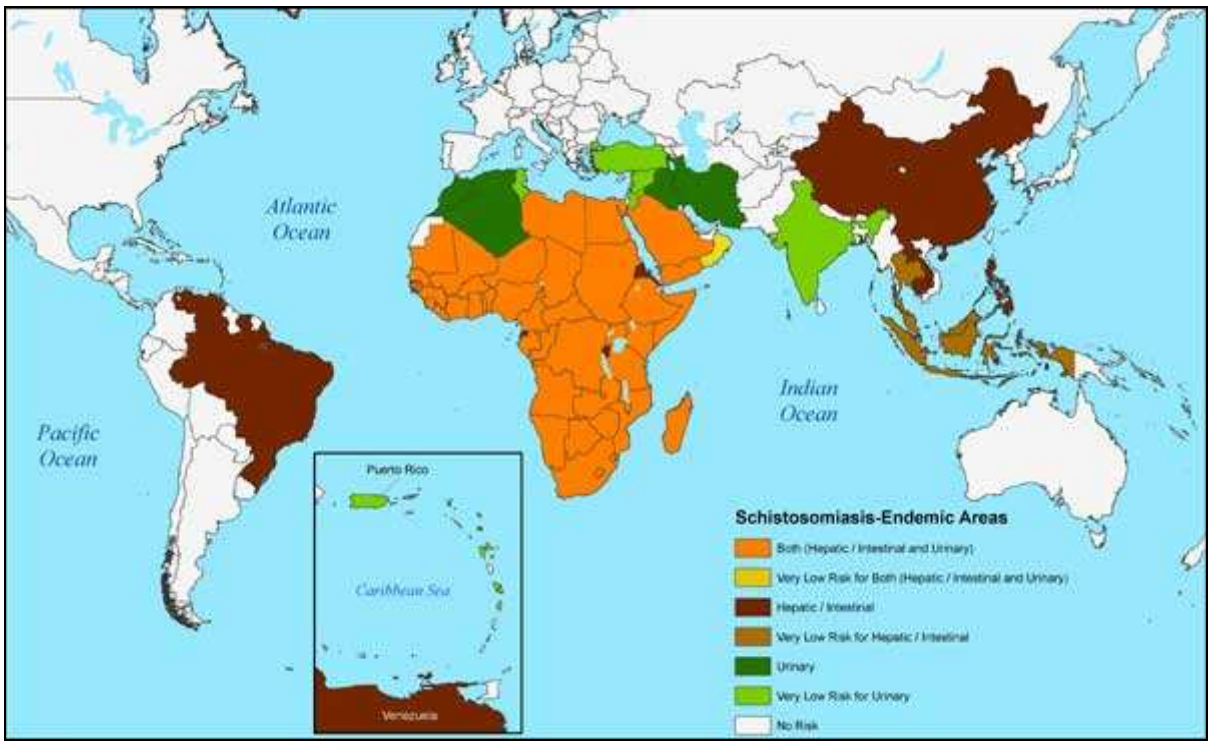
The two most common conditions that lead to small contracted bladders indicating cystoplasty are bilharziasis and tuberculosis. Bilharziasis (or schistosomiasis) is a parasitic condition that is commonly found in the tropics and sub-tropics. The responsible species, *Schistoma haematobium*, is endemic in 54 countries in Africa and the Middle East, and the WHO reports that 18 million sufferers endure the consequent bladder wall pathology (WHO, 2006). This presents a huge potential market, but

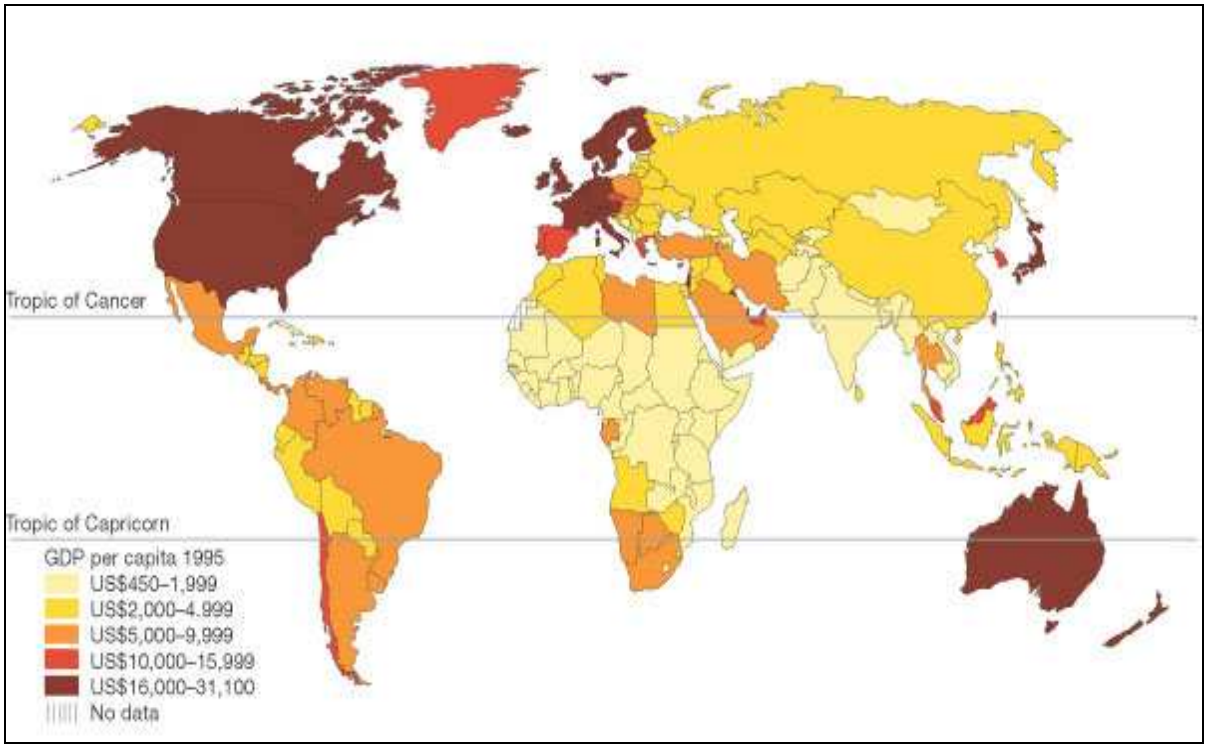
unfortunately not a viable one, with most countries where the condition is endemic having low GNP per capita (figure 4.3).

Tuberculosis has a total incidence of 439,000 in Europe and more than 8,810,000 worldwide. Recent resurgences in incidence are mainly attributed to opportunistic infections accompanying AIDS. Treatment for the tubercular bladder is by augmentation cystoplasty; indeed, the technique of augmentation cystoplasty was popularised in the context of tubercular contracted bladders (Couvelaire, 1951). However, the incidence of augmentation cystoplasty for tubercular contracted bladder is now very low and has been cited in single figures worldwide; therefore, it is sceptical that there would be any substantial market for this indication.

Interstitial cystitis (Hunner's ulcer) is the chronic non-septic inflammation of the bladder wall. Some believe it to be common (Curhan et al., 1999), but the urologists consulted believe it to be rare, being frequently suspected but seldom confirmed. It is generally treated conservatively, but in very rare instances may constitute an indication for cystoplasty (Venn et al, 2000).

Figure 4.3: Map of Bilharzias and per capita GNP





These diagrams illustrate that the potential market for augmentation cystoplasty is not a viable one. By comparing the two diagrams, it can be seen that the areas with highest levels of Bilharzias correspond to the areas with the lowest GNP per capita i.e. some of the world's poorest nations. The top diagram shows the distribution of Schistosomiasis (Bilharzias). Source: Centers for Disease Control and Prevention - http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-5/schistosomiasis.aspx. The bottom diagram shows the distribution of GNP per capita. Adapted by permission from Macmillian Publishers Ltd : Nature (Sachs et al., 2002), copyright 2002.

4.4.3 Bladder Carcinoma

Over 10,000 and 50,000 cases of bladder cancer are registered each year in the UK and the USA respectively (North American Association of Central Cancer Registries, 2006;Office for National Statistics, 2005). Incidence increases rapidly after the 6th decade of life and the mean age at diagnosis is 70 years in men and 73 years in women (Office for National Statistics, 2005).

Bladder cancer can be either invasive or superficial. Surgery is used for invasive cancers and usually (90-94%) takes the form of radical cystectomy, with removal of the trigone (Hollenbeck et al., 2005). However, partial cystectomy can be a treatment option where the tumour is “primary, solitary and amenable to removal with 2cm surgical margins” (Rivera et al., 2000). Partial cystectomy is a less complex operation and has been used for 3% to 19% of patients with five-year overall survival rates reported to range from 35% to 80%, (Brannan et al., 1978;Faysal et al., 1979;Hayter et al., 2000;Jardin et al., 1984;Merrell et al., 1979;Ojeda et al., 1983;Utz et al., 1973). Partial cystectomy is however less widely applicable as cancer recurrence rates can be as high as 80% in poorly selected patients (Hollenbeck et al, 2005).

The bladder is a particularly difficult organ to treat for cancer. The high rate of cancer recurrence following treatment is not only confined to the organ itself. For instance, the incidence of a subsequent upper urinary tract tumour after a diagnosis of superficial bladder cancer has been reported to range from 2% to 26%. This is in addition to the high recurrence rate in the actual bladder itself. In light of this, the current therapeutic gold standard in bladder treatment is the radical cystectomy (Palou et al., 2005).

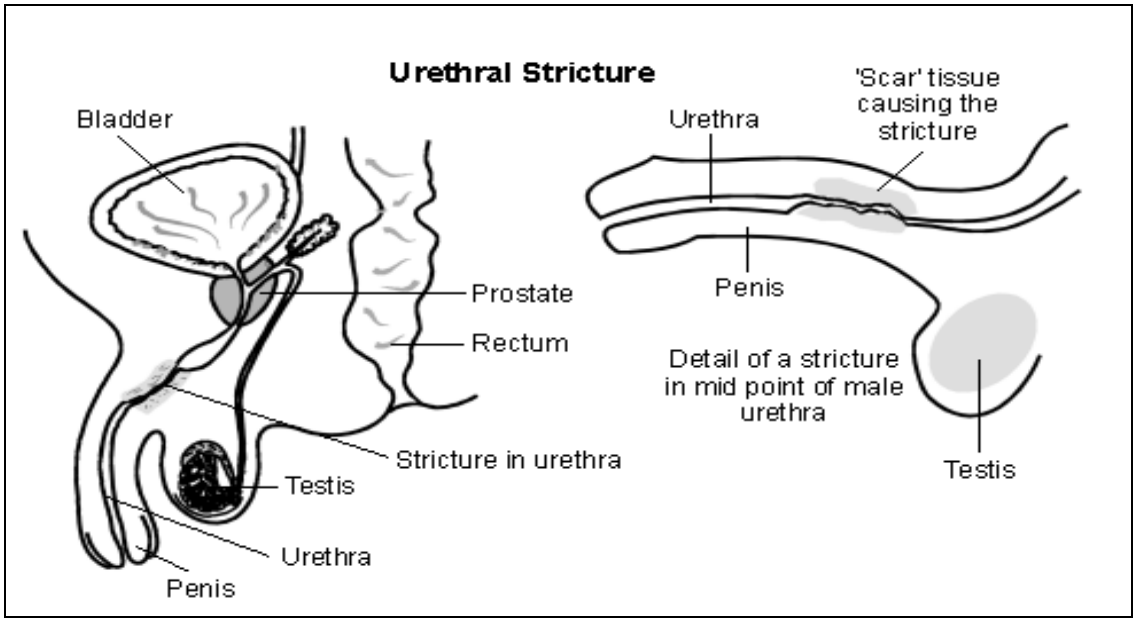
A successful TE bladder has an obvious potential application in patients who have been treated by cystectomy. The size of the potential market depends on whether the procedure is used only in the minority of cases undergoing trigone-sparing surgery (partial cystectomy) or whether the more exacting nerve-sparing operation catches on. Indeed, the latter may become more widely used if a TE solution replaces the need for complex bowel surgery.

4.4.4 Urethral Strictures

A urethral stricture is an abnormal narrowing of the urethra which adversely affects the passage of urine (illustrated in figure 4.4 below). Urethral strictures have a number of causative factors including scar tissue from previous surgery, the passage of kidney stones, physical injury to pelvic area and sexually transmitted diseases. It may also be caused by external pressure from an enlarging tumor near the urethra, although this is rare. They are most common in men as the female urethra is much shorter in length. In the western world, incidence rates increase from 1 in 10,000 at the age of 25 to 1 in 1,000 at the age of 65 (Wood et al., 2006).

Circumstances can arise, if the stricture is long or the first intervention is unsuccessful, where the surgeon is not able to perform a satisfactory operation by means of the existing urethral tissue alone and a substitution urethroplasty is required. This is required only in a small percentage of cases of stricture. There were 3,142 finished consultant episodes in English hospitals in 2005-06 (HES Online, 2007). On a purely "per head of population" basis, this would imply around 18,800 cases in the USA.

Figure 4.4: Schematic diagram of urethral strictures



Source: http://www.patient.co.uk/health/Urethral-Stricture.htm. Image reprinted with permission from Patient UK, copyright 2009, EMIS & PiP.

4.4.5 Conclusion

The analysis of the clinical problem suggests the potential market for a TE solution for dysfunctional bladder and small contracted or inflamed bladders is probably far too small. Therefore, at this stage there are two remaining potential indications for TE urogenital tissue, which show promise:

i. Bladder carcinoma
ii. Urethral stricture

The following section looks at the state of the art of TE that could be applied in these situations as a precursor for a 'headroom' cost-effectiveness analysis. Before making such an analysis I need to document the disadvantages of current treatment, which TE methods may overcome.

4.5 Clinical Effectiveness

Bladder Augmentation Cystoplasty using Bowel for Bladder Carcinoma

The majority of complications that occur following a cystoplasty are due at least in part to the use of bowel in regenerating the bladder and are the primary focus of this section. A TE solution would avoid such complications, and would not affect the complications due to the bladder surgery itself and as such are not considered here.

Short-term complications

The most notable short-term complication arising from the use of bowel is adhesive small bowel obstruction, which is estimated to occur in 3% to 6% of patients (Greenwell et al, 2001) although this complication has been reported to occur in up to 10% of patients (Gough, 2001).

Long-term Complications

The majority of the side effects associated with this procedure are long-term complications. There are a number of complications, which can arise and these are summarised below.

- *Bowel disturbance* - Terminal ileum resection may lead to bile acid malabsorption (diarrhoea), fat malabsorption (with consequent steatorrhea (excess fat in faeces) and reduced absorption of

vitamin B12. Diarrhoea has been reported to occur in up to 25% of patients, although whether this is a direct consequence of the bowel surgery or some associated disturbance of bowel function is unclear (Greenwell et al, 2001).

- *Metabolic disturbance* - The absorptive characteristics of the bowel when in contact with urine can lead to a series of metabolic reactions. Active reabsorption of ammonia, ammonium chloride, sodium, water and hydrogen ions and the increased loss of bicarbonate and potassium into urine can lead to hyperchloraemic acidosis (inability to excrete urine of normal acidity). This is easy to treat and seldom troublesome, except in children.
- *Mucus Production* - The average daily mucus production from both ileum and colon when used as a cystoplasty segment is 35-40g. In its natural environment, mucus provides the gut epithelium with a layer of protection from contact with urinary carcinogens and other substances (Greenwell et al, 2001). Mucus accumulation can predispose to urinary tract infection and stone formation (Greenwell et al, 2001).
- *Bacteraemia and Urinary Tract Infection* - All bowel segments are sites for bacteria. Recurrent bacteraemia (presence of bacteria in the urine with or without urinary tract infection) is found in 50 to 100% of patients. These infections may become asymptomatic and may led to pyelonephritis (inflammation of the kidney and pelvis due to bacterial infection) (Greenwell et al, 2001).
- *Stones* - Stone formation is a common complication (Greenwell et al, 2001) and urease-producing bacteria are a likely causative factor. In addition, mucus can bind with urinary calcium to form the stone nidus (the focus of infection). In a small proportion of cases bladder cancer may form (Stonehill et al., 1996).
- *Clean Intermittent Self-Catheterization (CISC)* - It is difficult to predict if CISC would be necessary for a patient treated using a TE bladder, this would depend on whether a TE graft could become innervated and functional.

Other Outcomes

Ileocystoplasty (cystoplasty involving the use of an isolated intestinal segment) incurs an average inpatient length of stay (LOS) of 13.3 days (HES Online, 2007), which is partly attributable to the

healing of the bowel. With no need for bowel surgery TE would be likely to reduce hospital stay. Re-implantation of ureters (urine carrying tubes) is a major bladder operation where bowel surgery is not involved. The average LOS is 9.6 days (HES Online, 2007). Using this as a plausible surrogate for LOS with a TE solution, an average saving of 4 days was calculated.

Urethroplasty using buccal mucosa for Urethral Strictures

The gold standard for urethroplasty is the use of buccal mucosa. This is successful in 90% of cases (Koraitim, 2003) and there are reports of 100% success rates for a mean stricture length of 3.4cm or less (Al-Qudah et al., 2005). However, success rates appear to gradually decline from 5 to 10 years (Wood et al, 2006).

A disadvantage of this procedure can be complications relating to the buccal mucosa donor site. Donor site morbidity can be associated with intraoperative haemorrhage, postoperative infection, pain, swelling, damage to the parotid duct (duct from parotid gland, a salivary gland into the mouth), limitation of oral opening and loss of or altered sensation of the lip or cheek, however all are infrequent complications (Bhargava et al, 2004). A recent systematic review found these complications occur for 1 in 25 patients (Markiewicz et al., 2008). The most common complaint, occurring for 1 in 2 patients is paraesthesia (numbness), which in most cases persist for the short term only (Bhargava et al, 2004) although this problem has been reported to persist for up to a year for 1 in 6 patients (Dublin et al., 2004). Overall, this procedure is considered less painful than a tonsillectomy (Nigel Borley, 2006) and graft harvest from the buccal mucosa is preferable to harvest from inside the lips (Bhargava et al, 2004).

Another outcome worthy of consideration is stricture recurrence, a long-term complication. Recurrence rates have been reported to range from 5% to 15% (Al-Qudah et al, 2005). Five-year follow-up results reporting stricture recurrence rates of 12.5% (Fichtner et al, 2004) and a recent systematic review of urethroplasty articles, published between 2000 and 2008, reports a recurrence rate of 15.6% (Meeks et al., 2009).

TE urethral tissue – if produced successfully – would avoid the problems of the donor site while retaining the advantage of being autologous and not prone to rejection by the patient's immune system. The patient would need to undergo an additional procedure to harvest urethral cells, unless some has been collected previously, say during an earlier attempt to overcome the urethral defect. On balance, though, the TE solution would be less morbid, yielding a higher HRQL than with the use of buccal mucosa (Atala, 2004), however, it is debatable if the TE solution would be functionally better (Nigel Borley, 2006)

4.5.1 Utility of Clinical Effects

As described in section 4.2.2 (page 87), the utility values for health state following a cystoplasty and an urethroplasty could not be derived from the literature so a questionnaire was devised to elicit the utility scores associated with each. Full details of the methods are described in section 4.2 (page 87). Below I summarise the key results of the questionnaires. All supplementary results can be found in appendix 4, following the relevant questionnaire.

Cystoplasty using Bowel

Four out of sixteen (25%) urologists completed and returned questionnaires. Two surgeons stated they did not wish to take part and although the others were followed up with phone calls, no other responses were received. A full descriptive analysis of the questionnaires is given in appendix 4.

Using equation 4.1 (section 4.2.2, page 88), the TTO responses given in the questionnaire were converted into utility scores. In conclusion, the mean utility for the period of maximum symptoms was calculated as 0.96 (95% CI: 0.94, 0.97) from four responses. This value will be used in all subsequent CEA. The urologists were also asked how much they would be willing to pay to avoid the clinical effects of an ileocystoplasty. To conclude, the mean WTP to avoid a 0.04 QALY decrease in utility for 6 months was calculated as £8,750 (95% CI: £1,400, £16,000) ($14,000, €9,900) from four responses. By combining the results of the above two questions, the mean WTP per QALY can be calculated as £275,000 (95% CI: £0 £617,993) ($445,000, €312,000) from four responses.

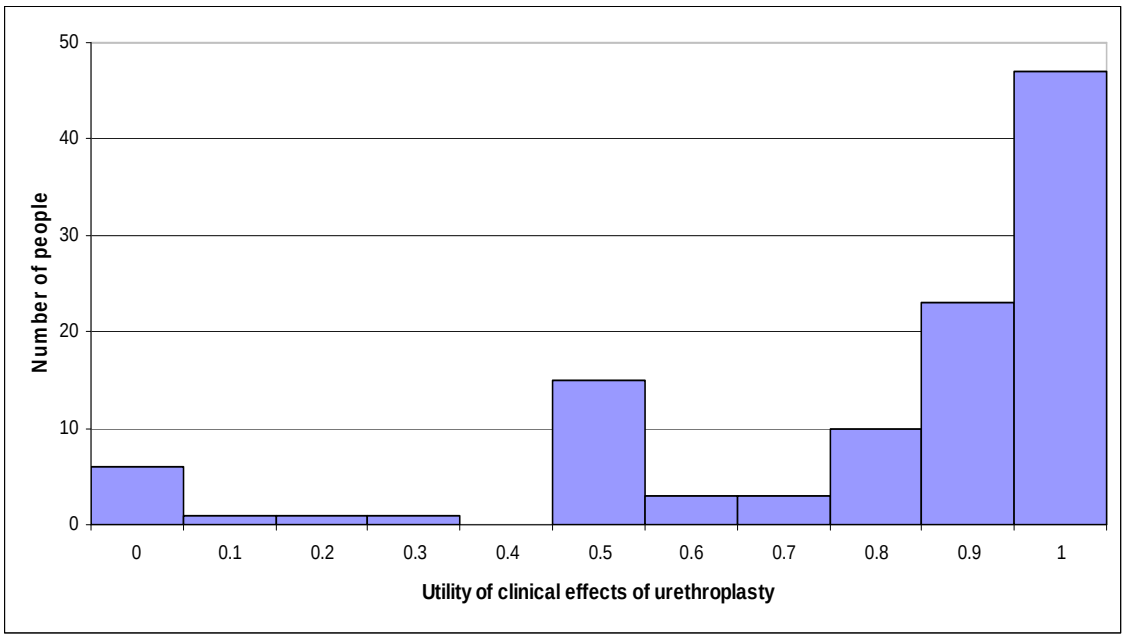
Urethroplasty using Buccal Mucosa

One hundred and ten individuals completed the question about TTO. A full descriptive analysis of the questionnaires is given in appendix 4.

Using equation 4.1 (section 4.2.2, page 88), the TTO responses given in the questionnaire were converted into utility scores. The distribution of the utility scores ranges from 0 to 1 and has a negative skew (figure 4.5). Two points are evident from this graph. Firstly, there appear to be a number of outliers. A number of the utility scores are close to zero. A utility of zero represents death. I find it difficult to imagine an individual would rate the health state following an urethroplasty using buccal mucosa donation as close to death. I think this may represent a misunderstanding of the question – it is conceivable that instead of recording life to trade an individual noted life they would prefer to keep. Alternatively, this could be a big error. Secondly, there is a tendency for the responses to be concentrated around the values of 0, 5 and 10 years, which is a possible exhibition of an anchoring effect (Lenert et al., 2001). To mitigate against the anchoring effect observed in figure 4.5, a summary measure more resistant to outliers than the mean is required (Huber, 1981). The median is the simplest of these to use (Ohkusa et al., 2006). In conclusion, the median utility for the period of maximum symptoms was calculated as 0.94 (95% CI: 0.89, 0.99) from 110 responses. This value will be used in the subsequent CEA.

The participants were also asked how much they would be willing to pay to avoid the clinical effects of an urethroplasty and this was answered by 108 individuals. The WTP values recorded by the respondents ranges from £0 to £30,000 and is positively skewed. This indicates that the respondents were not willing to pay large amounts to avoid the clinical effects of urethroplasty using buccal mucosa. To conclude, the median WTP to avoid a 0.06 QALY decrease in utility for 6 months was calculated as £500 (95% CI: £0, £1,418) ($800, €560) from 68 responses. Finally, by combining the results of the above two questions, I calculate the median WTP per QALY as £10,000 (95% CI: £0, £32,285) ($16,300, €11,300) from 53 responses.

Figure 4.5: The distribution of utility values associated with the clinical effects of urethroplasty using buccal mucosa



Utility values calculated from TTO questionnaire from 110 respondents.

4.6 Cost of Treatment

The only costs of treatment considered in the model are those of the operations, as it is assumed that all outpatient costs would be equal between current and TE treatment. A cystoplasty procedure (HRG code L14: Bladder Major Open Procedures or Reconstruction) has an average cost of £4,286 ($7,000, €4,800) (Department of Health, 2006b). In addition is the potential saving in hospital bed days that a TE solution might deliver. The cost of a bed day is estimated at £317 ($500, €350) (Department of Health, 2006b) (national average cost of an excess bed day).

A urethroplasty procedure (HRG code L33: Urethra Major Open Procedures) has an average total cost of £3,480 ($5,700, €3,900) (Department of Health, 2006b). In addition, a 40-minute saving in operation time would result from avoiding the need to harvest buccal mucosa (Nigel Borley, 2006). Based on a 75 minute operation time (Levine et al., 2001), the 40-minute saving in operation time was estimated (using unit cost of consultant surgeon and nurse, similar to Dong (Dong et al., 2006)) at £225 ($360, €250).

4.7 Cost-Effectiveness Analysis

4.7.1 Headroom Analysis

Cystoplasty using Bowel for Bladder Carcinoma

The median utility for the period of maximum symptoms was calculated as 0.96 (95% CI: 0.94, 0.97) from four responses. The mean age of presentation of bladder carcinoma is 72 years (Sangar et al., 2005). Survival rates vary widely, but it was assumed patients suitable for a TE solution will be younger than average and have a better than average survival, so a mean survival of 10 years of life was assumed among this group.

Before calculating the headroom, I must firstly estimate the maximum potential change in effectiveness, measured using QALYs, this is calculated as 0.4 (see equation 4.3). This in turn suggests headroom of £12,000 ($19,500, €13,600) (see equation 4.4) based on a threshold value of £30,000 ($49,000, €34,000). Although a threshold value of £20,000 ($33,000, €23,000) gives headroom of just £8,000 ($13,000, €9,000). However, this headroom value is very dependent on survival time. A decrease in survival time would result in an equivalent decrease in headroom, i.e. if the mean survival time was halved to 5 years, the headroom would be halved to £6,000 ($9,700, €6,800).

Equation 4.3: $\Delta QALY = 10 \times (1 - 0.96) = 0.4$

Equation 4.4: $\max \Delta Cost = £30,000 \times 0.4 = £12,000$

In addition to the headroom, a TE solution might deliver a saving of four hospital bed days (Dr Almallah, 2006). Based on the cost of a bed day given in section 4.6 (page 105), four hospital days would result in a total saving of £1,268 ($2,000, €1,400), thus the total headroom would be £13,268 ($21,600, €15,000). The companies consulted (Sofradim, FAB and Tengion (referred to in section 4.2, page 87) were optimistic that a headroom of £13,000 was a potentially viable price (including production costs and the need to recoup development costs). However, profit would be volume dependant. This is likely to depend on whether sphincter saving surgery catches on. If not, then the

market even in a country the size of the USA would only be about 5,000 cases per year (section 4.4, page 94).

Urethroplasty for Urethral Strictures

The literature review and urologist consultations made clear there is negligible (if any) risk of mortality from using buccal mucosa as a urethra substitute. It follows that there is no difference in mortality between the two treatments (TE vs. non-TE) and only the period of time during which the utility values of the two operations differ needs be considered.

The median utility for the period of maximum symptoms was calculated as 0.94 (95% CI: 0.89, 0.99) from 110 responses. In keeping with the literature review and urologist consultations, it was assumed this phase would last for 5 weeks (0.1 year) - this may be a little pessimistic for standard treatment but if so this is again in keeping with the headroom method philosophy.

Before calculating the headroom, I must firstly estimate the maximum potential change in effectiveness, measured using QALYs. Using equation 4.5 populated with the data above, I calculate the maximum change in benefit as 0.006 QALY. Next, using equation 4.6 I calculate the headroom as £180 ($300, €200) based on a threshold of £30,000 ($49,000, €34,000) or £120 ($190, €136) based on a threshold value of £20,000 ($33,000, €23,000). If I also assume the disutility of the clinical effects may have been overestimated by as much as 5% (i.e. to give a utility of 0.987), the headroom would be reduced further to £39 ($63, €45), based on a threshold of £30,000 ($49,000, €34,000) or £26 ($42, €30) based on a threshold of £20,000 ($33,000, €23,000).

Equation 4.5: $\Delta QALY = 0.1 \times (1-0.94) = 0.006$

Equation 4.6: $\max \Delta Cost = £30,000 \times 0.006 = £180$

Avoiding harvest of buccal mucosa would lead to a cost saving associated with operation time of £225 ($360, €250) (section 4.6, page 105). This cost should be added to the headroom of £180 to give a headroom total of £405 ($650, €450). From my consultations with the industry and from the prices of existing products, I conclude that there is no prospect of producing a commercially viable cell-bearing product at this price.

4.8 Return on Investment

The market size for a TE bladder relates mainly to patients with bladder cancer, most of whom are treated by radical cystectomy and urinary diversion by ileal conduit (isolated section of ileum). Only 4 to 19% (Brannan et al, 1978;Faysal et al, 1979;Hayter et al, 2000;Jardin et al, 1984;Merrell et al, 1979;Ojeda et al, 1983;Utz et al, 1973) are treated with the partial, or trigone sparing cystectomy suitable for bladder substitution cystoplasty. If this practice continues then only between 420 and 2000 of the average 10,470 (Office for National Statistics, 2005) bladder cancer patients in a country of 60 million such as the UK will be eligible for RM bladders. This represents a small market and therefore, possibly not a very exciting investment opportunity. However, in some cases a radical cystectomy can be "nerve sparing" - retaining the innervation in urethral sphincter and thus providing an opportunity for an TE vestibule (Venn et al, 1998). However, as Venn and colleagues note, "there are very few centres where these procedures are actually performed. The vast majority of patients undergoing cystectomy still seem to be offered an ileal conduit and no alternative" (Venn et al, 1998). The potential market size for TE bladders is thus sensitive to the adoption of this technique. To an extent, therefore, any investors will be "betting on" increasing use of the nerve sparing operations and possible stimulation of this approach through the availability of a TE bladder.

The revenue that can be generated is a function of headroom, the likely cost, and volumes, represented by equation 4.7. Here, R = revenue, maxΔCost = Headroom, C' = expected cost of production and V = cases per year.

Equation 4.7: $R = (\max\Delta \text{ Cost} - C') \times V$

In the case of a TE bladder, assuming each device costs £8,000 ($13,000, €9,000) and that there are 500 cases per year, the estimated revenue is £2.5 million per year (equation 4.8) ($4,000,000, €2,800,000). The expected profit however, must be discounted over a time horizon chosen to reflect the company strategy.

Equation 4.8: R = (£13,000 – £8,000) x 500 = £2,500,000

4.9 Discussion

4.9.1 Summary of Main Findings

Careful analysis of the clinical problem suggested urethral defects and bladder resection for cancer offer the most propitious applications for a TE urethral tissue technology. The headroom for TE urethra has optimistically been estimated to be £405 ($650, €450) over and above the current cost of a grafting operation. This is unlikely to be large enough to support the launch of a cell bearing TE product. This result can be attributed to two main reasons: Firstly, buccal grafts are very successful against the scale of healthcare outcomes, and secondly, the side effects are few, relatively short lived and benign. On the other hand, the headroom for TE bladders has been optimistically estimated at around £13,268 ($21,600, €15,000) over and above the cost of ileocystoplasty. It is likely a TE solution could come in cost below this, suggesting that if the market size were deemed large enough it could be worth proceeding with development. Two scenarios could lead to this: first, trigone/urethral sphincter sparing surgery does not catch on – therefore the market would be of limited size; and second, trigone urethral sphincter sparing surgery becomes widespread – in which case a substantial market could be grown.

4.9.2 Elicitation of Utilities

This chapter encompassed two questionnaires for the elicitation of utilities of two different health states, each of which had a different methodology.

First, I discuss the elicitation of the health utility associated with cystoplasty using bowel. Since it was not possible to obtain the health utility directly from patients, the utility was elicited from clinicians. I believe clinicians were a good proxy for patients as the health state associated with cystoplasty using the bowel is complex and as caregivers, they have a high level of understanding of the impact of the health state on the HRQL of the patient. However, this analysis was limited due to the very small sample size (N=4). The urologists were identified using the NHS website from hospitals within the Birmingham and Black Country area. The restriction of the geographical area limited the number of clinicians available for selection. In hindsight, once the decision was made to email the questionnaires

rather than arrange face-to-face interviews it would have been preferable to identify more urologists from outside the Birmingham and Black Country area. This would have increased the number of questionnaires sent, and even if the response rate of 25% remained unchanged, the sample size would have been increased, although, a response rate of 25% is not particularly high; closer to 40% would have been desirable. Efforts were made to increase the response rate but without much success. The reason is probably due to being unable to speak directly with the clinicians; the follow up phone call was with secretaries who either advised they would bring the questionnaire to the attention of the clinician and send it back (which didn't happen) or declined to assist. The success of this approach could have been improved by either posting the questionnaires rather than emailing, or by conducting a telephone interview with the clinician, I believe this would have been quicker and easier to organise than a face-to-face interview and more successful than a postal survey. Despite the low sample size, I believe the utility value elicited (0.96) is acceptable and reliable, as it is based on the opinions of specialist surgeons whom had a strong familiarity with the procedure (appendix 4).

Next, I discuss the elicitation of utility values associated with urethroplasty using buccal mucosa. Since it was not possible to obtain the health utility directly from patients, the utility was elicited from the general public. In this case, the sample size is more favourable at 112. However, a potential limitation of this analysis is associated with the sample of respondents. The sample should be representative of the general population. As the sample was taken from two sites, the university and the city centre of Birmingham, it could be argued that this is representative. However, those interviewed from the university site were all employees of the public health department and were more familiar with both the health state under investigation and the method of measuring preferences; therefore, it could be argued that this sample is not representative. Although interviewing a sample of the general public resulted in a larger sample size, I have reservations regarding how well the questions were understood. As described, there were a number of utility values of, or close to zero. This results in the headroom of TE urethra being based on quite severe utility values – although minimised by using the median rather than the mean, a median utility value of 0.94 implies that more than half the population would run a greater than 1 in 20 risk of death to avoid a buccal mucosa donation, which is probably unrealistic. I believe there are three explanations for this. Firstly, it may indicate a general lack of

understanding by the general public of both the health state being described and the methods being used for measuring preferences. Secondly, there may have been an error made at some stage (as previously described the data was collected and entered into Excel by previous staff members). Finally, this could be just a natural occurrence, the result of eliciting utilities from the general public. This has previously been reported by Ubel and colleagues (Ubel et al, 2003), who found that the general population tend to exaggerate the impact of disease on HRQL as patients tend to rate their health states higher than the general population, underestimating their need for healthcare. The utility associated with urethroplasty using buccal mucosa may have been more accurately calculated from interviewing urologists, despite the low sample size. The two questionnaires could have been completed by the urologists identified and the time taken interviewing the general public could have been spent trying to increase the number of urologists in the sample.

4.9.3 Implications of this Work

This work has received a great deal of interest since its publication in 2007 in the journal of regenerative medicine and tissue engineering. This was the first example of the headroom method and demonstrated to the industry that there is an approach, which may be useful in guiding investment decisions and helping to focus on those applications that may be most successful and economically viable.

This work has been of significant importance to the French TE firm, Sofradim, who had been working on the development of visceral tissue patches to be used in the urinary system for cystoplasty and urethroplasty. Following the completion of this CEA and the conclusion that the repair/replacement of urethra and bladder was not so promising Sofradim made the decision to scale back work on visceral tissue patches for the urinary system and focus their efforts on visceral tissue patches for the abdominal wall (will be explored in chapter 5).

However, this has not been the case everywhere. Tengion, a US based clinical stage Biotechnology Company, focuses on developing, manufacturing, and commercialising human neo-organs and neo-tissues. Their lead product is the Neo-Bladder Augment^{TM} for the treatment of neurogenic bladder in

Spina bifida in children. Since its foundation in 2003, Tengion has raised a total investment of $127 million. Tengion's CEO claims that "to procure an organ to show up in the operating room where it is about to be implanted – not the care of the patient who is about to get it or the after-surgical care – but just to get the organ to show up in the operating room is on the order of $50,000 to $150,000 per patient" (Filmore, 2007). It is unclear where Tengion intends to price and reimburse their product but they are "hopeful that if we deliver the safest and most effective product that we can deliver, we will have appropriate reimbursement" (Filmore, 2007). Only time will tell who is right. However, a break-even price of about $30,000 would have to be significantly out to justify, a price tag of $100,000; even life saving left ventricular assist devices struggle at this price. Also, no reference is given for the number of augmentations, but if they are correct and the profit were $10,000 per case, total profits would be about $100 million per year.

Another target for the Tengion Neo-Bladder is urge incontinence in patients, which have failed previous therapies. This application may have a particular appeal to the private healthcare market more than third party payer markets, for example, the retired person whose only wish is to be able to get through a round of golf without a break. This may well prove fruitful however to predict this would be an even greater challenge.

4.9.4 Conclusion

In this chapter, I have shown how the headroom method can be used early in product development to make a preliminary conclusion as to the potential cost-effectiveness of a new treatment, even when some of the parameters are extremely uncertain. There may be arguments for the development of TE urogenital tissue in terms of developing the general science, but in terms of clinical gain, it appears that it would be more profitable to redirect scarce resources to alternative applications. In the following chapter, I investigate the potential cost-effectiveness of TE visceral tissue for use in defects of the abdominal wall.

CHAPTER 5 COST EFFECTIVENESS ANALYSIS OF A TISSUE ENGINEERED SOLUTION FOR THE TREATMENT OF ABDOMINAL WALL DEFECTS

5.1 Introduction

Using the methodology described in chapter 3, I aim to assess the most propitious opportunities for a TE solution in the repair of abdominal wall defects. Where existing treatments are successful in making good the defect, preventing recurrence and avoiding side effects, there is less headroom for further gains from a new treatment. By applying the headroom method, I will determine whether the costs of developing a TE solution for abdominal wall defects can be justified.

Abdominal wall defects cover a broad spectrum of conditions, which occur following trauma, infection, or surgical resection. Some, such as an inguinal hernia are small, while others, such as an incisional hernia are massive. Some involve a defect in just one fascia (fibrous tissue) layer (e.g. a femoral hernia) while others involve loss of the entire abdominal wall, including muscle and skin. Clearly, the surgical challenges posed by these various lesions are very different.

Until recently, abdominal wall repair relied on a suture line to close the defect. However, this places excessive pressure across the repair line. Tension-free repair avoids this by using a mesh, placed over the defect. The mesh is a support framework for cells to grow and differentiate. It augments the strength of the weakened abdominal wall resulting in a repair that is less painful and more likely to endure. However, the current generation of (non-TE) mesh materials are synthetic and prone to complications such as infections and adhesions because of the foreign material. Biological meshes, either acellular or cellular, have emerged as an alternative to synthetic mesh. Due to their natural sourcing biological meshes avoid the complications of synthetic materials and could reduce or possibly prevent infection, simplifying the healing process, as well as improving mechanical integrity.

5.2 Methods

5.2.1 Overview

My first task was to identify the clinical conditions where a TE biological mesh could have potential and to document the effectiveness, safety, and costs of the current best treatment. Next, I built up a realistic picture of anticipated benefits, problems, and costs for such a TE solution, which might rival the current gold standard (synthetic mesh). Finally, once the clinical problem was clearly defined I selected the condition with greatest potential headroom and applied the headroom method to establish the maximum cost for a TE solution, which could be supported by the UK health service.

5.2.2 Defining the Clinical Problem

Literature searches were conducted using the search strings shown in appendix 5. I worked closely with the French TE firm Sofradim who assisted with the technical aspects surrounding the development of such a mesh and with costs of current and future meshes. When necessary, I contacted a colorectal surgeon based at the University Hospital Birmingham already known to my team, to assist with the understanding of the clinical need.

After careful analysis it appears synthetic meshes have problems when the defect is *large* and when there is *infection*. I decided the repair of infected or contaminated incisional hernias is worthy of further investigation. A systematic review of the relative effects of each treatment (synthetic versus biologic) is documented with special emphasis on overall recurrence rates, a long-term complication and on utility of the clinical effects. The methods of utility elicitation are described below.

Utility of Clinical Effects

In this chapter, a utility-based HRQL score associated with infected incisional hernia was required. A comprehensive literature search found no existing utility-based HRQL scores. I devised a questionnaire to elicit the utility scores required. The questionnaire is in appendix 6 and the justification for the wording of the questionnaire is in appendix 2. I used TTO and WTP approaches to measure preferences. In TTO, each interviewee is asked what amount of time they would give up from

a fixed specific length of time, to avoid the negative side effects of the procedure in question, and have perfect health for the remainder of their life. The TTO values are converted into utility scores using equation 5.1.

Equation 5.1: HRQL = TTO ÷ t

In WTP, each interviewee is asked how much they would pay for a treatment that would relieve them of the described health state. Combining the responses from each question makes it possible to calculate each individual's WTP per QALY.

Due to time and cost constraints, it was not possible to obtain a fully randomised sample of a national or international patient population. Instead, the HRQL weightings were elicited from a sample of colorectal surgeons (N=54). I sought to survey healthcare professionals rather than the general public due to the complex nature of the conditions. Ideally, patients are used to elicit utilities, but this was not possible for three reasons. Firstly, these patients are incredibly ill and most likely on intensive care. Secondly, there was insufficient time remaining in my project to seek ethics approval and finally, logistically it was easier and less time consuming to access a large sample of clinicians than it would have been to contact and visit the same number of patients.

I gained access to a large sample of colorectal surgeons through the attendance of a conference for the Association of Coloprotology of Great Britain and Ireland, which took place in Harrogate in June 2009. Using the internet search engine Google I found an advertisement for the conference and contacted the board to request permission to have a stand and handout my questionnaires to the delegates. With the help of a medical student on work experience and a temporary research associate within my team, 54 questionnaires were completed over two and a half days.

5.2.3 Cost-Effectiveness Analysis

Firstly, I reviewed previous CEA of incisional repair using suture, synthetic mesh, and acellular mesh. Secondly, I conducted the headroom analysis. Using the data collected from the survey of colorectal

surgeons, I calculated a utility-based HRQL score associated with the clinical effects of a large and infected incisional hernia. Using these utility scores, I populated equation 5.2 and calculated the headroom - the maximum cost for which a TE solution for cystoplasty and urethroplasty would be considered cost effective for two scenarios: i) assuming a TE solution eliminates early complications and results in more rapid wound repair, and ii) accounting for a reduction in recurrence rate (a long-term complication). Overall, recurrence rates were calculated for each material using review manager.

Equation 5.2: max∆Cost = max∆QALY x willingness-to-pay threshold

Where, ∆Cost = ∆QALY x willingness-to-pay threshold, where ∆Cost is the maximum headroom, ∆QALY is the change in benefit measured in QALYs and willingness-to-pay threshold is the threshold for reimbursement of £30,000 ($49,000, €34,000).

5.3 Treatment

5.3.1 Current Treatment

Synthetic Mesh

Types of Synthetic Mesh

There are two main types of mesh (Millenium Research Group, 2007):

1. A flatsheet mesh that is inexpensive at a cost of less than $100 (£60, €70) (Yves Bayon, 2008);
2. A non-adhesive mesh, which has a protective coating placed on one side and is ultra lightweight. The additional coating on this mesh increases the cost of this product to between $500 - $700 (£300-430; €350-500) (Yves Bayon, 2008).

The most common synthetic materials used are polypropylene (Marlex and Prolene), polyester (Mersilene and Parietex), and polytetrafluoroethylene (PTFE or Gore-Tex) (Lai et al., 2003;Park et al., 2006).

Clinical Effects of Synthetic Mesh

Four systematic reviews of RCTs comparing mesh with non-mesh repair for inguinal hernias have been identified (EUHTC, 2000;EUHTC et al., 2002;Grant et al., 2002;Scott et al., 2002). These studies have reported similar rates of haematomas (localised collection of blood, often clotted), seromas (a mass or swelling caused by the localised accumulation of blood plasma within a tissue or organ), and infections for mesh and non-mesh repair, but significantly fewer hernia recurrences for mesh repair. Operative time is longer for mesh repair than for non-mesh repair (Scott et al, 2002). However, mesh repair is associated with reduced length of hospital stay (reported in 5 of 6 trials (p=0.22) (EUHTC, 2000)) and a more rapid return to usual activities (reported in 7 of 10 trials (p=0.34) (EUHTC, 2000)). Levels of persisting pain are highly variable among trials however the 2002 (EUHTC et al, 2002;Grant et al, 2002) reviews found that pain was lower in patients receiving mesh repair compared to non-mesh repair. A detailed review of these trials can be found in appendix 7.

Despite the advantages of synthetic meshes over suture, they are not without limitations. Complications arise if there is contact between the abdominal viscera (intestines) and the synthetic mesh. The complications are due to infection and are classified as early (<1 month) complications and long-term (>1 month) complications:

- ***Early complications*** - Bruising, haematoma and seroma are common complications following hernia repair of all types. The most frequent and significant early complication to occur following mesh repair is wound infection, which is frequently associated with pain. This in turn is related to wound dehiscence and repair failure. The risk of infection is increased with synthetic mesh.

- ***Long-term complications*** – The most frequent and significant long-term complication is hernia recurrence and the rates vary depending on the type of defect being repaired (more detail given in later sections); however, the recurrence rates associated with synthetic mesh are lower than those associated with simple suture. Chronic pain (pain persisting for 3 months after repair) is another frequently reported complication. Less frequently reported nevertheless major long-term complications include small bowel obstruction, fistula (a permanent abnormal passageway

between two organs in the body or between an organ and the exterior of the body) formation, and enterocutaneous fistula (abnormal opening between two organs or from an organ to the outside of the body) all of which can result in infertility.

Anatomical siting of the mesh

Mesh is secured in either an intraperitoneal (within the peritoneal cavity, the area that contains the abdominal organs) or an extraperitoneal (outside of the peritoneal cavity) position. Current evidence on the relative advantages and disadvantages of these methods is equivocal. Two comparative studies using animal models demonstrate conflicting outcomes. The porcine model (N=15) (Attwood et al., 1994) compared the two placement techniques on the same animal; the left side received extraperitoneal mesh placement and the right side received intraperitoneal mesh placement. The evidence demonstrated that both methods were associated with adhesion formation to viscera. Conversely, the rat model (N=50) (Farmer et al., 1998), which used ten rats per treatment group (extraperitoneal pocket with and without mesh; intraperitoneal mesh; ischemic defect with and without mesh) concluded that, as might be expected, intraperitoneal placement was associated with a higher rate of intra-abdominal adhesion formation than extraperitoneal placement.

More recently Arnaud and colleagues (Arnaud et al., 2003) carried out a prospective comparative clinical study to examine intraperitoneal placement and extraperitoneal placement using a mesh lined with a protective hydrophilic resorbable film (Parietex composite) on the side facing the abdominal cavity (N=51) compared to an unprotected Mersilene mesh (N=22). They found a reduction in the percentage of adhesions (18% for protected mesh compared to 77% for unprotected mesh ($P<0.001$)) when the mesh was placed in an intraperitoneal position. I consulted colorectal surgeons to obtain a current view; it appears that intraperitoneal placement of mesh is favoured for large defects associated with ventral (post-incisional) hernia. However, extraperitoneal placement, although technically more demanding, is favoured when the defect is small – as is the case for groin hernias.

Open or laparoscopic procedures

Laparoscopic repair is a minimally invasive safe alternative to open repair but is technically more demanding (Reuben et al., 2006). There is not yet a consensus amongst surgeons on a preference for open or laparoscopic procedures. A systematic review (McCormack et al., 2005) of laparoscopic versus open procedures for inguinal hernia repair identified 37 RCTs and 14 cost-effectiveness studies. Overall, open surgery led to improved outcomes except for recurrence rate, which showed no difference. The economic evaluation of laparoscopic versus open repair found that laparoscopic repair is more costly to the health service. A comparison of laparoscopic and open techniques for incisional hernia repair (Bencini et al., 2003;Engledow et al., 2007) found no significant difference in overall rate of complications and concluded that there is insufficient evidence to determine the most superior technique. A detailed account of the evidence of laparoscopic versus open repair for inguinal and incisional hernia repair can be found in appendix 8.

Lightweight or heavyweight mesh

Synthetic mesh can be lightweight or heavyweight depending on mesh pore size, approximately 4mm for lightweight mesh and 1mm for heavyweight mesh. Two RCTs compared lightweight and heavyweight mesh. One in incisional hernia repair (Conze et al., 2005) and one in inguinal hernia repair (O'Dwyer, 2004).

Conze and colleagues (n=165) compared lightweight composite mesh (n=83) with standard polyester (Atrium and Marlex) or polypropylene (Mersilene) mesh (n=82) for incisional hernia repair. Mean operating time was 1.8 hours for both groups. Mean number of days spent in hospital after surgery differed by 0.8 days (14.0 days for composite mesh and 13.2 days for standard mesh) but this was not significant (no p value given). Infection rate following mesh repair was similar in the two groups, varying between 4% and 16%. Infections were mainly subcutaneous and it was never necessary to remove the mesh. Overall, there were 20 recurrent hernias; 14 in the composite mesh group and 6 in the standard mesh group (no p value given). Time of recurrence varied from 131 to 742 days for composite mesh and from 164 to 833 days for standard mesh. HRQL score (measured using SF-36 taken at day 21) for composite mesh and standard mesh was 50.4 and 48.4, respectively.

O'Dwyer and colleagues (n=321) compared lightweight mesh (n=162) and heavyweight mesh (n=159) in inguinal hernia repair and found significantly fewer patients in the lightweight group experienced pain (40% vs. 52%, p=0.033) but the recurrence rate was higher (5.6% vs. 0.4%, P=0.037), which concurs with the Conze et al. study.

Myocutaneous Flaps

A less common alternative to synthetic mesh is myocutaneous flaps (vascularised autologous tissue composed of, or supplying both muscles and skin) used to cover very large defects. If skin coverage over the defect is absent or unviable, myocutaneous flaps provide tissue transfers for reconstruction of abdominal wall defects. Such defects often result from saprophytic (gangrenous) infections through numerous layers of abdominal wall. They also result, when the surgeon wishes to avoid closing the abdomen under pressure in patients with severe intraabdominal pathology such as peritonitis and pancreatitis (Mathes et al., 2000). Drawbacks of myocutaneous flaps include necrosis of transposed tissue and complications associated with donor site (Mathes et al, 2000). This is a large operation only suitable for complicated cases requiring immediate importation of a composite viable tissue.

5.3.2 State of the Art in Tissue Engineering

A biological mesh is a construct composed of a biodegradable scaffold (either xenogenic (from another species) or allogenic (genetically different but from the same species)) that may or may not be seeded with viable cells (cellular or acellular). The ideal mesh should be a natural biodegradable substance, biocompatible, cause little or no foreign body response, and be resistant to bacteria and infection. It should be able to withstand physiological stress, cause no additional pain after implantation, promote strong tissue in-growth to help maintain mechanical strength, avoid substantial contraction and developing adhesions to visceral structures and be readily available and affordable (Bellows et al., 2006;Drewa et al., 2005;Lai et al, 2003). Unlike synthetic meshes a biological mesh decreases in strength over time as the wound gains strength and new fascia is formed (Bellows et al, 2006;Drewa et al, 2005;Lai et al, 2003;Parker et al., 2006). Table 5.1 (page 124) summarises the advantages and disadvantages of both synthetic and biological meshes, along with current costs.

Acellular Mesh

Acellular mesh can be derived from dermis (connective tissue under skin), submucosa (tissue beneath mucus membrane) or pericardium (membranous sac which envelops and protects the heart) and these can be xenogenic or allogenic. The following are three of the most common acellular mesh currently available:

i. ***Porcine Dermal Collagen*** - Permacol® (a Tissue Sciences Laboratories plc product) is derived from porcine dermal collagen with the cellular content removed.

ii. ***Porcine Small Intestine Submucosa*** - Surgisis® (Cook Surgical, Bloomington, Ind., USA) is derived from porcine small intestinal submucosa (SIS). Preclinical studies showed that SIS is a viable alternative for placement of mesh in contaminated fields with respect to resistance of infection and maintenance of tensile strength (Franklin, Jr. et al., 2002). Acellular mesh derived from porcine SIS has been used for incisional hernia repair in animal studies (Adedeji et al., 2002;Park et al, 2006). This evidence suggests that acellular mesh is superior to synthetic mesh and enhances structural organisation of the new connective tissue (Adedeji et al, 2002).

iii. ***Human Acellular Dermal Matrix*** - Alloderm® (Life Cell Corporation) is derived from freeze-dried donated cadaver skin. Alloderm is more expensive than Permacol ($28.01/cm^2 compared to $8.73/cm^2 for Permacol) and unlike Permacol, Alloderm requires refrigeration and rehydration before use, a process which can take 15 to 20 minutes with some thicker implants. It is believed that Alloderm is theoretically capable of clearing bacteria, a property not found in synthetic meshes. In the past Alloderm® has been used in the treatment of severe burns, replacement of soft tissue, bladder support, and skin grafting (Buinewicz et al., 2004;Schuster et al., 2006). Unlike autologous materials such as skin grafts and muscle flaps, acellular dermal matrix can be used without subjecting the patient to additional morbidity in the form of donor site complications (Holton et al., 2005).

Cellular Mesh

Creation of a cellular mesh involves the harvesting of cells from a patient and culturing *in vitro* before seeding onto a biogradeable material such as polyglycolic acid (PGA). The number of cells required depends on the defect size. Approximately 1 x 10^7 for $1cm^2$ of a 1-2 mm thick scaffold is recommended, but this varies depending on the cell type used (Drewa et al, 2005). The optimal cell type has yet to be determined but fibroblasts, skeletal muscle cells, and myoblasts are being investigated. Based on the cost of TE skin I estimate that a cellular TE solution is likely to cost at least £2,370 for an 8x8cm sheet ($3,800, €2,700) (Cristiano Occhipinti, 2007).

There are no human studies and few animal studies using cellular mesh to repair abdominal wall defects. Cellular SIS mesh has been used successfully in diaphragmatic repair in a fetal lamb model (Fauza et al., 2001) and has been compared to acellular SIS mesh for the repair of large abdominal wall defects in syngenic (genetically identical) Lewis rats (Lai et al, 2003). The cellular mesh demonstrated better facilitation of tissue regeneration, improved tissue ingrowth, and better mechanical strength compared to acellular mesh (no data provided). The acellular mesh degraded gradually over 3 months and had a significantly higher hernia rate ($p = 0.005$) compared to cellular mesh; a hernia recurred in 16 of 21 (76%) acellular meshes versus 5 of 21 (23%) skeletal muscle cell meshes versus 6 of 24 (25%) fibroblast cell meshes (no significant difference ($p = 0.82$) in hernia rate between grafts seeded with fibroblasts or skeletal muscle cells) (Lai et al, 2003). In separate studies hernia rate was reported as 63% for suture repair and 32% for synthetic mesh repair for large abdominal hernias in rats (Burger et al., 2006).

Summary

Observational studies of acellular grafts have shown they could be more effective than synthetic meshes. Unfortunately limited literature is available on the use of acellular mesh in humans, in particular there are no head-to-head studies comparing biologics to the synthetic mesh or biologics with each other. Based on preclinical studies, it appears cellular grafts could prove superior to acellular grafts; they have shown better cell infiltration, cell regeneration, mechanical performance, and a reduced inflammatory reaction, in addition to more rapid revascularisation (restoration of blood supply)

(Drewa et al, 2005;Lai et al, 2003). Whether a RM solution with better long-term mechanical strength can be devised has yet to be seen. The major limiting factor is the high cost of the mesh; any new product must prove to be more effective at improving healing of the defect and reducing complications.

A market evaluation of synthetic meshes compared with biologic meshes was conducted in the US by Medpanel, Inc (Yves Bayon, 2008). The aim was to gain an understanding of potential market for biologics from a clinical perspective. It found agreement amongst surgeons that biologics offer improved clinical outcomes compared to synthetic mesh, but high cost restricts current use. A summary of the findings of this market research are in appendix 9.

Table 5.1: The advantages and disadvantages of synthetic and biological meshes

Material	Brand	Cost	Advantages	Disadvantages
Synthetic Mesh: Flatsheet			Allow tension free repair[1,2]; lower long-term hernia recurrence rates[2].	Wound infection[1,3,4]; bowel fistula[1,3,4]; erosion into abdominal viscera[1,4]; repair failure[1,4]; mesh extrusion[1,4]; early hernia recurrence rate of around 5%[2]; dense adhesion[3]; chronic sinus formation[3]; mesh removal[3].
Polypropylene	Marlex	<US$100		
	Prolene			
	Surgipro			
Polyester	Mersilene			
	Parietex			
Polytetrafluoroethylene (PTFE)	Gortex			
	Dualmesh			
Titanium-polypropylene composite	Timesh			
Polypropylene-polyglecaprone composite	Ultrapro			
Synthetic Mesh: Non-adhesive				
Polyester with collagen-polyethylene glycol-glycerol coating	Parietex Composite	US$500 - 700		
Polypropylene with carboxymethylcellulose-sodium hyaluronate coating	Sepramesh			
Polypropylene-polydioxanone composite with oxidised cellulose coating	Proceed			
Biological mesh: Acellular		**US$/cm^2**	Resistant to infection[2, 3, 4]; erosion[2]; extrusion[2]; rejection[2]; allow tension free repair[1]; lower recurrence rates[1, 2]; fewer adhesions[3]; incorporated into host tissue[3]; improved biocompatibility[4]	Can cause inflammatory response in neighbouring tissues leading to wound infection[4]; Decreased strength over time compared to synthetic meshes[1]
Dermis (Porcine)	Permacol	8.33		
	CollaMend	16.00		
Dermis (Bovine)	SurgiMend	22.00		
Dermis (Cadaveric)	Alloderm	26.08		
	Allomax	28.00		
Submucosa (Porcine)	Surgisis	3.40		
Pericardium (Bovine)	Tutopatch	NA		
	Veritas	8.60		
	Periguard	1.90		
Tissue engineering meshes: Cellular			Allows tension free repair[1,2]; better mechanical strength[1]; hernia recurrence rates do not increase over time[1]; revascularisation[1,4]; cell regeneration[1]; resistant to infection[2, 4]; erosion[2]; extrusion[2]; rejection[2]; biocompatibility[4].	Time delay required for cell proliferation (4).

(1) Lai et al. 2003; (2) Park et al. 2006; (3) Adedeji et al. 2002; (4) Drewa et al. 2005

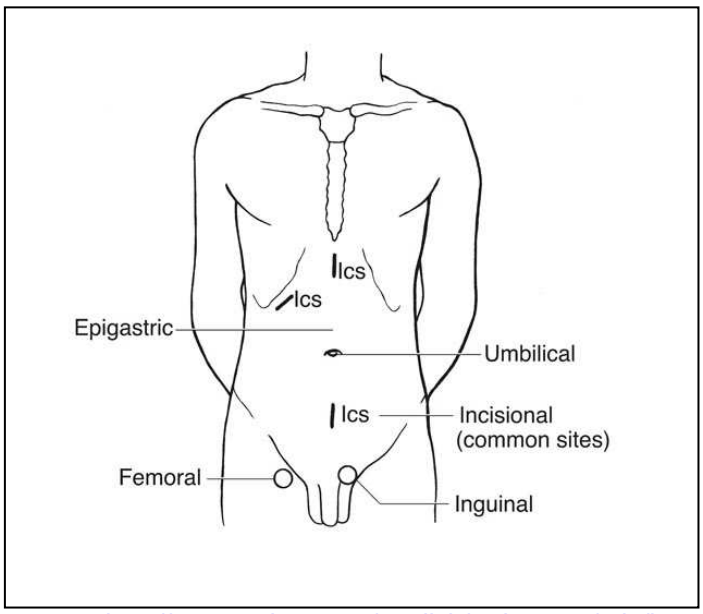
5.4 Potential Applications for a TE solution

Having described the current treatment methods along with the state-of-the-art in TE I now consider different types of abdominal wall defects in turn. In each case, I use my knowledge of standard treatment to draw conclusions about the headroom for further improvements in clinical outcome.

5.4.1 Hernia

Hernia is defined as a protrusion of abdominal viscera outside the abdominal cavity through a natural or acquired defect (Gurusamy et al., 2006) (figure 5.1 and table 5.2). They occur mostly in the abdomen and result from weakening of the abdominal wall (Franz, 2006;Park et al, 2006). Risk factors include cigarette smoke, obesity, and family history. Mechanical strain can damage tissue which leads to hernia and makes it harder to repair (Franz, 2006). Growing evidence suggests that incisional hernias and recurrent hernias usually result from failure of early surgical wound healing (Franz, 2006). Research into a possible biochemical basis of incisional hernias is still in its infancy but it has been speculated that a dysfunction in collagen synthesis or deposition may predispose to hernias (Park et al, 2006). The size of hernias can vary greatly; they can be small (less than 4cm^2) and relatively asymptomatic, or large (greater than 40cm^2) and cause significant pain and discomfort. Life threatening complications can occur in the form of incarceration (trapped bowel), and strangulation of the bowel and other viscera (Park et al, 2006). In England and Wales in 2005/06 almost 160,000 cases of hernia were reported (HES Online, 2007). Hernias are repaired surgically (herniorrhaphy) with the aim of reducing the herniated tissue and repairing the muscle tissue weakness. The current gold standard treatment is tension free closure using a synthetic mesh.

Figure 5.1: Diagram to illustrate the locations of different types of hernia



Source: http://www.wsiat.on.ca/english/wsiatDocs/mlo/hernias_screen.htm
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Table 5.2: Description of characteristics and location of the main hernia types

Hernia Type	Location	Characteristics
Diaphragmatic Hernia	High in abdomen through defect in diaphragm	Hiatus hernia - functional defect between stomach and chest Congenital diaphragmatic hernia - occurs in 1 in 2000 births
Femoral Hernia	Groin (just below inguinal hernia location)	More common in women than men Smaller and rounder than inguinal hernia Bowel can become trapped (incarcerated)
Incisional Hernia (Ventral Hernia)	Abdominal wall	Weakness in abdominal wall muscle resulting from uncompleted sealed wound Bowel can become incarcerated Can be dangerous and difficult to treat
Inguinal Hernia	Groin	Commonest type Predominant in men Can result after mechanical strain
Parastomal Hernia	An incisional hernia related to an abdominal wall stoma.	Formation commonly occurs following an ileostomy or colostomy
Umbilical Hernia	Naval (belly button)	Small and causes no problems More common in boys

Inguinal Hernia

Inguinal hernias are the most common type of hernia (80% of abdominal wall hernias occur in the groin (Aufenacker et al., 2006)), and their repair is the most frequent operation in general surgery (Amato et al., 2006). They are about eight times more common in males than females (Thaha et al., 2007); in England and Wales in 2005/06 there were 83,500 hospital admissions for inguinal hernia compared to 4,000 for femoral hernia (HES Online, 2007).

Surgical repair is the current mainstay treatment and can be performed as a day case procedure under local anaesthetic. There are three categories of operative approach; herniotomy (cutting for relief), herniorrhaphy (surgical repair, includes Bassini, Shouldlice and nylon darn methods) and hernioplasty (surgical repair, popularised by the Lichtenstein institute), now the most common method, which uses a mesh to generate a tension-free closure (Thaha et al, 2007) via an open or laparoscopic approach.

The synthetic mesh technique works adequately for inguinal hernia repair. There is little risk of serious morbidity and frequency of complications is low. Recurrence rates and infection rates for repair of primary inguinal hernias are less than 2% and 3%, respectively. Pain is the most common complication, reported to last 2 to 3 weeks (Dion Morton, 2008). The headroom for future improvement for inguinal hernia repair is limited and the putative advantages of a TE solution are unlikely to justify their costs.

Incisional Hernia

Incisional (or ventral) hernias are one of the most common wound complications encountered by gastrointestinal surgeons (Mathes et al, 2000;Park et al, 2006) and the second most common abdominal wall hernia (Aufenacker et al, 2006). Following laparotomy (surgical incision into the peritoneal cavity) as many as 1 in 5 patients will develop an incisional hernia (Burger et al, 2006;Gurusamy et al, 2006;Mathes et al, 2000;Park et al, 2006). In the US 4 to 5 million laparotomies are performed annually suggesting 400,000 to 500,000 incisional hernias develop each year (Burger

et al, 2006). In England and Wales there were 16,500 incisional hernias in 2005/06 (HES Online, 2007).

Risk factors for developing an incisional hernia may be surgical or medical (Kim et al., 2006b). Surgical risk factors include emergency procedures, early reoperation, type of original incision, suture material and closure technique. Medical risk factors include obesity, malnutrition, anemia, liver disease, pulmonary disease and wound infection. The biggest and most consistent causative factor is wound infection (Adotey, 2006;Franz, 2006;Kim et al, 2006b). Patients receiving peritoneal dialysis (removal of soluble substances and water from the body by transfer across the peritoneum) may be more susceptible to incisional hernias with a reported incidence of approximately 60% (Park et al, 2006).

Incisional hernias tend to be much larger than other types of hernia, with an average size of about 105 cm^2 (LeBlanc, 2005). They are a significant source of morbidity (Franz, 2006) and are associated with complications including pain and discomfort, which increases when standing and after eating meals (Dion Morton, 2008), incarceration (reported incidence of 10% and mortality rate of 25%) and bowel strangulation requiring resection (reported in 20% of incarcerations and has a mortality rate of 20%) (Park et al, 2006). The frequency of complications is lower for synthetic mesh repair compared to suture, however complications still occur including hernia recurrence (occurring a third of all cases with mesh), pain and infection. The incidence of infection is less than 10% but the clinical consequences of infected intraperitoneal or abdominal wall mesh are severe (Helton et al., 2005). Complications sufficient to prompt re-operation occur in approximately 5% of incisional hernia cases (Adedeji et al, 2002).

There is headroom for improvement in effectiveness of incisional hernia repair but whether a TE mesh would perform better than a synthetic mesh for the repair of primary ventral hernias is uncertain.

Parastomal Hernia

Parastomal hernia is an incisional hernia occurring in the gap between the intestinal segment forming the stoma and the surrounding tissue (Baig et al., 2006). It is a known complication of stoma surgery, such as a colostomy or ileostomy (surgical procedures to create an opening for removal of faeces), and occurs in up to 50% of stoma patients (Janes et al., 2004b). Risk factors associated with a parastomal hernia include obesity, prostatism (compression or obstruction of the urethra), malnutrition, urinary obstruction, and chronic cough (Baig et al, 2006). In England and Wales in 2005/06 there were around 500 hospital admissions for parastomal hernia, 3,776 for ileostomy and 2,019 colostomy (HES Online, 2007).

Stomal hernias develop gradually, increasing in size over time during the first few years of stoma formation, but the risk of herniation persists for 20 years (Carne et al., 2003). Parastomal hernias are classified into four subtypes: interstitial, where the hernial sac lies within the layers of abdominal wall; subcutaneous, where the hernial sac lies in the subcutaneous plane; intrastomal, where the sac penetrates into a spout ileostomy; and peristomal, where the sac is within a prolapsing stoma (Carne et al, 2003). Parastomal hernias can be asymptomatic, induce mild symptoms or even life threatening symptoms (Baig et al, 2006). They are uncomfortable and cause embarrassment to the patient. Although rare, complications can arise, such as strangulation, obstruction and perforation, causing significant pain and discomfort (Carne et al, 2003).

Recurrent peristomal (area of skin surrounding a stoma in the abdominal wall) pain is an indication for surgical repair (Carne et al, 2003). One in three parastomal hernias require surgical intervention (Janes et al, 2004b). The techniques for parastomal hernia repair fall into two categories:

1. Local fascial repair, which keeps the stoma in place but removes the hernia;
2. Stoma relocation followed by standard hernia repair (discussed earlier) (Carne et al, 2003).

Controversy exists regarding which procedure should be used at which point in hernia development. Rubin and colleagues (Rubin et al., 1994) suggest first time hernia repair should be via stoma relocation and recurrent hernias should be treated by local repair using synthetic mesh. However, the

ideal solution is to prevent the formation of a parastomal hernia altogether. A mesh could be used in this situation.

An RCT by Janes and colleagues observed the effect of synthetic mesh in prevention of parastomal hernia. Lightweight synthetic mesh was successful in preventing complications (including wound infection, fistula formation, or pain) and the development of parastomal hernia. The reported incidence of parastomal hernia, published in the British Journal of Surgery (Janes et al, 2004b) was 0 of 16 patients in mesh group compared with 8 of 18 in non-mesh group, conversely, in a later publication in the Archives of Surgery (Janes et al., 2004a) incidence is reported as 1 of 27 patients in the mesh group compared to 13 of 27 in the non-mesh group. The mesh proved so successful at 12 months the trial was stopped on ethical grounds. The authors now employ a prosthetic mesh for all colostomies, including emergencies, and intend to follow these patients for 5 years to assess longer term effectiveness (Janes et al, 2004b).

A parastomal hernia is a contaminated non-epithelialised defect. Hernia repair in a contaminated field represents one of the highest risks for failure and a difficult clinical problem (Kim et al, 2006b). Synthetic mesh use is contraindicated in a contaminated defect. Clinicians are not in favour of using synthetic meshes to repair parastomal hernias as potential complications can be severe (Dion Morton, 2008). The general consensus is that prevention of parastomal hernias is the way forward. There is some headroom for improvement in treatments to prevent parastomal hernias, although, as with incisional hernias, the headroom may not be sufficient to justify the cost of a TE approach.

5.4.2 Laparostomy

Creation of a laparostomy (open abdominal management) occurs following:

- ***Infection*** **-** Wounds are classified based on level of infection (table 5.3). Contamination can result from exposure to enteric (small intestine) contents, ostomy (surgical opening) creation, fistula, incarcerated (closed hernia, cannot be manipulated) or strangulated (constricted blood supply, can lead to gangrene) hernias, defects created after excision of infected mesh and defects associated with acute tissue loss after severe trauma. As previously stated, one of the main disadvantages of

synthetic mesh repair is infectious complications; PTFE and polypropylene have infectious rates that range from 0.5% to 7.7% (Ueno et al., 2004). When a permanent mesh becomes colonised with bacteria a recurrent hernia will almost always develop, necessitating further operations to remove the infected mesh and insert a new mesh (Helton et al, 2005;Kim et al, 2006b;Patton et al., 2007). The removal of mesh results in a larger defect, repair cannot happen immediately as there is a high risk of continuing infection.

- ***Emergency Surgery*** **-** Abdominal Compartment Syndrome (ACS) is a potentially lethal condition defined by intraabdominal hypertension exceeding 20mmHg (Tons et al., 2000;Walker et al., 2003). Primary abdominal compartment syndrome occurs prior to surgery, often as a consequence of intraabdominal inflammation and infection resulting from conditions such as pancreatitis (inflammation of the pancreas) and infective peritonitis (inflammation of the peritoneum). Secondary compartment syndrome is a result of previous medical or surgical treatment or trauma, including forced closure of the abdominal wall following abdominal surgery, again following serious intraabdominal pathology (Tons et al, 2000). Treatment of ACS is via an emergency decompressive laparotomy followed by creation of a laparostomy.

Table 5.3: Classification of wound Infection

Classification	Description	Infection Rates
Clean (Class I)	Uninfected operative wound No acute inflammation Closed primarily Respiratory, gastrointestinal and urinary tracts not entered No break in aseptic technique Closed drainage used if necessary	<2%
Clean-contaminated (Class II)	Elective entry into respiratory, gastrointestinal, urinary tracts with minimal spillage No evidence of infection or major break in aseptic technique	<10%
Contaminated (Class III)	Nonpurulent inflammation present Gross spillage from gastrointestinal tract Penetrating traumatic wounds <4 hours Major break in aseptic technique	20%
Dirty-infected (Class IV)	Purulent inflammation present Preoperative perforation of viscera Penetrating traumatic wounds >4 hours	40%

Table reprinted with permission from eMedicine.com, 2009.
Available at: http://emedicine.medscape.com/article/188988-overview

Repair of a contaminated field represents a number of challenges in terms of wound management. A laparostomy can be used prophylactically if it is clear that primary closure under tension will create extensive intra-abdominal pressure. It is also used following mesh infection when there is a 2 to 3 week delay to allow the infection to clear-up before attempting repair (Dion Morton, 2008).

In a laparostomy the exposed contents are covered with a sterile mesh, which aids drainage of infectious materials, permits visual control of the underlying viscera, facilitates access to the abdominal wall, preserves the fascial margin and allows mobilisation of the patient (Schachtrupp et al., 2002). However, there is currently no ideal mesh for use in these infected defects. The re-implantation of synthetic mesh into a contaminated area exacerbates wound infection resulting in infection rates as high as 50% to 90% (Kim et al, 2006b;Patton et al, 2007;Ueno et al, 2004). Following laparostomy repair is attempted. This staged approach carries increased morbidity compared to a single surgical approach and the initial phase provides minimal support (Patton et al, 2007).

Four out of every six patients who end up in intensive care following a laparostomy as a result of infection will survive and require reconstruction of their non–epithelialised abdominal wall (Dion Morton, 2008). However, a laparostomy is often left to heal by secondary intention, which can take a very long time and almost always results in the development of a hernia, resulting in a prolonged stay in intensive care (Liyanage et al., 2006;Schachtrupp et al, 2002).

A state-of-the-art primary repair technique that is resistant to infection or overlying skin breakdown is a worthy goal. A TE mesh could provide initial gains by overcoming primary morbidity through facilitation of early closure of the wound and later gains by aiding the formation of a stronger abdominal wall. The underlying hypothesis here is that a TE solution would be superior to synthetic mesh because, being natural tissue it would be less prone to infection.

The role of TE could be limited by the time delay required to prepare the tissue, approximately 2 to 3 weeks (Yves Bayon, 2008). This approach would not be appropriate for immediate primary closure in an emergency. However, in planned surgery a cellular TE solution could be suitable. For example, in

staged repair (following a laparostomy), an infection must be cleared prior to closure and thus there would be sufficient time to prepare the TE tissue. Cells can be taken during the initial surgery (laparotomy or mesh removal) or 3 weeks prior to the planned surgery (if it is expected patient will require longer recovery) and second surgery can be planned to coincide with finished tissue. It is thought this would still lead to more rapid recovery and would be preferable when the alternative is healing by secondary intention (Dion Morton, 2008;Yves Bayon, 2008). Consideration is required on how to store tissue if it is ready but surgery is delayed.

5.4.3 Tissue Necrosis

There are many causes of tissue necrosis (death) including infection, inflammation, and trauma. An abdominal wall defect may be caused by synergistic gangrene: a polymicrobial necrotising infection, caused by Beta-haemolytic *streptococci* Group A (*Streptococcus pyogenes*), a gram-positive organism that cause several serious infections plus *Staphylococcus aureus* gram negative aerobes or anaerobes (British Society for Antimicrobial Chemotherapy, 2007). These necrotising infections can present with a hernia and often follow local tissue injury, including surgery and abscess drainage. Diabetes is a common predisposing disease.

Fournier's gangrene is a rare but aggressive form of synergistic gangrene affecting the perineum (area between the opening of the vagina and the anus in a woman, or the area between the scrotum and the anus in a man). The condition presents with scrotal skin pain, itching, tenderness, oedema (swelling), and redness, with severe swelling of the scrotum, crepitation (a dry, crackling sound, or sensation) and necrosis of the skin. It progresses rapidly and can cause multiple organ failure and death, with mortality rates averaging between 20% to 30% (Paty et al., 1992). Diabetes Mellitus and alcoholism predispose to the condition and most cases are diagnosed in elderly patients with immunodeficiency (Yanar et al., 2006).

The treatment for Fournier's Gangrene requires rapid administration of antibiotics and immediate surgical debridement. In the majority of cases this is extensive and almost always results in loss of the scrotum and testes and often the penis (Pawlowski et al., 2004). This surgical intervention leaves

behind a large defect, and as with a laparostomy, the open wound results in fluid and protein loss, increasing recovery time, and hospital stay.

Reconstructive surgery is essential following a gangrenous infection of the perineum. This is a complex and difficult challenge both cosmetically and functionally. Synthetic mesh use for open repair is generally contraindicated following debridement of infected tissues (Guzzo et al., 2007) because synthetic material may allow the infection to regain its foothold (Dion Morton, 2008). The current most commonly used approach to reconstruction is to use skin and tissue grafts such as a myocutaneous flap (Guzzo et al, 2007). Meshed, unexpanded skin grafts have shown to be highly successful for penile reconstruction, with graft up-take of 100% recorded and 6 month follow-up improvements in functional and cosmetic outcomes were reported as satisfactory (Black et al., 2004). However, there are drawbacks to skin grafting such as donor-site morbidity and post-operative complications.

A TE mesh could provide an alternative, potentially superior solution to reconstructive surgery following tissue necrosis. One approach would be to develop a biological mesh. However, this could be difficult due to the large and irregular shape of the defect. Another approach would be engineered tissue as an alternative to autologous tissue, which would prevent skin graft shortage problems and complications relating to the donor site. In addition, eliminating a need to harvest tissue could reduce operating theatre time and thus reduce overall cost of treatment. These are highly contaminated and dirty wounds. However, they are infrequent and the small market might not justify the additional cost of TE products.

5.4.4 Omphalocele

Omphalocele is a congenital defect (the aetiology of which is unknown), characterised by herniation of intraabdominal viscera through an open umbilical ring, which fails to close during embryogenesis (Salomon et al., 2002). This condition causes significant morbidity and mortality (Wilson et al., 2004), and is often associated with chromosomal defects and additional congenital abnormalities. The birth prevalence has been estimated at 2.5 in 10,000 in Western countries. The prognosis for the patient is dependent on the size of the hernia and associated congenital abnormalities. Immediate postoperative

complications usually relate to significant changes in intra-abdominal pressures and are more frequent with giant defects. Short-term complications include necrotising enterocolitis (inflammation of the small intestine and colon), prolonged ileus (a partial or complete non-mechanical blockage of the small and/or large intestine), and respiratory distress. Long-term complications include parenteral nutrition dependence (given through the veins of the circulatory system, rather than through the digestive system), gastroesophageal (stomach and oesophagus) reflux, parenteral nutrition-related liver disease, feeding intolerance, and neurodevelopmental delay (McNair et al., 2006).

Postnatal management includes protection of herniated viscera, maintenance of fluids and electrolytes, prevention of hypothermia, gastric decompression, prevention of sepsis, and maintenance of cardio respiratory stability (McNair et al, 2006). Current treatment strategies include delayed closure using a synthetic graft or large skin flaps, or topical treatment to promote epithelialisation. Drawbacks to these methods are wound infection, fascial separation, abdominal domain loss (Kapfer et al., 2006) and formation of an incisional hernia, requiring surgical intervention in the future (Alaish et al., 2006).

There is certainly headroom for improvement in treatment. The most attractive possibility for the surgical repair of congenital abdominal wall defects, would be the immediate availability of a non-immunogenic and non-synthetic biomaterial that could guide the regeneration of normal tissue (Gamba et al., 2002). The size of the potential market may be limited as this is a rare condition. However, investigation into the use of TE products has already begun.

5.4.5 Conclusion

After careful analysis of the clinical problem it appears synthetic meshes have problems when the defect is *large* and when there is *infection* (table 5.4). In the latter situation, a mesh may be needed to replace skin as well as deeper tissue layers. Infected defects pose a particular challenge in terms of treatment as synthetic mesh use is contraindicated. In such circumstances an alternative product is desirable.

Table 5.4: Abdominal wall defects with potential for a TE/RM solution

		Size of defect	
		Small	**Large**
Presence of contamination or infection	**No**	Little or no scope	Possible potential for a TE solution
	Yes	Possible potential for a TE solution	Large potential for a TE solution

Many of the indications discussed above have headroom for improvement in effectiveness, but many have low prevalence and therefore the potential market will be limited. I conclude that the applications with the greatest potential headroom for a TE solution worth further investigation are:

i. Treatment of incisional hernias - when defect is infected or contaminated;
ii. Prevention of parastomal hernias;
iii. Laparostomy - planned staged repair and repair of non-epithelialised abdominal wall defects that result from infection following a laparostomy.

In the following section I will apply the headroom method to large, infected incisional hernias. If a TE solution is cost-effective in this scenario, I predict it is likely to be cost-effective in the other two scenarios, which have greater headroom for improvement in effectiveness.

5.5 Clinical Effectiveness

Here I review the clinical effectiveness of different meshes used for incisional hernia repair before summarising the overall recurrence rate for different types of incisional repair. Next, I elicit the utility score associated with the clinical effects of having an infected incisional hernia.

5.5.1 Synthetic Mesh for Incisional Hernia Repair

There are currently no systematic reviews comparing mesh repair with non-mesh repair in the treatment of incisional hernias. Two RCTs (Burger et al., 2004;Luijendijk et al., 2000) comparing suture to synthetic mesh have been identified, but they involve the same patient cohort over different follow-up periods (n=200). Luijendijk and colleagues report 36-month follow-up and Burger and

colleagues report 10-year follow-up (table 5.5). In addition, one retrospective study (Conze et al., 2007) assesses the challenges of reoperation following mesh repair, and a cost analysis (Israelsson et al., 2003) has compared hernia recurrence following suture and synthetic mesh in incisional hernia repair.

The RCT by Burger and colleagues compared suture repair to mesh repair in patients undergoing primary incisional hernia repair (n=171) and first recurrent hernia repair (n=29). The 3-year cumulative recurrence rates were 23% for mesh repair (24% for primary repair and 20% for first recurrence repair, P=0.02) versus 46% for suture repair (43% for primary repair and 58% for first recurrence repair, P=0.10) (P=0.009) (Luijendijk et al, 2000). The 10-year overall cumulative hernia recurrence rates were 63% for suture repair and 32% for synthetic mesh repair (P<0.001). In a subgroup of 50 patients with small incisional hernia (<10cm^2) the recurrence rates were 67% following suture repair and 17% following mesh repair (Burger et al, 2004). The independent risk factors identified for recurrence were abdominal aortic aneurysm (P=0.01) and infection (P=0.02). In addition mesh repair is associated with a higher rate of hernia repair-related complications (17% compared to 8% for suture repair, P=0.17) and a lower rate of abdominal pain (20% compared to 27% for suture repair, P=0.53) but these are not significant. The results for cosmetic results and patient satisfaction were also comparable between the suture and mesh groups. Israelsson and colleagues (Israelsson et al, 2003) followed up 44 patients who received suture repair (mean follow-up of 67 days) and mesh repair (mean follow-up of 30 days). Hernia recurrence was reported in none of 19 patients in the mesh group and 5 of 13 patients in the suture group (P<0.01).

A retrospective study (n=77) by Conze and colleagues found the number of re-operations following initial incisional repair rises linearly over time in both mesh and suture groups. Half the patients required re-operation within 14 months and 75% within 24 months. Despite the improvements associated with mesh, hernia recurrence still occurs in 25% or more (compared with 1 in 50 or less with inguinal hernias) and these occur at the border of the implant. Local mesh-related problems, such as infection and adhesion (reported in 73% of cases in this study) are a further problem; severe adhesions can lead to a need for bowel resection. The authors conclude that every re-operation after

previous mesh repair remains a demanding and challenging procedure. This highlights again the headroom available for a treatment for a complicated incisional hernia.

Table 5.5: Synthetic mesh repair versus non-mesh repair for treatment of incisional hernias

Study		Burger et al. 2004	
Type		RCT	
N		200	
Follow-up		10 yr	
method of repair		Suture (97 patients)	Mesh (84 Patients)
Type of hernia (patients)		171 patients primary repair; 29 patients first recurrence	
mean size of defect (cm2)		20 (range: 1-225)	24 (range: 1-160)
Mean age of patient (years)		63 (25-82)	57 (23-85)
Body mass index		26 (range: 20 - 41.5)	26.2 (range: 19.7 - 41.5)
Duration of Operation		45 minutes	58 Minutes
Number of recurrences		54*	27*
10 yr cumulative Recurrence rate	**Overall**	63%*	32%*
	Defects <10cm2	67%*	17%*
risk factors for hernia recurrence		abdominal aortic aneurysm*; infection*	
Complication rate	**Overall**	8%	17%
	Small bowel obstruction	3%	8%
	Fistula	0%	6%
	Wound Infection	0%	1%
	Strangulated hernia	1%	0%
	Burst Abdomen	1%	0%
Further hernia repair		35%*	12%*
Pain	**Scar**	23%	20%
	Abdominal	39%	18%
Satisfaction	**Overall**	64%	77%
	Cosmetic	46%	51%

**Statistically significant (p<0.05)*

5.5.2 Acellular Grafts for Incisional Hernia Repair

The effectiveness of porcine dermis, porcine submucosa, and cadaveric dermis has been assessed in humans with a complex (infected or contaminated) incisional hernia undergoing non-primary hernia repair (tables 5.6, page126).

Porcine Dermal Collagen

There are no RCTs investigating the effectiveness of porcine dermis. A retrospective study of 9 patients (Parker et al, 2006) and a prospective study of 20 patients (Shaikh et al., 2007) have been identified. Parker and colleagues retrospectively investigated the effectiveness of Permacol in complicated incisional hernias. Two post-operative complications were reported: 1 patient (11%) had a recurrent hernia after intentional removal of Permacol mesh following a wound infection at month 13 and 1 patient (11%) developed skin separation with exposure of mesh but following general wound care went on to heal with no evidence of infection. The authors (Parker et al, 2006) conclude Permacol is a safe and acceptable alternative to synthetic mesh for repair of complicated incisional hernia repair.

Shaikh and colleagues prospectively investigated the use or Permacol in large abdominal wall defects (8 patients) and complex incisional hernias (12 patients). Twelve of twenty (60%) patients experienced no complications and were sent home within 7 days, 7 (35%) patients experience complications (2 (10%) seromas, 2 (10%) minor wound infections, 1 (5%) wound haematoma, 1 (5%) skin edge necrosis, 1 (5%) superficial wound dehiscence) and 1 (5%) patient died of multiple organ failure.

Overall, it can be concluded that the use of porcine dermal collagen or Permacol® for the repair of complex abdominal wall defects shows good outcomes, demonstrating good ease of handling, good tensile strength, non-immunogenicity, and good gradual incorporation by host fibrous tissue when used for abdominal wall repair (infected or contaminated) (Adedeji et al, 2002;Liyanage et al, 2006;Parker et al, 2006;Shaikh et al, 2007;Ueno et al, 2004).

An ongoing RCT aims to assess the effectiveness of preventing parastomal hernias using Permacol®, placed around the stoma to reinforce the tissue, versus the surgeons standard technique to construct a stoma with no reinforcement (Dion Morton, 2008). The pilot study preceding this RCT suggested collagen mesh is likely to result in less complications than synthetic mesh, particularly with regard to sepsis and erosion, as well as easier to manipulate and separate from surrounding tissues if re-operation is required (Dion Morton, 2008). The major drawback is its cost; with a sheet of Permacol of size 18cm x 28cm costing around £3,700 ($6,000, €4,200) (Emma Rowley, 2007).

Porcine Small Intestine Submucosa

Two prospective studies (Franklin, Jr. et al., 2004;Ueno et al, 2004) and one retrospective study (Helton et al, 2005) have investigated the effectiveness of porcine small intestine submucosa in contaminated abdominal wall defects.

Franklin and colleagues (Franklin, Jr. et al, 2004) followed up 53 patients who underwent a total of 58 hernia repairs (incisional (n=43) or inguinal (n=15)) in a partially contaminated setting for 2 years. Wound infection was reported in 2% of patients but no other mesh-related or hernia related complications were reported and histological analysis confirmed good incorporation of the mesh and in growth.

Ueno and colleagues (Ueno et al, 2004) also prospectively investigated the use of porcine small intestinal submucosa in the management of infected (11 patients) and partially contaminated (9 patients) abdominal defects (18 ventral and 2 inguinal hernias). Overall, wound infection occurred in 8 of 20 (40%) cases, hernia recurrence occurred in 6 of 20 (30%) cases and seromas occurred in 2 of 20 (10%) cases. As expected patients' with prior infection reported greater incidence of recurrence (45% compared with 11%) whilst patients with contamination reported a greater incidence of wound infection (44% compared to 36%) and a greater number of seromas (11% compared to 9%).

Finally, Helton and colleagues (Helton et al, 2005) retrospectively investigated the use of porcine small intestine submucosa (Surgisis) in 53 patients over 14 months. Patients were classified by wound class (see table 5.3, page 131); 31 of 53 (58%) patients had a clean wound, and 22 of 53 (42%) patients had a contaminated or dirty wound. The authors note that two important complications are related. The likelihood of a hernia recurrence is increased with mesh infection, which is increased by wound dehiscence. Overall, 13 (25%) patients experienced wound dehiscence and 9 (17%) patients developed a recurrent hernia. As might be expected the rate of both complications was higher in the contaminated repair group (table 5.6) and based on this finding the authors advise caution when using Surgisis in contaminated and infected defects. The authors conclude that the short-term results for Surgisis are equivalent to that of prosthetic mesh, when used in clean defects.

The drawbacks of Surgisis (porcine submucosa) are due to its anatomy; the maximum width is 8cm when manufactured into a four-ply sheet. This will limit its potential for use in large hernia repair. In such instances, more than one mesh is required, thus increasing the cost. A sheet of Surgisis, 7x10cm 4-ply, costs around $500. Franklin and colleagues (Franklin, Jr. et al, 2004) suggest that the additional cost of Surgisis will be compensated by downstream benefits such as the abolition of further surgery. However, there are no head-to-head comparisons to back up such claims.

Human Acellular Dermal Matrix (HADM)

Using HADM has been investigated in a number of animal studies and a few human studies. It is well tolerated by the host immune system, has mechanical properties similar to synthetic materials and some ability to revascularise (Holton et al, 2005). More recently Alloderm has been investigated for use in contaminated sites when synthetic mesh is contraindicated and in patient cohorts whose defects would conventionally be closed by staged repair.

Seven cohort studies assessed the effectiveness of HADM or Alloderm in contaminated (wound classification II, III, or IV; see table 5.3) or infected defects (primarily incisional hernias). Six were retrospective (Bellows et al., 2007;Buinewicz et al, 2004;Holton et al, 2005;Jin et al., 2007;Patton et al, 2007;Schuster et al, 2006) and one prospective (Kim et al, 2006b).

Bruinewicz and colleagues (N=44) found Alloderm exhibits good biomechanical properties and is successful for the repair of challenging hernias. The authors identified a 4.5% incidence of hernia recurrence, wound dehiscence and haematomas or seromas, and a 6.8% incidence of wound infection; the lowest complication rates reported in any study when using any material to repair a complex hernia. Holton and colleagues (N=49) reported a hernia recurrence rate of 10% and found that patients who developed a recurrence were younger and less obese on average. Wound infection occurred in 20% (of which 20% subsequently lead to reherniation and 10% lead to mesh removal), seromas occurred in 10% and 2% developed wound dehiscence. No complications were reported when HADM was used near a stoma (Buinewicz et al, 2004).

Schuster and colleagues (Schuster et al, 2006) concluded that Alloderm “works satisfactory” for primary closure of contaminated defects based on a retrospective study of 18 patients. Overall hernia recurrence was 50%; 33% was recorded amongst patients with primary closure compared to 83% amongst patients who did not have primary closure (p=0.03). Based on 20 patients, Bellows and colleagues (Bellows et al, 2007) concluded that Alloderm was safe for tension-free closure of large contaminated defects. Postoperative complications were experienced in 55%; 30% experienced a hernia recurrence after 8 months, 25% reported wound infection, 30% (6 patients) experienced wound dehiscence and 25% had the mesh removed. Complications were higher in dirty/contaminated wounds compared with clean-contaminated/clean wounds (p=0.049).

Patton and colleagues (Patton et al, 2007) conducted a study of 67 patients with contaminated ventral hernia and found wound infection occurred in 16%, recurrent hernias occurred in 18% and mesh graft removal was required in 3%. The author has concluded that this was an improvement on synthetic mesh in contaminated defects and was comparable to synthetic mesh in non-contaminated defects.

Finally, Jin and colleagues (N=37) used Alloderm in bridged hernia repair (an intraperitoneal interposition graft providing a single layer repair from the edges of the fascia under tension) (n=11) and reinforced hernia repair (graft placed in an onlay, underlay, or sandwich technique after primary re-approximation) (n=26) to investigate whether the method has an effect on effectiveness. Hernia recurrence rate was 35% overall (83% following bridged repair; 80% following reinforced repair). The method used to place Alloderm in the abdominal wall defect has a significant impact on recurrence rates; the only predictive value was the use of bridging technique. The authors concluded that Alloderm should be used only as reinforcement after primary fascia re-approximation (Jin et al, 2007).

The only prospective study identified (N=29) (Kim et al, 2006b) found a success rate (determined by intact repairs at 182 days follow-up) of 89% with just 10% of patients experiencing a recurrence following repair using acellular dermal matrix. Postoperative complications were reported in 45% of patients wound infection was the most common (41%), of which 31% required further treatment and 96% healed without further complication.

Table 5.6: Effectiveness of acellular meshes for treatment of incisional hernias

Study	Franklin et al. 2004	Uneo et al. 2004		Helton et al. 2005		Parker et al 2006
Type	prospective cohort	prospective cohort		Retrospective case series		retrospective cohort
N	58	20		53		9
Follow-up	19 months	15.7 months		14 months		18.2 months
Material	Surgisis	Porcine SIS		Surgisis		Permacol
Defect	incisional hernia (43); inguinal hernia (15)	Infected defect (11 patients; [9 incisional hernia; 2 inguinal hernia])	Contaminated defect (9 patients)	Incisional Hernia		Complex incisional Hernia (5 contaminated; 2 type IV)
Indication for surgery	20 (34%) potentially contaminated (incarcerated/ strangulated bowel or coincidence with a laparoscopic cholecystectomy/colectomy); 13 (22%) grossly contaminated (puss or faecal spillage, infected synthetic mesh and dead bowel)	removal of infected synthetic mesh (8), contaminated gastrointestinal field (3), Bowel incarceration (3); cholecystitis (2), infected wound (1); enterotomy (1), fascia necrosis (1); enterocutaneous fistula (1)		Clean defect - 22 patients	Contaminated defects -31 patients	removal of infected synthetic mesh (4); fascial defect (2); infection (1); parastomal hernia (1); incarcerated hernia (1)
mean size of defect (cm^2)				326		
Mean age (years)		57	63	234	391	58
operative time (min)				51		
hospital stay (days)				47	54	
primary closure		50%		68%		
Complication rate	2%	overall, 50%		41%		22%
Recurrence rate	0%	Overall, 30%		17%		11%
Wound Infection	2%	Overall, 40%		5%	26%	11%
Wound Dehiscence	0%			21%		
Haematomas and Seromas	0%	9%	11%	9%	35%	

Study	Shaikh et al. 2007		Buinewicz et al. 2004	Holton et al 2005	Schuster et al 2006
Type	prospective cohort		retrospective cohort	retrospective cohort	retrospective cohort
N	20		44	49	18
Follow-up	18 months		20 months	6 months	9.1 months
Material	Permacol		Alloderm	HADM	Alloderm
Defect	abdominal wall defects (8 patients)	Complex incisional hernia (12 patients)	Incisional hernia	Incisional hernia	complex abdominal wall defects
Indication for surgery	Strangulated incisional hernia (3); re-exploration laparotomy (2); stab wound (2); tumour resection (1)	Primary incisional hernia repair (3); recurrent hernia repair (9)	12 primary repairs, 32 non-primary repairs Those for non-primary repair were result of synthetic mesh infection	20 primary repair, 18 second repair, 11 third or greater repair	Infected synthetic mesh (8), colon anastomotic leak (4); dehiscence (3); bowel resection (2); stomach resection (1)
mean size of defect (cm^2)	280	110	86.43		
Mean age (years)	48	52	49	52	68
operative time (min)	85	68			
hospital stay (days)	9	5			
primary closure	60%				67%
Complication rate	75%		23%		
Recurrence rate	overall, 15%		7%	12%	30% (wound closure = 33%; wound not closed 83%)
	25%	8%			
Wound Infection	Overall, 10%		5%	20%	
	25%	0%			
Wound Dehiscence	overall, 5%		5%	2%	
Haematomas and Seromas	Overall 15%		5%	10%	
	13%	16%			

Study	Bellows et al 2007	Jin et al 2007	Patton et al 2007	Kim et al 2006
Type	retrospective cohort	retrospective cohort	retrospective cohort	prospective cohort
N	20	37	67	29
Follow-up	9.4 months	21.4 months	10.6 months	182 days (~6 months)
Material	Alloderm	Alloderm	Alloderm	HADM
Defect	complex abdominal wall defects	Complex Incisional hernia (Bridged repair (11 patients), reinforced fascial repair (26 patients))	complex abdominal wall defects	Infected incisional hernia
Indication for surgery	fascia necrosis (8); incisional hernia (5);removal of infected mesh (3); tumour resection (1) enterocutaneous fistula (1); incarcerated incisional hernia (1); wound dehiscence (1)	synthetic mesh removal (9); immunocompromised (9); bowel resection (8); non-healing wound (4); cancer (4); fistula takedown (3)	reconstruction following intra-abdominal infection 39%	74% non-primary repair - recurrent hernia and/or synthetic mesh complication
mean size of defect (cm^2)	209.7	175 (bridged); 89 (reinforced)		
Mean age (years)	62	53	55	54
operative time (min)				
hospital stay (days)				
primary closure	25%			97%
Complication rate	55%		35%	45%
Wound Infection	25%		16%	41%
Recurrence rate	30%	35%	18%	10%
Wound Dehiscence	30%			
Haematomas and Seromas			5%	3%

5.5.3 Recurrence Rate

Table 5.6 above reports the hernia recurrence rate for each study identified. Here, I summarise the recurrence rate, by type of material. Using review manager, I conduct meta-analysis of recurrence rate. These results are shown in table 5.7 below. This information will be required later in the headroom analysis. As hernia recurrence is the most significant long-term complication. An ideal new generation mesh would reduce recurrence rate as well as reducing the early complications.

From the results below it can be seen that for type 1 hernias the use of acellular mesh has resulted in a reduction in hernia recurrence, an improvement over the use of synthetic mesh and suture alone. However, for type 2 hernias the use of acellular mesh is not as effective, resulting in a larger recurrence rate. In conclusion, type 2 hernias have a larger headroom for improvement over type 1 hernias and will be the focus of the headroom analysis to follow.

Table 5.7: Summary of recurrence rate for each material

Defect		Material		study	N	follow-up (yrs)	Recurrence rate		
Type 1	Incisional hernia repair (primary and non-primary repair)	suture		Burger 2004	97	10.0	63%	63%	63%
		synthetic		Burger 2004	84	10.0	32%	32%	32%
		Acellular	porcine	Helton 2005	22	1.2	5%	10%	11%
				Shaikh 2007	8	1.5	25%		
			human	Buinewicz 2004	44	1.7	5%	12%	
				Holton 2005	49	0.5	12%		
				Schuster 2006	12	0.8	33%		
Type 2	Complicated Incisional Hernia (contaminated or infected defects)	Acellular	porcine	Franklin 2004	58	1.6	0%	22%	23%
				Helton 2005	31	1.2	26%		
				Parker 2006	9	1.5	11%		
				Shaikh 2007	12	1.5	8%		
				Ueno 2004	20	1.3	30%		
			human	Bellows 2007	20	0.8	30%	24%	
				Jin 2007	37	1.8	35%		
				Kim 2006	29	0.5	10%		
				Patton 2007	67	0.9	18%		
				Schuster 2006	6	0.8	83%		

5.5.4 Utility of Clinical Effects

Based on the evidence provided previously, I have concluded that the headroom analysis should focus specifically on infected and complicated incisional hernia repair as this particular type has the greatest headroom for improvement over current treatment. However, as previously described there were no utility values associated with a health state following repair of an infected incisional hernia available in the literature. Instead, I wrote a questionnaire and elicited this value directly from a sample of healthcare professionals. Full details of the methods are described in section 5.2.2 (page 114). The questionnaire used to elicit the health utility associated with the repair of an infected incisional hernia can be seen in appendix 6.

The questionnaire was completed by 54 healthcare professionals. Fifty of fifty-four (93%) individuals answered the TTO question. Using equation 5.1 (section 5.2.2, page 114), the TTO responses given in the questionnaire were converted into utility scores. The utility scores elicited ranged from 0 to 1 and had a negative skew. Full descriptive analysis can be found in appendix 6 following the questionnaire. In conclusion the mean utility for the period of maximum symptoms was calculated as 0.85 (95%CI: 0.79, 0.91) from 50 responses.

Forty-four of fifty-four individuals completed the question about WTP. The WTP to avoid a 0.15 decrease in utility for 10 years ranged from £500 to £250,000 with 64% (28 of 44) of healthcare professionals stating that they would be prepared to pay between £1,001 and £10,000 for the new treatment. Full descriptive analysis is in appendix 6. In conclusion, the mean WTP to avoid a 0.15 decrease in utility for 10 years was calculated as £18,611 (95%CI: £9,262, 17,198) ($30,500, €21,350) from 44 responses. Finally, by combining the responses from the two questions I calculated the mean WTP per QALY as £273,846 (95%CI: £158,340, £389,353) ($448,200, €314,200) from 39 responses.

5.6 Cost of Treatment

Cost data of incisional hernia repair using synthetic and acellular mesh has been reported by Kaleya and colleagues (Kaleya et al., 2005). The average price for an 8x12cm sheet of synthetic

polypropylene mesh is $350 (£200, €240). However, the cost for the same amount of Alloderm is substantially higher at $2,580 (£1,600, €1,800). Although, elsewhere it has been reported that the average cost per patient for Alloderm is $4,680 (£2,800, €3,200) (Schuster et al, 2006).

The 2007 NHS national average unit operative cost for an infected incisional hernia repair is estimated at £2,907 ($4,700, €3,300), based on the HRG code FA17A (Abdominal Hernia Procedures 19 years and over with Major CC) (Department of Health, 2007). An additional consideration is the potential saving in hospital bed days that a TE solution might deliver. The cost of a bed day is estimated at £210 ($350, €240) (Department of Health, 2006b) from the national average cost of an excess bed day, based on HRG code FA17A.

5.7 Cost-Effectiveness Analysis

5.7.1 Review of Previous Cost Analysis Studies

Cost Analysis of Incisional Hernia Repair by Suture or Synthetic Mesh

Israelsson and colleagues (Israelsson et al, 2003) conducted a cost-analysis (n=44) of incisional hernia repair by suture and by synthetic mesh. Overall, the costs were 6034 SEK (£520, €600, $850) lower for mesh repair in working patients and in retired patients the costs were 1898 SEK (£160, €190, $270) lower with mesh repair. The authors conclude that lower postoperative costs due to shorter hospital stay and more rapid return to work outweigh the higher operative costs associated with mesh.

Cost-Minimisation Analysis of Alloderm

A cost-minimisation analysis comparing Alloderm to a synthetic mesh for the treatment of incisional hernias was conducted in 2005 by Lifecell (although the authors referred to as a cost-benefit analysis), the manufacturer of Alloderm (Kaleya et al, 2005). The risks of complications associated with each material were established from the literature and physician interviews. The total overall surgical cost, including material and procedure costs, related to the use of synthetic mesh and Alloderm has been estimated at $5,790 (£3,500, €4,000) and $8,170 (£5,000, €5,700), respectively (Kaleya et al, 2005). Although the synthetic material may be associated with lesser surgical costs, it is also associated with

greater complications and more challenging post-surgical care compared to Alloderm. Early complications (wound dehiscence with or without infection) result in an additional risk-adjusted, per-patient cost of polypropylene of $765 (£470, €530), compared to $212 (£130, €150) for Alloderm. Long-term complications, including recurrence, small bowel obstruction, fistula formation, or planned reoperation, were estimated to add an average of $3,548 (£2,100, €2,500) to mesh hernia repairs, compared to $662 (£400, €460) with Alloderm, due to a lower incidence of long-term complications associated with Alloderm (Kaleya et al, 2005).

After complications and long-term (>1 month) care costs are considered Alloderm is associated with risk-adjusted net savings of $2,170 (£1,300, €1,500); $554 (£340, €380) per-patient cost savings associated with minimising early complications, $2,887 (£1,700, €2,000) associated with reducing late complications, and $1,110 (£680, €770) related to gains in lost patient productivity (Kaleya et al, 2005) (table 5.7). However, this analysis is sensitive to effectiveness estimates and complication rates. Here these are estimated by the manufacturer and may be uncertain given the absence of head-to-head studies as detected by my review.

Table 5.8: Cost-benefit analysis of Alloderm versus synthetic mesh to repair incisional hernia

	Synthetic	Alloderm	Alloderm Savings (additional charges)
Complication Rate			
Infection	6%	5.10%	
Dehiscence with exposure of mesh	1.80%	1.80%	
Recurrence	16.80%	5%	
Enterocutaneous fistulae	3.50%	0.50%	
Adhesive small bowel obstruction	5.40%	0.50%	
Cost Driver			
Materials cost	$350	$2,580	($2230)
Procedure-related costs	$5,440	$5,590	($150)
hospitalisation	$3,190	$3,190	
OR costs	$2,250	$2,400	
Risk-adjusted cost of complications	$5,812	$1,261	$4,551
direct cost of early complications (<1 month)	$765	$212	$553
inpatient	$554	$94	$460
other direct	$211	$117	$94
direct cost of long-term complications (>1 month)	$3,548	$662	$2,886
inpatient	$3,429	$645	$2,784
other direct	$119	$17	$102
Lost productivity	$1,498	$388	$1,110
Total	$ 11,601	$ 9,432	$2,169

Table adapted from Kaleya et al. 2005. Early complications include infection, dehiscence with exposure of mesh and recurrence, and late complications include enterocutaneous fistulae and adhesive small bowel obstruction.

5.7.2 Headroom Analysis

Duration and Severity of Clinical effects

If a synthetic mesh becomes infected the current treatment strategy is to leave the wound open for 3-6 months to allow the infection to clear before undergoing second surgery to close the wound. Patient recovery is slow and complex and requires a further 6 months of hospital visits for wound management. Following consultations with clinicians (Dion Morton, 2008), I predict that a TE mesh could be used to close the wound after 1-2 weeks. Patient recovery would be more rapid and wound management reduced to around 1 month. Taking into account more rapid closure of the wound and reduced recovery time I estimate the best-case scenario for the duration of the improvement of the clinical effects associated with a TE mesh would be approximately 6 months. This will fit with the premise of the headroom method, which states that I must assume the most optimistic effectiveness of

the new treatment. The mean utility associated with the period of maximum symptoms following repair of a recurrent incisional hernia was calculated as 0.85 (95%CI: 0.79, 0.91) from 50 responses. The headroom method is based on optimistic assumptions of the new treatment, therefore I assume that the new TE biological mesh could give patients perfect HRQL i.e. a utility value of 1.0.

Calculating the Headroom

I predict a TE solution will do two things: firstly, eliminate early complications such as wound infection and the subsequent side effects, resulting in more rapid healing and recovery; secondly, eliminate late complications, primary hernia recurrence, and the need for further surgery, thus also eliminating the additional associated costs.

Early complications

Firstly, I calculate the effectiveness gap and the disutility of the current treatment. Using equation 5.3 populated with the information given above I calculate the maximum potential change in effectiveness, measured using QALYs, as 0.15.

Equation 5.3: $\Delta QALY = 0.5 \times (1-0.85) = 0.075$

Next, using equation 5.4 I calculate the headroom (maxΔCost). Based on a reimbursement level of £30,000 ($49,000, €34,000), the headroom is calculated as £2,250 ($3,600, €2,600). However, based on a reimbursement threshold of £20,000 ($33,000, €23,000), the headroom is calculated as £1,500 ($2,400, €1,700).

Equation 5.4: $\max \Delta Cost = £30,000 \times 0.075 = £2,250$

In addition, a TE solution might deliver a saving in hospital stay. Based on the findings in section 5.5 (page 136) I will assume a reduction in hospital stay of four days. Based on the cost per bed day given in section 5.6 (page 147) this will give a total saving of £840 ($1,370, €960). Thus, the total headroom is now £3,090 ($5,000, €3,500). However, this value only takes account of the elimination of early

complications. As described above, a TE solution might also reduce long-term complications and thus the need for further surgery.

Late complications

Finally, I use the recurrence rates and costs of further surgery described in the sections above to calculate the headroom associated with eliminating late complications. Recurrence rate associated with infected incisional hernia repair using acellular mesh is 23% (section 5.5.3, page 146). I estimated the cost of a complex incisional hernia to be £2,907 ($4,700, €3,300) (see section 5.6, page 147). This gives an additional cost per case of approximately £668 ($1,000, €760). By adding this cost saving to the headroom calculated from eliminating early complications I calculate total headroom of £3,758 ($6,000, €4,300).

5.8 Return on Investment

The revenue that can be generated is a function of the headroom, the likely cost, and volumes, represented by equation 5.5. Here, R = revenue, max ΔCost = headroom, C' = expected cost of production and V = cases per year.

Equation 5.5: $R = (\max \Delta Cost - C') \times V$

In the case of a TE mesh, in the previous section, I found a headroom of £3,700 ($6,000, €4,300). I make an assumption about the cost of production, assuming this to be £3,000 ($4,800, €3,400) and based on the information gleamed from clinicians I estimate there are 1000 cases per year, the estimated revenue is £70,000 per year ($113,500, €80,700).

5.9 Discussion

5.9.1 Summary of Main Findings

Tension-free mesh is the current gold standard approach for abdominal wall defect repair. Mesh augments the strength of the weakened abdominal wall resulting in a repair that is less painful and

more likely to endure. Current generations of (non-TE) mesh materials are synthetic and prone to complications such as infections and adhesions, particularly when the defect is large and/or infected.

New generations of mesh are biological and due to their natural sourcing, could reduce, or prevent complications associated with synthetic mesh, simplifying the healing process as well as improving mechanical integrity of the abdominal wall. There are two alternatives for a biological mesh:

i) acellular biological mesh (relatively new);

ii) Cellular biological mesh (a new generation TE mesh, not yet available); the latter would undoubtedly be the most expensive option.

Current data, from short-term non-randomised studies, suggests biologics are preferable to synthetic mesh for infected defect repair. Due to the lack of long-term, head-to-head studies it is unclear which biologics are more effective. However, the available literature seems to suggest that acellular meshes are still at risk of complications and may be quite expensive; therefore there could be headroom for cellular meshes in large and infected defects.

The target of the headroom analysis was incisional hernias, focusing on large complicated defects. The headroom was calculated as £3,700 ($6,000, €4,300), based avoiding the short-term complications and a reimbursement threshold of £30,000 ($49,000, €34,000). Our consultations with industry suggest that this is sufficient headroom for an acellular mesh to be cost-effective for use in large, infected incisional hernias. However, this may not be sufficient headroom for a cellular TE mesh.

5.9.2 Elicitation of Utilities

Before conducting the headroom analysis, it was necessary to elicit a utility score associated with the negative effects of current treatment approach to a large infected incisional hernia. Since it was not possible to obtain the health utility directly from patients, the utility was elicited from clinicians. I believe clinicians were a good proxy for patients as the health state associated with incisional hernia repair is complex and as caregivers, they have a high level of understanding of the impact of the health state on the HRQL of the patient. I reviewed how the utilities were elicited for chapter 4 and decided that

emailing questionnaires to clinicians would not be successful in gaining an acceptable sample size. I considered arranging face-to-face interviews but thought this would be too time consuming. I decided that the less time consuming but reliable approach would be telephone interviews, although I was aware this would still take a considerable amount of time to arrange the appointments. However, I then found out about a conference of colorectal surgeons in Harrogate and as there were sufficient funds, I decided this would be the most efficient way in which to proceed. Around 500 surgeons were expected to attend the conference over the two and half days. I managed to collect 54 completed responses. I had expected that I would have had a larger sample size but not all attendees wished to complete the questionnaire, and I had not anticipated that some would find it difficult to complete and require more time and explanation. Overall, I am happy with the number of questionnaires I had completed, I do not think the sample size limits the interpretation of the results and I believe the utility value of 0.85 is acceptable and reliable, as it was based on the opinions of specialist surgeons whom were familiar with this type of repair and the associated complications. This impression was gleaned from conversations, which took place at the time the questionnaire was completed, as there was not a specific question asked regarding familiarity with the procedure as there had been for the questionnaires used in chapter 4. If I were to do this again, I might consider the inclusion of such a question. However, I did ask about experience, which could be used as a proxy for familiarity.

5.9.3 Implications of Work

It is always important to continue defining the clinical problem as new technologies may be produced that affect the potential headroom. For example, there may be advances in synthetic biomaterials or natural materials that may supersede the current generation of synthetic meshes, such as advances in coatings that can strike a balance between bacterial infection and tissue in growth. Furthermore, changes in the payment of current technologies may also affect the headroom. For example, in the UK, some PCTs are beginning to reimburse the cost of Permacol on a case-by-case basis (this information was gained from personal communication with a consultant at the conference for colorectal surgeons, where the utility questionnaires were completed). Therefore, anyone attempting to develop an expensive TE cellular construct needs to keep close track of new developments in

synthetic and acellular meshes. Improvements in either of these meshes will impact on and most likely diminish the headroom available for the TE mesh.

5.10 Conclusion

Once again, the headroom method has been shown to be a simple and rigorous way to make a preliminary conclusion as to the cost-effectiveness of a new treatment, even when some of the parameters are extremely uncertain, without having to build a complex model with very wide parameter uncertainty. The headroom method reduces the risk of industry investing in a TE technology that may never be cost effective. However, it by no means answers all the questions. It is important to remember that this method is based on many assumptions, notably the complete effectiveness of the new technology. Therefore, if a TE biological mesh does not work as one hopes, the headroom would be reduced.

In the following chapter I demonstrate how health economics can be used as a negotiating and not just a rationing tool, illustrated using an example based on bone RM technologies

CHAPTER 6 EARLY STAGE COST EFFECTIVENESS ANALYSIS OF BONE REGENERATIVE MEDICINE TECHNOLOGIES

6.1 Introduction

Bone has two main forms; cancellous and cortical (figure 6.1). It is an extraordinary living tissue, providing structural support and protection to bodily organs. Involved in metabolism and storage of minerals, it is a site of blood cell synthesis. It has the unique capacity to remodel and heal itself through a continual process, stimulated by mechanical stress, in which osteoclasts (bone cells that break down bone tissue) break down and resorb old bone of inferior quality, and osteoblasts (bone cells that build bone tissue) replace it with new bone. However, as we age the balance of this remodelling becomes negative, i.e. osteoclasts are more active than osteoblasts, resulting in a gradual loss of bone mass.

An abnormal environment, both mechanical and biological, can affect the functional capacity of bone for healing and regeneration and there are times when this remodelling process may fail, such as in fracture nonunion and segmental defects. Currently, the mechanical environment is stabilised using metallic fixation devices and the biologic environment is aided by bone graft and ceramics, the former to stimulate healing and provide extra material, the latter as a bulking agent. The purpose of RM is to replace the need for bone graft and ceramics and to promote bone healing.

The purpose of this chapter is to demonstrate how using the headroom method can be used as a pricing and negotiating tool. I illustrate how this might work using bone morphogenic protein (BMP) as an example. BMP is used to promote bone healing *in vivo*. It is an alternative to autograft. It prevents the need to harvest bone from the iliac crest and may also improve bone healing when compared to autograft.

Figure 6.1: Anatomy of the bone

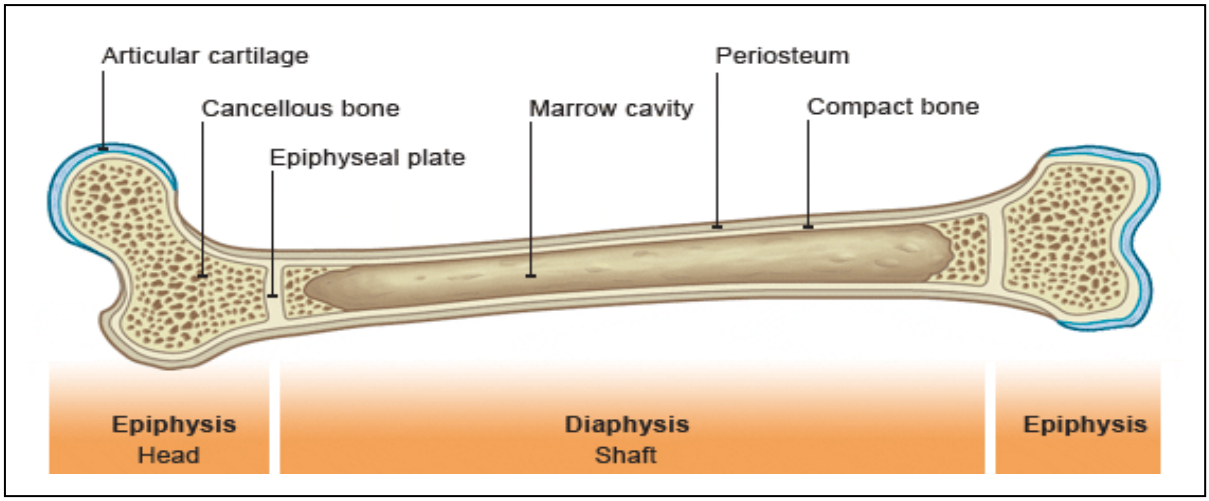


Diagram to show the anatomy of the bone and illustrate cancellous (spongy) bone and cortical (compact or solid) bone.
Source: BBC GCSE BItesize
http://www.bbc.co.uk/schools/gcsebitesize/pe/appliedanatomy/2_anatomy_skeleton_rev4.shtml

6.2 Methodology

6.2.1 Overview

Firstly, I reviewed disorders of the skeleton to identify the main clinical conditions where a RM alternative to bone grafting may have a place and I documented the various RM and non-RM treatments proposed. Secondly, I selected two conditions which I felt had the greatest potential and were worthy of further investigation before comparing clinical effectiveness and costs of the current gold standard treatment (autograft) with *in-vivo* and *in-vitro* methods of bone production. Finally, I conducted economic analysis. This part had two stages. First, I reviewed standard demand side cost utility analysis of BMP. Second, I carried out a supply side analysis to determine the threshold price of BMP for each condition.

6.2.2 Defining the Clinical Problem

Literature was identified using the search strings shown in appendix 10. During the course of the literature search, I discovered a HTA systematic review and economic analysis by Garrison and

colleagues (Garrison et al., 2007), which I have critiqued and updated. When necessary, the information from the literature was supplemented by discussions with an Orthopaedic surgeon based at Birmingham Royal Orthopaedic Hospital. In addition, I had the opportunity to consult with other orthopaedic surgeons through technical meetings, which were part of the European STEPS project. The technical aspects surrounding the development of RM bone was discussed with tissue-engineers (these were known to me through the EPSRC REMEDI and EU STEPS projects). After careful analysis of the clinical problem, it appears the greatest market potential is in moderate to large defects. I conduct a systematic review of the relative effects and cost of BMP as an alternative for autograft for two conditions – spinal fusion and fracture healing. Finally, I document the clinical effects of donor site morbidity with special emphasis on HRQL and utility.

6.2.3 Cost-Effectiveness

This method has two stages. Firstly, I review the CEA of the use of BMP for two conditions where it is most widely advocated as an alternative to autograft. I was aided here by the economic analysis published in a HTA report by Garrison and colleagues (Garrison et al, 2007). However, I present the results based on costs per patient rather than costs per 100,000.

Secondly, I carried out a supply side analysis to determine the threshold price of BMP for each condition. This section contains four stages:

1. I calculate the mean cost per case associated with using BMP for spinal fusion and fracture repair. This is calculated by offsetting the total cost savings per case against the additional cost of BMP.

2. I performed supply side analysis to find out the price at which BMP would demonstrate cost-effectiveness for use in spinal fusion and fracture repair. Using Excel I replicate and update, where necessary, the model from the Garrison review but I keep the QALY gains the same. Using equation 6.1, I calculate the price at which BMP would be considered cost-effective by changing the unit cost of BMP until the ICER falls below the UK WTP thresholds.

Equation 6.1: WTP threshold=Δcost/Δbenefit

Where, ∆cost is the total incremental cost to the NHS; ∆benefit is total incremental benefit, measured in QALYs; WTP threshold is the reimbursement level i.e. the health care providers' willingness to pay for 1 QALY – in the UK, this is assumed to be between £20,000 ($33,000, €23,000) and £30,000 ($49,000, €34,000).

3. I perform a cost minimisation analysis (CMA) of BMP. It is certain that BMP reduces operation time due to time saved by avoiding bone harvest. Here I consider only the cost saving associated with reduced operation time because of using BMP. No other clinical outcomes associated with BMP are accounted for. Using Excel I replicate and update, where necessary, the model from the Garrison report. Using equation 6.2 I calculate the price BMP would need to be in order to be cost effective, assuming incremental benefit is zero.

Equation 6.2: ∆benefit = ∆cost/ willingness-to-pay threshold

Where, ∆benefit = zero, ∆cost is the recalculated incremental cost to NHS and willingness-to-pay threshold is the reimbursement level of £30,000 ($49,000, €34,000).

4. Finally, I use the headroom method, described in chapter 3, to calculate the maximum cost for which a RM bone product would be considered cost effective. I use the equation:

Equation 6.3: ∆Cost = ∆QALY x willingness-to-pay threshold

Where, ∆Cost is the maximum headroom, ∆QALY is the change in benefit measured in QALYs and willingness-to-pay threshold is the threshold for reimbursement of £30,000 ($49,000, €34,000).

6.3 Treatment

6.3.1 Current Treatment

The current gold standard treatment for bone healing is the use of autologous bone grafts; usually harvested from the patient's iliac crest and implanted into the defect site to stimulate bone formation and add bulk. The success rate is high due to the presence of osteoconductive, osteoinductive, and osteogenic properties, but it has limitations, most commonly that of donor site morbidity (Dimitriou et al., 2005;Giannoudis et al., 2005a). The side effects of donor site morbidity include haematoma formation, blood loss, nerve injury, hernia formation, infection, arterial injury, ureteral injury, fracture, pelvic instability, cosmetic defects, tumour transplantation, and most frequently chronic pain at the donor site (Giannoudis et al., 2005c;Kessler et al., 2005) (discussed further in section 6.6, page 182). Furthermore, the technique is limited for large defects because of the exhaustible supply. This could be overcome through the use of allograft (donor bone grafts). However, the rate of healing and graft incorporation for allografts is lower than for autografts. A further alternative is demineralised bone matrix (DBM) - pulverised and decalcified allograft bone. This process reduces immunogenicity while improving osteoconductivity (Fleming, Jr. et al., 2000). The resulting material can be used as a gel, flexible strips, malleable putty, or injectable paste. However DBM is widely used as bone graft extender rather than as a bone graft substitute (Giannoudis et al, 2005a).

6.3.2 State of the Art in Regenerative Medicine

RM is seldom designed to provide immediate mechanical support, this will usually be provided by conventional internal fixation (use of internal metal plates, screws, or rods to stabilise bone fragments. Used when bone defect cannot be stabilised by casting or splinting) or external fixation (use of metal orthopaedic device (external fixator) placed outside skin, to stabilise regions of bone) using metals, however in due course the aim is that the regenerated bone will provide support.

A scaffold for use in bone defects should be biocompatible and mimic the body's natural matrix – topography, surface chemistry, porosity and osteoinductivity - to provide a suitable environment for cell attachment (Logeart-Avramoglou et al., 2005;Salgado et al., 2004). In addition, the scaffold needs to

degrade at the same rate as the growth of new tissue. A wide range of natural and synthetic materials has been suggested as scaffold materials for bone regeneration (table 6.1). Two materials that have particular promise are ceramics and collagen. Ceramics have been widely used with encouraging results although they do posses several limitations; they are brittle, have low mechanical stability, and have varying degradation rates. Collagen is a biodegradable polymer and provides an ideal alternative to ceramics with very few limitations. Although collagen is available naturally, synthetic biodegradable polymers are preferred due to their chemical versatility and processability (Salgado et al, 2004); they have less property variation and the materials used to produce them have much better traceability, which is important for the regulator. The performance of these scaffolds is improved with the addition of cells and growth factors.

Osteogenic cells are integral to the development of new bone. They can either be implanted into the defect or attracted from the host by osteoinductive factors (Kneser et al., 2006). For implantation the cell type used must be reliable, easily isolated, stably expanded, and non-immunogenic (Salgado et al, 2004). Osteoinductive growth factors are naturally occurring proteins, which function as signalling molecules to promote and modulate the proliferation and differentiation of osteogenic (bone forming) cells. The most potent of these growth factors are BMPs (Giannoudis et al., 2005b). It is currently unknown which cell type and growth factors will be most suitable. Table 6.2 and 6.3 summarise the main characteristics of the most commonly used cells and growth factors.

However to date no traditional TE (scaffolds plus cells) products that might replace bone have been found. My feeling is that the recent availability of growth factors is likely to change the nature of RM solutions in bone. Before growth factors became available, scaffolds (such as ceramics) that mimic the architecture of cancellous bone were the most promising materials. However, simpler polymer scaffolds impregnated with growth factors (particularly BMP) seem to work equally well or better, thus scaffolds that mimic the micro-architecture of cancellous bone may no longer be necessary. Traditionally RM solutions have been produced *in vitro* and efforts to generate ceramics with similar architecture to bone, and perhaps impregnate these with cells, were consistent with this idea. However, I perceive a strong move to use the body as a factory and to stimulate *in vivo* bone

production by means of simple polymer scaffolds impregnated with growth factors. I feel this will prove to be the most effective and cost-effective approach.

In the following section, I consider a variety of applications for bone RM and discuss whether the potential RM solutions might surpass the current treatment with the purpose of identifying which applications will have greatest benefit.

Table 6.1: Summary of materials used for scaffolds and their various characteristics

Material	Characteristics
Ceramics	
Hydroxyapatite	Brittle Low mechanical stability
Tricalcium Phosphate	Small grain size - making for easier osteoclastic resorption
Coralline Hydroxyapatite	Performs as well as well as autograft for metaphyseal defects
Natural biodegradable polymers	
Collagen	Low immune response Good substrate for cell adhesion Chemotactic Scaffolds with low mechanical properties
Fibrin	Promotes cell migration and vascularisation Promotes Osteoconduction Usually is used as a cell carrier for cell seeding on scaffolds
Chitosan	Hemostatic Promotes osteoconduction and wound healing
Starch	Thermoplastic behaviour Good substrates for cell adhesion Non-cytotoxic and biocompatible Bone bonding behaviour when reinforced with hydroxylapatite Scaffolds based on these materials have good mechanical properties
Hyaluronic acid	Minimal immunogenicity Chemotactic when combined with appropriate agents Scaffolds with low mechanical properties
Poly(hydroxybutyrate)	Natural occurring hydroxyacid Adequate substrate for bone growth Utility is limited due to brittle nature
Synthetic Biodegradable Polymers	
Poly(a-hydroxy acids)	Extensively studied aliphatic polyesters Degradation by hydrolysis Already approved for other health related applications Acidic by products (e.g. lactic acid, glycolic acid), that enter the tricarboxylic acid cycle or in alternative (e.g. glycolic acid) are excreted in the urine It can present problems regarding biocompatibility and cytotoxicity in the surrounding area of the implantation site
Poly(e-caprolactone)	Aliphatic polyester Degraded by hydrolysis or bulk erosion Slow degrading Degradation products incorporated in the tricarboxylic acid cycle Low chemical versatility Some problems related with withstanding mechanical loads
Poly(propylene fumarates)	Unsaturated polyester consisting of alternating propylene glycol and fumaric acids Main degradation products are fumaric acid and propylene glycol Satisfactory biological results
Poly(BPA iminocarbonates)	Good biocompatibility when implanted in a bone canine chamber model
Poly(phosphazenes)	Contain alternating nitrogen and phosphorous with no carbon atoms in the backbone structure Degradation through hydrolysis
Poly(anhydrides)	Mainly developed as drug delivery carriers Biocompatible Support both endosteal and cortical bone regeneration

Adapted from (Salgado et al, 2004)

Table 6.2: Osteogenic cells and their characteristics

Cells	Characteristics					Reference
	Immunogenic	Isolated	Cell number yields	Expansion rates	Other	
Osteoblasts	No	Easily via biopsies	Low	Low in vitro		(Salgado et al, 2004)
Mesenchymal stem cells (MSCs);	No	Easily from connective tissue, bone marrow or muscle biopsy	Low	High in vitro	High differentiation potential which is not lost during expansion process	(Heath, 2000;Salgado et al, 2004)
Bone marrow stromal cells	No	From bone marrow	Low	High in vitro	Lose stem cell properties during *in vitro* expansion	(Bianco et al., 2001;Cheng et al., 1994)
Periosteal cells	No	Enzymatically	Low	High in vitro		(Nakahara et al., 1990)
Genetically Modified cells	No	From patient and genetically modified	Low	High in vitro	Genetically engineered with BMPs. Enhanced Osteogenic capacity relative to unmodified cells	(Sugiyama et al., 2003;Tabata, 2005)

Table 6.3: Growth factors: their functions, characteristics, and potential application

Growth Factor (GF)		Main Functions	Characteristics	Potential applications and where tested	Reference
Bone morphogenetic proteins (BMPs)	BMP	• Recruit mesenchymal cells to defect site • Modulate MSC differentiation into osteoblasts and chondroblasts	• There are some 20 BMPs • BMP 2, 4, 6 & 7 are most osteoinductive • Stored in bone matrix and released following injury Expression rates vary causing up or down regulation of other BMPs • Intervene in expression of other GFs • Main signal regulating skeletal formation and repair	The role of BMP's as a bone stimulating agent is safe, well established and an application in clinical practice is promising for the treatment of challenging clinical conditions.	(De Biase P. et al., 2005;Giannoudis et al, 2005a;Hing, 2004;Salgado et al, 2004)
	BMP-2	• Role in the expression of osteogenic markers	• Significantly improve bone healing • A necessary component of signalling cascade for fracture repair	Used in repair of skull and mandibular bone in rat, dog and monkey Preclinical and clinical studies have shown potential use in bone defects, non-union fractures, spinal fusion, osteoporosis and root canal surgery.	(Chen et al., 2004;Hing, 2004;Salgado et al, 2004;Tabata, 2005;Tsuji et al., 2006)
	BMP-7	• Regulate osteoblast differentiation and expression		Potential use in non-union fractures	(Giannoudis et al, 2005c;Hing, 2004)
Transforming growth factor-b (TGF-b)		• Stimulate cell proliferation • Enhance osteoblast activity	• Most prevalent GF in bone • Diverse biological actions • Released during bone absorption • Regulated by conversion into an active peptide	Repair of skull bone in rabbit and monkey	(Hing, 2004;Salgado et al, 2004;Tabata, 2005)

Fibroblast growth factors (FGFs)	• Bone remodelling • Regulates balance between bone forming cells and bone resorbing cells	• Improves vascularisation of engineered tissues	Repair of mandibular (jaw) bone in dog; Repair of skull and long bone in rat, rabbit and monkey	(Salgado et al, 2004;Tabata, 2005)
Insulin growth factor (IGF)	• Maintain collagen integrity in bone • Maintenance of normal bone mass	• IGF-1 and IGF-2 are produced by fibroblasts and osteoblasts, and have similar effects on bone metabolism • IGF-1 more potent than IGF-2	Potential therapeutic use in treatment of age-associated bone conditions, such as osteoporosis. Studies currently performed in old rats.	(Salgado et al, 2004;Tanaka et al., 2002;Wakisaka et al., 1998)
Platelet derived growth factor (PDGF)	• Role in migration of MSCs to defect site • A local cytokine regulator, attracting inflammatory cells to fracture site	• Produced by osteoblasts, platelets, monocytes / macrophages	Studies in old rats for potential use as agent for use in age-related bone conditions	(Salgado et al, 2004;Tanaka et al, 2002;Wakisaka et al, 1998)
Interleukins (ILs)	• Promotes proliferation and differentiation of osteoclasts	• IL-1 is a powerful stimulant of bone resorption		www.worldortho.com
Vascular Endothelial growth factor (VEGF)	• Induces angiogenesis	• Commonly found in bone fracture sites and plate growth • Regulates vascularisation	VEGF delivery systems to enhance angiogenesis and bone formation at sites where blood supply has been compromised	(Kaigler et al., 2006;Salgado et al, 2004)
Parathyroid hormone (PTH), commonly called teriparatide	• Major hormonal regulator of calcium homeostasis	• An anabolic agent, which reduces fracture incidence by improving bone qualities, including bone mass • Directly stimulates bone formation	Clinical use in treatment of osteoporosis	(Girotra et al., 2006;Hodsman et al., 2006)

6.4 Potential Indications for a RM solution

In this section, I review the conditions where the capacity for bone to heal and regenerate has broken down and discuss which application has the greatest potential for a RM bone product before proceeding with the CEA. The bony defects reviewed are divided into three groups:

i. Defects in the spine - degenerative disc disease (DDD) and osteoporotic fractures of the spine
ii. Non-healing Fractures – non-union of fractures and segmental defects
iii. Bone cysts

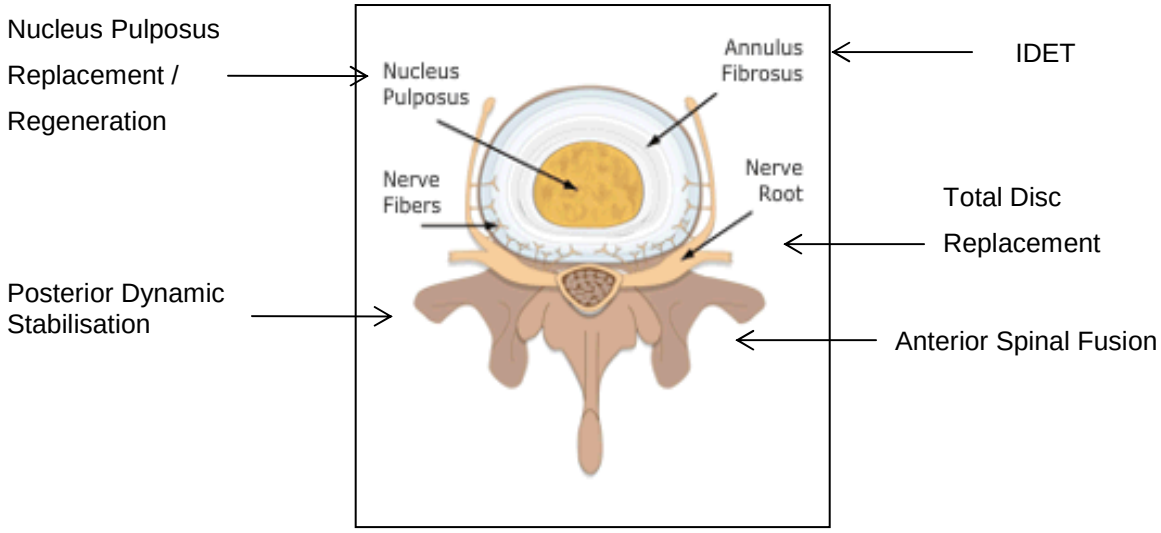
6.4.1 Degenerative Disc Disease

DDD (also known as intervertebral disc (IVD) degeneration) results from weakening of the intervertebral disc through loss of water. Triggered predominantly by genetic risk factors (Battie et al., 2006), although environmental factors, such as heavy or repetitive loading can have an affect (Adams et al., 2006;la-Kokko, 2002), it is characterised by chronic low back pain. It is the leading cause of pain and disability for adults in the US and UK and has an incidence which increases with age. An epidemiological review (Battie et al, 2006) reveals extreme variations in prevalence rates, possibly due to inconsistencies in definitions - measurements of disc degeneration are usually qualitative and lack precision. Each year in England and Wales there are approximately 9,000 cases of DDD (HES Online, 2007).

Initial treatment is conservative care (non-surgical) in the form of medication (NSAIDs) or physical therapy. Surgery is considered if symptoms persist beyond 6 months. Spinal fusion is the current gold standard surgical treatment and approximately 1400 are carried out each year in the UK (the UK is more conservative in its use of spinal fusion compared to the USA (Brigitte Scammell, 2007)). There is potential for a RM alternative to autograft in spinal fusion. However, over recent years, many other surgical treatments have emerged. The focus is shifting away from strengthening the bone towards improving mobilisation, which is increasing the number of treatments targeted towards the disc (both mechanical and biological) rather than stabilisation of the spine. Furthermore, recent research, prompted by the notion that repair and restoration of function is the ideal therapeutic approach, is

targeting new areas of the disc, predominantly the nucleus pulposus - the fluid filled centre portion of the disc. Figure 6.2 illustrates the structure of the disc, its location within the spinal cord and the targets of various treatments for DDD, each of which is summarised below with a full comparative review in appendix 11.

Figure 6.2: The intervertebral disc



Reprinted with permission from Spine Restoration, inc.
www.spinalrestoration.com/patients/index.html

Operations to Stabilise the Spine

a) *Spinal Fusion* - is the surgical fusion of the vertebrae of the spine so motion no longer occurs between them. Gold standard approach uses a metal plate and screws reinforced with autograft. Although spinal fusion is the current mainstay treatment, there is continued debate in the literature surrounding its appropriateness and effectiveness. Alternative treatment options are being examined, both surgical (disc and nucleus pulposus replacement) and non-surgical (intensive rehabilitation), but currently, although some preliminary results have been encouraging, no intervention has shown to be significantly superior to spinal fusion.

b) *Posterior Dynamic Stabilisation* - (or soft stabilisation or flexible stabilisation) is an alternative to spinal fusion designed to control rather than eliminate motion between vertebrae (Schnake et al., 2006;Sengupta, 2005).

Operations on the Disc

a) *Intradiscal Electrothermal Therapy (IDET)* - is a minimally invasive technique, involving the placement of an intradiscal catheter with a temperature controlled thermal resistive heating coil to a position at the inner posterior annulus (the outer core of the disc) (Freeman, 2006).

b) *Total Disc Replacement* - artificial discs are used to replace painful discs in the spine, with the goal of preserving normal motion, unlike fusion, which eliminates motion at the painful spinal segment. The use of artificial discs should, in theory, prevent adjacent level degeneration (a complication which can be associated with spinal fusion) (Freeman et al., 2006).

c) *Whole Disc Transplantation* - disc transplantation has the theoretical advantage over artificial disc replacement and disc regeneration, of providing a young, non-degenerated scaffold that could offer the best environment for the cells to survive or regenerate (Ruan et al., 2007).

d) *Nucleus Pulposus Replacement* – a recent alternative to total disc replacement, designed to provide stable motion, increased space height, and minimise transmission of shear forces on the remaining annulus, facet joints and stabilising structures (Goins et al., 2005). Nucleus pulposus replacement exchanges just the inner part of the disc for prosthesis, leaving the remainder intact, with the aim of restoring biomechanical function.

e) *Nucleus Pulposus Regeneration* – this form of disc regeneration uses gene therapy to repair damaged tissue and re-populate the Nucleus pulposus with cells, this has the potential to make the greatest clinical impact (Ruan et al, 2007;Zigler et al., 2003). The next step is to move this technology forwards from the lab into clinical trials.

6.4.2 Osteoporotic Fractures of the Spine

Osteoporotic vertebral compression fractures affect over 700,000 people in the US each year; this is twice the number of hip fractures (Lieberman et al., 2005). These fractures (figure 6.3) result in spinal pain, loss of height, spinal instability, and, in many cases, kyphotic deformity (curvature of the back), which can further lead to depression, decreased appetite, decreased pulmonary function and impaired mobility (Hulme et al., 2006). The most significant risk factor is osteoporosis, which affects an estimated 3 million post-menopausal women in the UK (NICE, 2005a). Spinal fractures is reported to affect 1 in 4 of all post-menopausal women (Kim et al., 2006a).

Figure 6.3: Spinal compression fracture

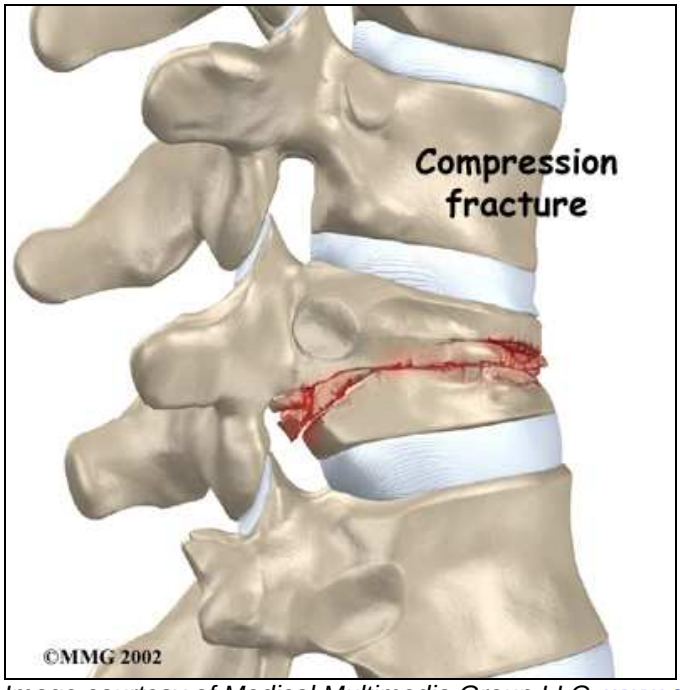


Image courtesy of Medical Multimedia Group LLC, www.eOrthopod.com
Source: http://www.eorthopod.com/public/patient_education/6547/spinal_compression_fractures.html

Primary treatment is targeted at increasing bone density for which there is a variety of treatments (documented elsewhere (NICE, 2005a)). There are two main surgical treatment options for vertebral compression fractures: vertebroplasty and kyphoplasty (Kim et al, 2006a) (for more information see videos at http://www.spine-health.com/video/kyphoplasty-osteoporosis-fracture-treatment and http://www.spine-health.com/video/vertebroplasty-interactive-video). Both are technically similar

minimally invasive treatments designed to target pain relief through fracture stabilisation, but the latter has the addition of using an inflatable balloon in order to restore height to the vertebrae before insertion of the filler material (Hulme et al, 2006). Rates of pain relief and functional improvement have been reported as equivalent at between 78% and 90% in short-term follow-up (Kim et al, 2006a).

The potential for RM is as an injectable biological filler material. Bone cements (particularly polymethylmethacrylate (PMMA)) and ceramics (particularly calcium sulphate) are currently the most frequently used filler materials but each has a long list of disadvantages (Lieberman et al, 2005). The most severe is bone cement leakage – a common complication occurring in both kyphoplasty and vertebroplasty – which produces heat as it hardens it can result in burnt nerves (Kim et al, 2006a). An ideal filler material would be biocompatible, have good biomechanical strength and stiffness, and have radiopacity for the fluoroscopy guided procedures (Lieberman et al, 2005). Vertebroplasty requires a material with a long liquid phase and working time, combined with a very short set time, whereas kyphoplasty requires a material with a short liquid phase and a longer partially cured “doughy” phase (Lieberman et al, 2005). The School of Mechanical engineering in Atlanta, US, is investigating the use of gene therapy to stimulate the surrounding cells to make bone. The hope is that this gene could lead to an increase in bone density, preventing or delaying the onset of osteoporosis and thus decreasing the incidence of ventral compression fractures (Sanders et al., 2001).

6.4.3 Non-Healing Fracture Repair

Here, I use the term non-healing fractures to refer to fracture nonunions and large segmental defects. A fracture nonunion is a fracture that has failed to achieve bony healing at a fracture site within six months. This can lead to significant pain and inhibition of function (Garrison et al, 2007). There are around 300,000 fractures per year in England and Wales (HES Online, 2007) and nonunions occur in 4% to 10% (Garrison et al, 2007). They can be either hypertrophic (caused by insufficient fracture stability) or atrophic (the result of insufficient blood supply or insufficient bone forming cells) - the proportion of each depends on the site of fracture. The first can be treated using stable internal fixation to improve the mechanical environment (Panagiotis, 2005). The latter is more difficult to treat; requiring stabilisation of the fracture and support of the biologic environment. The current best

treatment for atrophic nonunions is stable fixation with autograft (Ring et al., 1997). Segmental defects result from bone loss due to trauma, necrosis, or tumour resection. They are much larger defects than those seen in fracture nonunion; for example, they can affect the full length of the shaft of a long bone. There is greater damage to the soft tissues surrounding segmental defects, which reduces the chances of a blood supply forming (a necessary part of healing), which in turn reduces the chance of a biological response to healing. As a result, segmental defects can never heal without intervention. As with atrophic nonunion, the principles of conventional treatment of segmental defects involves metal fixation to stabilise mechanical environment and support to biological environment, currently using autograft (figure 6.4).

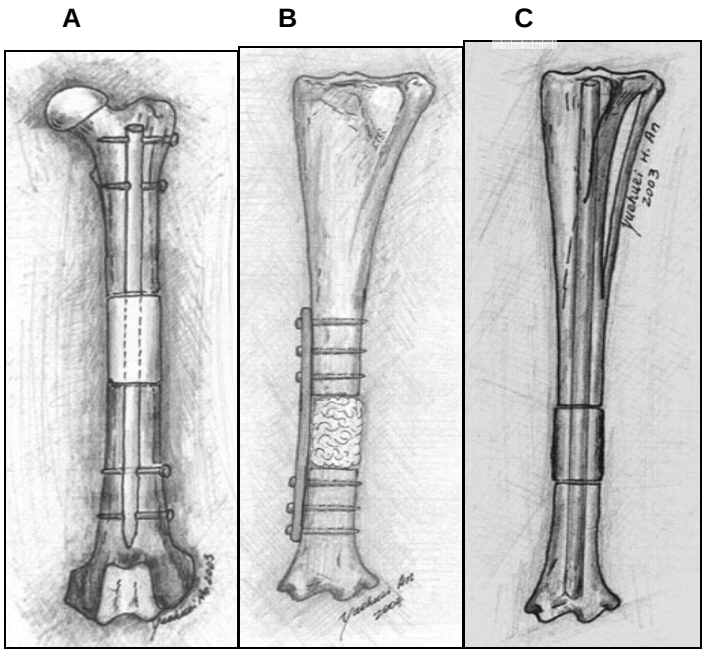
There are a number of other non-RM approaches to segmental defect repair:

i. Insertion of a cortical bone graft, which incorporates into the distracted bone ends but does not become viable throughout its length;
ii. Filling the defect with autologous bone granules;
iii. The Ilizarov procedure of external fixation for limb lengthening which allows bone to grow and bridge the gap;
iv. Use of a fibula free vascularised graft, especially in large defects

There are severe and common drawbacks to all treatments and in extreme cases if the above fail amputation may be necessary (DeCoster et al., 2004). Table 6.4 summarises the benefits and drawbacks along with the proposed management of segmental defects based on defect size.

The potential for RM in this area is as a functional support to the biological environment in atrophic nonunion and segmental defects as a direct replacement for autologous bone graft. The ideal material to bridge a defect would be one that is easily cut into shape and able to maintain its shape (Kon, 2007).

Figure 6.4: Conventional treatment of segmental defects



Conventional treatment uses stable fixation (metal plate, nail or blot) and a material to bridge the defect. This diagram illustrates the conventional treatment in weight-bearing bone segmental defects from a canine femur (A), a sheep tibia (B) and a rabbit tibia (C). Kindly provided by Yuehuei An, MD. Source: http://www.musc.edu/orthores/Labs%20and%20Models%20htmls/jpg.BoneDefect.html

Table 6.4: Summary of treatments for Segmental Defects

Treatment	Major Benefits	Major Drawbacks	Length of Defect (cm)	Cost
Amputation	Shortest treatment time	Total loss of limb function	10-30	£110,000
Limb shortening	Short treatment time; fewest complications	Some loss of limb function	0.1-1	
Autologous non-vascularised cancellous bone graft	Generally applicable; reasonable results	Slow, unreliable consolidation; donor site; morbidity; less applicable to large defects	0.5-3	£68,500
Bone transport distraction osteogenesis	Ultimately, the best quality of bone; applicable to large defects	Frequent complications; long time to heal	2-10	£36,000 - £51,000
Free vascularised graft	Acute fill of defect with living bone; micro-vascular capability; applicable to large defects	Donor site morbidity; fracture; lack of hypertrophy	5-12	£41,500
Local fibula	Acute spanning of defect; donor morbidity limited; no special equipment required	Not always possible; not very strong; poor muscle function		

Adapted from DeCoster et al, 2004

6.4.4 Bone Cysts

A bone cyst is a benign serum filled cavity in the bone, which causes weakening, increasing the likelihood of fracture. The aetiology is poorly understood but the primary cause is reported as obstruction of venous drainage and an increase in internal pressure (Chigira et al., 1983). There are two main types of cysts: the simple bone cyst and the aneurysmal bone cyst. The unicameral (or solitary cyst) is the classical form of simple cyst, mostly affecting long tubular bones in boys, although have also been reported in flat bones of the pelvis, jaw, rib cage, or skull. There are three less common varieties of simple cysts: non-tubular bone cysts – accounting for 4-10%; multiple cysts - an underestimated category; epiphyseal cysts - accounting for around 2% (Abdel-Wanis et al., 2002). The aneurysmal bone cyst is a blood-filled cyst caused by specific pathological change, a result of trauma. It is less common than the simple bone cyst and 75% occur in 10-20 year olds, primarily women. More than half occur in long bones, 12-30% occur in the spine and half of all flat bone cysts occur in the pelvis (Kransdorf et al., 1995). Pain and swelling result although symptoms are reported to last less than six months (Kransdorf et al, 1995). In a third of all cases the aneurysmal cyst occurs as a secondary defect in a pre-existing lesion, most frequently a giant cell tumour (Schreuder et al., 1997).

Conventional treatment is directed at surgical removal; the most common approach is curettage with bone grafting (cyst removal and cavity filled with autograft). Simple cysts usually heal without intervention. In contrast, aneurysmal cysts are associated with a high recurrence rate (149 in 484 cases) (Schreuder et al, 1997), with 90% recurring in two years (Kransdorf et al, 1995;Schreuder et al, 1997). The risk of recurrence is eliminated by wide resection, but this leads to greater bone loss and the need for greater reconstruction (Schreuder et al, 1997). There are variations on the standard techniques and debate about which is best, but each is associated with disadvantages and occasional serious complications.

The potential for RM is as a biological filler material, an alternative to autograft or allograft. The biomaterial should be biocompatible, have good mechanical stability, be easy to handle, lack of radiopacity, and non-antigenic (Pradel et al., 2006).

6.4.5 Conclusion

The information suggests RM could have an application in a variety of defects. However, I feel the greatest market potential is in moderate to large defects such as DDD and non-healing fracture repair (nonunion and segmental defects). However, there may also be a relatively large market an improved filler material for use in small to moderate defects such as those following spinal fractures and bone cyst removal.

The literature suggests it seems seldom necessary to provide immediate mechanical strength with rigid bone structures. Instead, it appears quite adequate to induce the body to form bone across the area to be bridged, and mechanical strength can come later once new bone is laid down. This means that many traditional TE applications consisting of a firm body platform populated by cells and/or growth factors is unnecessary.

In conclusion, I discern three broad alternatives for the management of a moderate size bone defect.

1. Autograft using bone graft harvested from the iliac crest (the current gold standard approach)
2. *In vivo* bone production (via implantation of growth factors and/or uncultured cells on some form of matrix/scaffold)
3. *In vitro* bone production using cells grown on a scaffold (with or without growth factors)

A RM solution provides an alternative to autograft and avoids the time, pain, and complications associated with harvesting bone. *In-vivo* production uses the body as a factory and avoids the logistical difficulties and cost of culturing the patient's cells *in-vitro*. Currently growth factors are preferred; they have the advantage over cells of being able to be used immediately. However, this method can use different types of scaffold with different costs and benefits.

In the following sections, I aim to summarise the incremental costs and benefits of autograft versus the alternatives and establish the likely cost at which *in vivo* and *in vitro* methods could be deemed cost-effective within the UK NHS. I will illustrate the economic analysis by taking spinal fusion and nonunion of fractures as examples of conditions that could use each of the methods discussed above.

6.5 Clinical Effectiveness

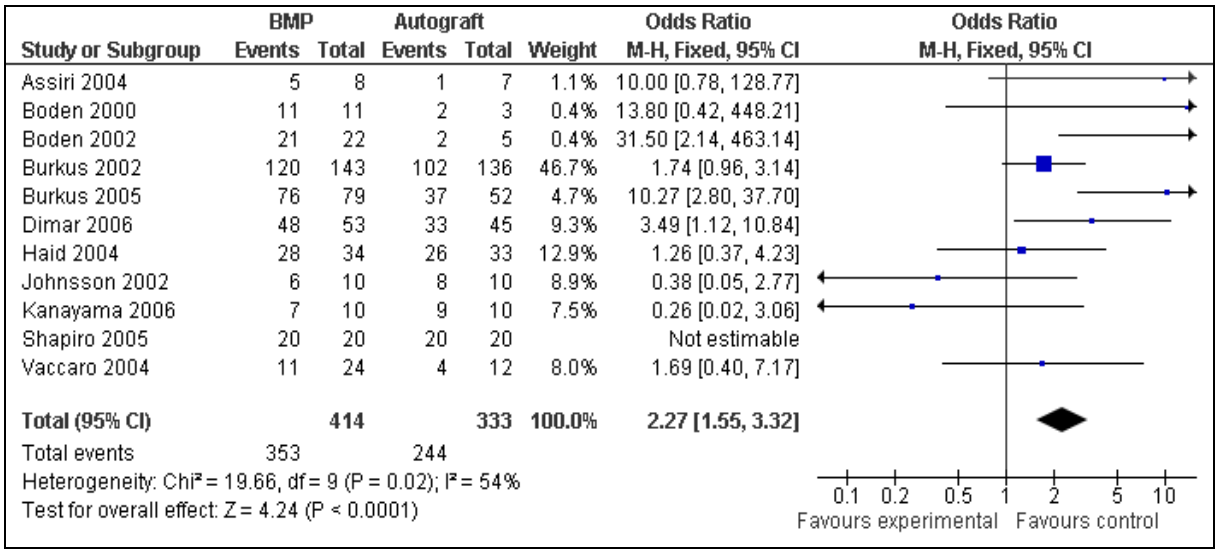
6.5.1 Union Rates

Spinal Fusion

The Garrison review (Garrison et al, 2007) identified eleven RCTs (Assiri et al., 2004;Boden et al., 2000;Boden et al., 2002;Burkus et al., 2002;Burkus et al., 2005;Dimar et al., 2006;Haid, Jr. et al., 2004;Johnsson et al., 2002;Kanayama et al., 2006;Shapiro et al., 2005;Vaccaro et al., 2004) comparing spinal fusion using autograft with spinal fusion using BMP (N=631). The authors determined the quality of the included studies as low to moderate. Overall, the meta-analysis showed that BMP improves fusion rates compared to autograft in spinal fusion surgery (85% in BMP group versus 73% in autograft group (OR=2.27, 95%CI: 1.55 to 3.32)) (table 6.5).

The literature does not report on the success rate for *in vitro* bone production, as there have not yet been any trials of this method. However, *in vitro* bone production is almost certain to be more expensive than an *in vivo* method using BMPs. *In vitro* methods are therefore dominated unless they are more effective than *in vivo* methods. Success rates for *in vivo* methods have been reported as 85% (above). The headroom for *in vitro* methods is therefore 12%.

Table 6.5: Fusion success rates of BMP versus autograft in DDD



Adapted from Garrison et al.2007

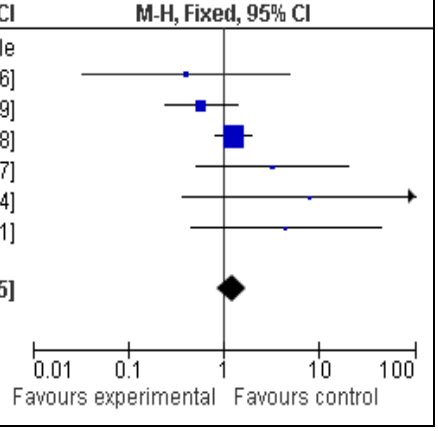
Non-Healing Fracture Repair

The Garrison review (Garrison et al, 2007) identified seven RCTs (Chen et al., 2000;Cook, 1999;Friedlaender et al., 2001;Govender et al., 2002;Jones et al., 2006;Maniscalco et al., 2002;Perry et al., 1997) comparing autograft with BMP for fracture healing. Again, the authors concluded that the quality of the included studies was low to moderate. The meta-analysis showed that rate of successful union favoured BMP (68% in BMP group versus 63% in autograft group, OR=1.21, 95%CI: 0.83 to 1.75) (table 6.6). It should be noted, the trial of nonunion with the second largest sample size (Friedlaender et al, 2001) reported differences in baseline characteristics between the autograft and BMP group. Of most importance was the significantly higher number of atrophic nonunions in the BMP group (41% versus 25%, P = 0.048). Atrophic non-unions are more difficult to heal because they lack a blood supply, which is one of the main components necessary for fracture healing.

Once again, the literature does not report on the success rate for *in vitro* bone production. As previously stated, *in vitro* bone production is almost certain to be more expensive than an *in vivo* method using BMP. *In vitro* methods are therefore dominated unless they are more effective than *in vivo* methods. Success rates for *in vivo* methods for non-healing fracture repair are reported as 68%. The headroom for *in vitro* methods is 32%.

Table 6.6: Fracture repair rates of BMP compared to autograft

	BMP		Autograft			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Chen 2000	30	30	20	20		Not estimable	
Cook 1999	12	14	15	16	3.9%	0.40 [0.03, 4.96]	
Friedlaender 2001	47	63	51	61	25.8%	0.58 [0.24, 1.39]	
Govender 2002	75	151	66	150	65.2%	1.26 [0.80, 1.98]	
Jones 2006	13	15	10	15	2.6%	3.25 [0.52, 20.37]	
Maniscalo 2002	7	7	10	15	0.9%	7.86 [0.37, 164.74]	
Perry 1997	19	20	17	21	1.6%	4.47 [0.45, 44.01]	
Total (95% CI)		**300**		**298**	**100.0%**	**1.21 [0.83, 1.75]**	
Total events	203		189				
Heterogeneity: Chi² = 7.30, df = 5 (P = 0.20); I² = 31%							
Test for overall effect: Z = 1.00 (P = 0.32)							



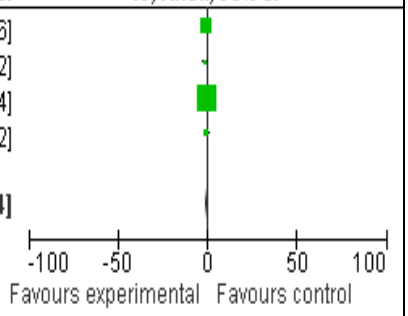
Adapted from Garrison et al. 2007.

6.5.2 Operative Results

BMP impacts on the global costs of surgery by avoiding bone harvesting. The meta-analysis in the Garrison review finds that using BMP in spinal fusion reduces operation time by 25 minutes (range: 11 to 37 minutes) and hospital stay by 0.75 days (table 6.8). However, I note the meta-analysis of reduction in hospital stay omits the largest trial (Burkus et al, 2002). Therefore, I re-perform the meta-analysis (table 6.7) to include this missing trial and found a reduction in hospital stay of 0.41 days (table 6.8). The data for fracture healing is limited. Two studies (Friedlaender et al, 2001;Jones et al, 2006) report an average reduction in operation time of 14 minutes and two studies (Friedlaender et al, 2001;Maniscalco et al, 2002) report an average reduction in hospital stay of 0.35 days (table 6.8).

Table 6.7: Mean hospital stay for patients receiving BMP and autograft

	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Boden 2000	3.65	0.5	20	4.4	0.5	5	30.4%	-0.75 [-1.24, -0.26]	
Boden 2002	2	0.6	11	3.3	1.4	3	2.8%	-1.30 [-2.92, 0.32]	
Burkus 2002	3.1	1.6	143	3.3	1.3	136	62.6%	-0.20 [-0.54, 0.14]	
Vaccaro 2004	3.9	1.7	24	4.3	2	12	4.2%	-0.40 [-1.72, 0.92]	
Total (95% CI)			**198**			**156**	**100.0%**	**-0.41 [-0.68, -0.14]**	
Heterogeneity: Chi² = 4.46, df = 3 (P = 0.22); I² = 33%									
Test for overall effect: Z = 2.95 (P = 0.003)									



Adapted from Garrison et al, 2007.

6.5.3 Other Clinical Outcomes

The Garrison review finds that secondary interventions in fracture healing are reduced by 2% in favour of the BMP group (34% for BMP group versus 36% for autograft group, OR=1.43, 95% CI: 1.03, 2.00). The Garrison review also reports findings of two studies (Friedlaender et al, 2001;Govender et al, 2002) with respect to reduction in infection rates associated with using BMP in fracture healing. The average reduction in infection is calculated as 19%. These results, along with those reported above are summarised in table 6.8.

Table 6.8: Overall effectiveness of BMP compared to autograft

Outcomes	Spinal Fusion	Non-Healing Fracture Repair
Increase in union rates	9%	5%
Reduction in operation time	25 minutes	14 minutes
Reduction in hospital stay	0.41 days	0.35 days
Reduction in secondary interventions	NA	2%
Reduction in infection rates	NA	19%

6.5.4 Disutility of Autograft

Donor Site Morbidity

Donor site morbidity has been investigated in 6 retrospective and 2 prospective observational studies (Ahlmann et al., 2002;Arrington et al., 1996;Goulet et al., 1997;Robertson et al., 2001;Sawin et al., 1998;Schnee et al., 1997;Skaggs et al., 2000;Younger et al., 1989) and 3 RCTs (Banwart et al., 1995;Sasso et al., 2005;Singh et al., 2005). Reported complications include haematoma formation, infection, hyperaesthesia, hypoaesthesia, blood loss, arterial injury, hernia formation, urethral injury, fracture, pelvic instability, cosmetic defects, tumour transplantation, and most frequently chronic pain at the donor site. Younger and Chapman (1989) were one of the first to conclude that morbidity associated with harvesting bone was low but significant and the first to establish definitions for major and minor complications occurring at early and late stages (table 6.9). The reported frequency of major complications is from 2% (Goulet et al, 1997) to 6% (Ahlmann et al, 2002), and for minor complications is from 9% (Ahlmann et al, 2002) to 39% (Banwart et al, 1995). The high rate of minor complications is primarily due to chronic pain which is still present in some 30% of patients at 2 years (although pain intensity is low) (Banwart et al, 1995;Robertson et al, 2001;Sasso et al, 2005;Sawin et al, 1998;Singh et al, 2005;Skaggs et al, 2000).

The literature suggests using two separate incisions for harvest and surgery is preferable to using one incision (major complication rate 17.9% verses 5.1% and minor complication rate 23.9% verses 19.3% (p=0.002)) (Younger et al, 1989). In addition, a posterior approach is preferable to an anterior approach (major complication rate 5.7% versus 20.4% and minor complication rate 12.6% versus

27.8% (p=0.008) (Younger et al, 1989)) (major complication rate 0% versus 2% and minor complication rate 8% versus 15% (no p value given) (Ahlmann et al, 2002)).

Table 6.9: Definition of complications

	Early Complications	Late Complications
Major Complications	Deep Infection; Prolonged wound drainage; Large Haematoma; Reoperation	Sensory Loss; Chronic severe pain; Chronic infection; Unsightly scar; Large bony defect
Minor Complications	Haematoma; Wound drainage; Severe pain; Temporary sensory loss	Chronic mild pain; Superficial infection; Delayed Wound healing; Minor wound problems

Adapted from Younger et al. 1989

Consultation with orthopaedic surgeons contradicted some of the literature. It is suggested the literature may be out if date in terms of surgical procedures and hence may overestimate morbidity. It was claimed the use of minimally invasive techniques is resulting in decreases in the frequency, intensity, and duration of donor site morbidity. The surgeons consulted suggested there is no significant difference between anterior and posterior approach and between using one or two incisions for harvesting and surgery, if the surgical technique is minimally invasive. I observed harvesting of bone from the iliac crest using a technique, which leaves the soft bone attached to the muscle. Bone is then removed from inside the crest and the hole covered using the flap of soft bone attached to the muscle. This is not by all accounts a standard procedure. However, those that have adopted this technique claim to have seen decreases in donor site morbidity, believed to be the result of increased bone healing at the harvest site and less interruption to the surrounding muscle area. However, this technique has not been subjected to a trial and I found no competitive studies of any type.

Health-related quality of life and Utility

As discussed, a major limitation of the current treatment is the need to harvest bone and the associated donor site morbidity. BMP could affect the HRQL of the patient in the short term by avoiding donor site morbidity and in the longer term by increased fusion rates. For spinal fusion, improvements in Oswestry low back pain scores in favour of the BMP group were observed in 6 of the 7 trials identified in the Garrison review (improvement ranged from 24.5 to 33.4 for BMP group and

from 15 to 29.5 for autograft group (no p values)). General health status was measured using the SF-36 questionnaire in 6 of the 7 trials identified in the Garrison review. Higher mean score improvements for the BMP group compare to the autograft group were seen in all but one study (Dimar et al, 2006).

For economic analysis, I need a utility-based HRQL score. Garrison and colleagues concluded that there was limited data on utility score. I corroborate this finding and report their results. The Garrison review calculated utility scores for spinal fusion using the Brazier Index from SF-36 scores reported in an RCT by Burkus and colleagues (Burkus et al., 2003). The results are summarised in table 6.10. A 24-month utility difference of 0.0056 in favour of those patients who received BMP is reported.

As all other aspects of the spinal fusion operation are constant apart from the harvesting of bone, I assume the difference in utility represents the disutility of donor site morbidity. This may overestimate this effect; however, a pessimistic view of the current treatment is consistent with the headroom approach. The information gleamed from the literature and discussions with surgeons suggest the maximum duration of donor site morbidity is 12 months. I calculate the disutility of donor site morbidity from table 6.10. A patient experiences a disutility of 0.0087 for 3 months, 0.003 for a further 3 months and 0.0018 for 6 months. This results in an overall disutility of 0.0038 [(0.0087*0.25)+(0.003*0.25)+(0.0018*0.5)]. This value will be used later in the headroom analysis.

I have not used the utility difference stated at 24 months, as it is inconceivable that the disutility would then increase between months 12 and 24. Instead, I believe this difference is due to the long-term effectiveness of BMP over autograft.

Table 6.10: Utility scores associated with using autograft and BMP in spinal fusion

Period	Preoperative	3 months	6 months	12 months	24 months
BMP	0.5387	0.5948	0.6191	0.6332	0.6537
Control	0.5417	0.5861	0.6161	0.6314	0.6481
Difference (BMP – Control)	-0.003	0.0087	0.0030	0.0018	0.0056

Adapted from Garrison et al, 2007

The Garrison review estimated a QALY gain of 0.032 per nonunion repair, in favour of BMP, calculated from additional well patient weeks (derived from the RCT by Govender et al. 2002), and disutility values extrapolated from estimates of hip and general fractures.

A search of the database of utility weights held by TUFTS (Tufts Medical Centre, 2009) identified a study (Sprague et al., 2002) which reports the utility (based on expert opinion) of a nonunion fracture requiring reoperation as 0.5. This value will be used later in the headroom analysis.

6.6 Costs of Treatment

I review the costs associated with BMP, including health service costs. Costs of treatment were ascertained, where available, from published papers (primarily the Garrison review) supplemented by the 2006 NHS national schedule of reference costs (Department of Health, 2006b) and the 2006/07 national tariff (Department of Health, 2006a). Some of the unit costs for spinal fusion I calculate differ from those in the Garrison review. These differences were due to a) errors, which have been subsequently rectified following personal communication (as for cost per bed day); b) differences in raw data used in calculations (as for cost per hour operating time); and c) more recent department of health reference costs (revisional procedures). As an addition to the Garrison review, I calculated the cost per hour of operating time and the cost per bed day associated with fracture repair. However, the necessary data to calculate these values was limited. The cost of the *in vivo* method of bone production for spinal fusion is dependent on the additional cost of BMP. The cost of BMP was given as £1,790 ($2,900, €2,000) and was obtained from Wyeth Pharmaceuticals. The tissue engineers I consulted agreed that the cost provided in the HTA review remains accurate and therefore I have not updated this cost. A summary of the unit costs associated with spinal fusion and nonunion repair are provided in table 6.11 and table 6.12, respectively. The updated unit costs are used in all subsequent analysis.

Table 6.11: Unit costs associated with spinal fusion

Parameters	Garrison Review	Source	Updated Unit Costs	Source
Initial treatment cost	£ 5,283	National schedule of Reference costs: HRG R03, 2005	£ 5,308	National schedule of Reference costs: HRG R03, 2006
BMP	£ 1,790	Wyeth Pharmaceuticals	£ 1,790	Wyeth Pharmaceuticals
Revisional Procedures	£ 4,452	National Schedule of Reference costs: HRG R09, 2005	£ 4,430	National Schedule of Reference costs: HRG R09, 2006
Cost per hour operating time	£ 1,034	Based on total cost of £2863.07 and average duration of 182 minutes (both extracted from (Rivero-Arias et al. 2005))	£ 1,966	Based on total operation cost above and mean operation time of 162 minutes (extracted from meta-analysis in (Garrison et al. 2007))
Cost per bed day	£ 264	National tariff: R03, 2006/07 (long-stay payment for days exceeding trimpoint)	£ 242	National tariff: R03, 2006/07 (long-stay payment for days exceeding trimpoint)

Cost per bed day in Garrison review was incorrectly given as HRG R02 instead of HRG code R03. I used data from 2006 rather than the more recent 2007 as the HRG coding system has changed and I would have been unable to make comparisons with the 2005 results given in the HTA report.

Table 6.12: Unit costs associated with fracture repair

Parameters	Garrison Review	Source	Updated Unit Costs	Source
Initial treatment cost	£3,521	National schedule of reference costs: HRG H35, 2005	£ 3,521	National schedule of reference costs: HRG H35, 2005
BMP	£1,790	Wyeth Pharmaceuticals	£ 1,790	Wyeth Pharmaceuticals
Infections	£1,952	National schedule of reference costs: HRG S20, 2003	£ 1,952	National schedule of reference costs: HRG S20, 2003
secondary interventions	£2,738	National tariff: H16 and H17, 2006 (admitted patient care, non elective)	£ 2,738	National tariff: H16 and H17, 2006 (admitted patient care, non elective)
Cost per hour operating time	NR	NA	£ 1,017	Based on total treatment cost above and total operation time of 178 minutes (Friedlaender et al. 2001)
Cost per bed day	NR	NA	£ 194	National tariff: H35, 2006/07 (long-stay payment for days exceeding trimpoint)

Cost per infection not updated as the code is no longer available. NR=Not reported, NA= Not applicable.

6.7 Cost-effectiveness

6.7.1 Review of Previous Cost-Effectiveness Analysis

Three previous cost-effectiveness analyses (Dahabreh et al., 2006;Garrison et al, 2007;Polly, Jr. et al., 2003) of BMP versus autograft exist. Dahabreh and colleagues conducted a prospective cost analysis study (n=29) of BMP in nonunion fractures. BMP was applied to the nonunion site either alone or in addition to autograft. The authors found a 47% reduction in the average cost of treatment compared to all previous unsuccessful treatments of a nonunion ($p<0.05$) and concluded that the use of BMP would probably be of benefit in the treatment of fracture nonunions where the conventional treatment is expected to be difficult, lengthy, and possibly unsuccessful. Polly and colleagues assessed the cost-effectiveness of BMP in spinal fusion and suggested that the initial cost of BMP would be offset by avoiding bone harvesting (and related complications) and improving successful fusion. However, the input estimates were based on expert opinion rather than empirical evidence and will not be considered here.

Here I will discuss the findings of the Garrison economic analysis of BMP for spinal fusion and for fracture healing. The economic models were provided by ABACUS International (healthcare consultancy). The spinal fusion economic model was populated with effectiveness data from an RCT by Burkus and colleagues (Burkus et al, 2002) and the unit costs reported above. The fracture repair model was populated with effectiveness data from an RCT by Govender and colleagues (Govender et al, 2002) and the unit costs reported above. Garrison and colleagues reported their results on a per 100,000 basis; here I present these findings as cost per treatment.

BMP increases initial treatment costs by £1,790 ($2,900, €2,000) per surgery (the cost of BMP itself). After taking account of savings associated with reduced operating time, hospital stay, and secondary interventions, BMP increases initial treatment costs of spinal fusion by £1,242 ($2,000, €1,400) and is associated with a 0.011 QALY gain per spinal fusion. The estimated incremental cost per QALY gain was £120,390 ($197,000, €138,000) and the probability that BMP is cost-effective in the UK is only 6.4% (table 6.13). Garrison and colleagues conclude that using BMP in spinal fusion is unlikely to be

cost-effective. After taking account of savings associated with reduced infections, secondary interventions, and outpatient contacts BMP increases initial treatment cost of fracture repair by £1,055 ($1,700, €1,200) and is associated with a 0.032 QALY gain per fracture repair. The estimated incremental cost per QALY gain was £32,603 (95% CI £14,085 to £61,257) ($53,400, €37,400) and the probability that BMP is cost-effective in the UK is 35.5% (table 6.13).

Table 6.13: Results from previous cost-effectiveness analysis

Main Results	Spinal Fusion	Non-Healing Fractures
Initial cost impact per treatment	£1,790	£1,790
Costs offset by avoiding bone harvesting	£496	£736
Net cost per treatment	£1,294	£1,054
Additional QALY per treatment	0.011	0.032
Incremental cost per QALY gained	£120,390	£32,603
Probability of BMP being cost effective at £30,000	6.4%	35.5%

The results here are given on a per treatment basis based on the results given in the Garrison review. Results are presented to the nearest pound.

6.7.2 Mean Incremental Cost per Case

Here I calculate the mean incremental cost per case associated with using BMP compared to autograft. Using the effectiveness data (table 6.8, page 179) and the updated unit costs (table 6.11 and 6.12, page 183) reported above I calculate the potential cost savings associated with BMP and offset this against the cost of BMP (table 6.14). The cost savings consist of:

i. Cost savings contingent on improvement in success rates – this is estimated by using the unit costs associated with resurgery (secondary interventions) multiplied by the probability of having a resurgery (based on union success rates).

ii. The costs associated with avoiding donor site morbidity – this is linked with two savings. Firstly, the reduction in operation time, calculated using the cost per hour of operation calculated in section 6.8, and secondly, the reduction in hospital stay, calculated using the cost per bed day.

iii. Reduction in infections – applies to fracture repair only and is estimated by using the unit costs associated with infections multiplied by the reduction in infections associated with BMP reported in the Garrison report.

Table 6.14: The incremental cost per case associated with the use of BMP

	Spinal Fusion		Nonunion repair	
	BMP	**Autograft**	**BMP**	**Autograft**
Cost saving associated with reduction in reoperations (A)	£532		£137	
Cost of reoperation	£4,430	£4,430	£2,738	£2,738
Probability of reoperation	0.15	0.27	0.32	0.37
Total cost of Reoperations	£5,095	£5,626	£876	£1,013
Cost Saving associated with reduction in operation time (B)	£819		£283	
Cost per hour of operation	£1,966	£1,966	£1,214	£1,214
Reduction in operation (minutes)	25		14	
Cost savings associated with reduction in hospital bed days (C)	£99		£68	
Cost per bed day	£242	£242	£194	£194
Reduction in length of stay (days)	0.41		0.35	
Cost saving associated with reduction in infections (D)	NA	NA	£371	
Cost of treating infection			£1,952	£1,952
Probability of an infection			0.19	
Total Cost Saving (A+B+C+D)	£1,450		£859	
Cost of BMP (E)	£1,790		£1,790	
Overall Cost Difference (E-A+B+C+D)	**£340**		**£931**	

In conclusion, although BMP does appear to be slightly more effective than autograft, the current increase in effectiveness is insufficient to offset the additional cost of BMP, resulting in an incremental cost of approximately £340 ($560, €400) per spinal fusion and £930 ($1,500 €1,000) per fracture repair. There is a lower incremental cost per case associated with spinal fusion compared to non-healing fracture repair. This result may be surprising considering the findings from the previous cost-analysis. There are a number of possible explanations for this. Firstly, the unit costs used in this analysis differ from those used in the Garrison report (table 6.11 and 6.12, page 183). Secondly, the economic models in the Garrison report used clinical outcome data from one RCT only (Govender et al, 2002). Finally, here, the clinical data is taken from all trials but is heavily based on a trial (Friedlaender et al, 2001) where the baseline characteristics of the two treatments differ. Furthermore, this analysis accounts for just one aspect of the CEA, the cost savings associated with surgery costs and avoiding bone harvest. To demonstrate cost-effectiveness a product must also increase effectiveness and patient HRQL (if new treatment is more expensive than current treatment).

6.7.3 Supply-Side Analysis on Price of BMP

Here, I recreate and use the economic model from the Garrison review. I keep the QALY gains the same as stated in the Garrison review but I use the updated unit costs (table 6.11 and 6.12, page 183). I calculate the price at which BMP may be cost-effective in the UK. Using equation 6.4 I vary the cost of BMP until the ICER falls below the WTP thresholds of £30,000 ($49,000, €34,000) and £20,000 ($33,000, €23,000).

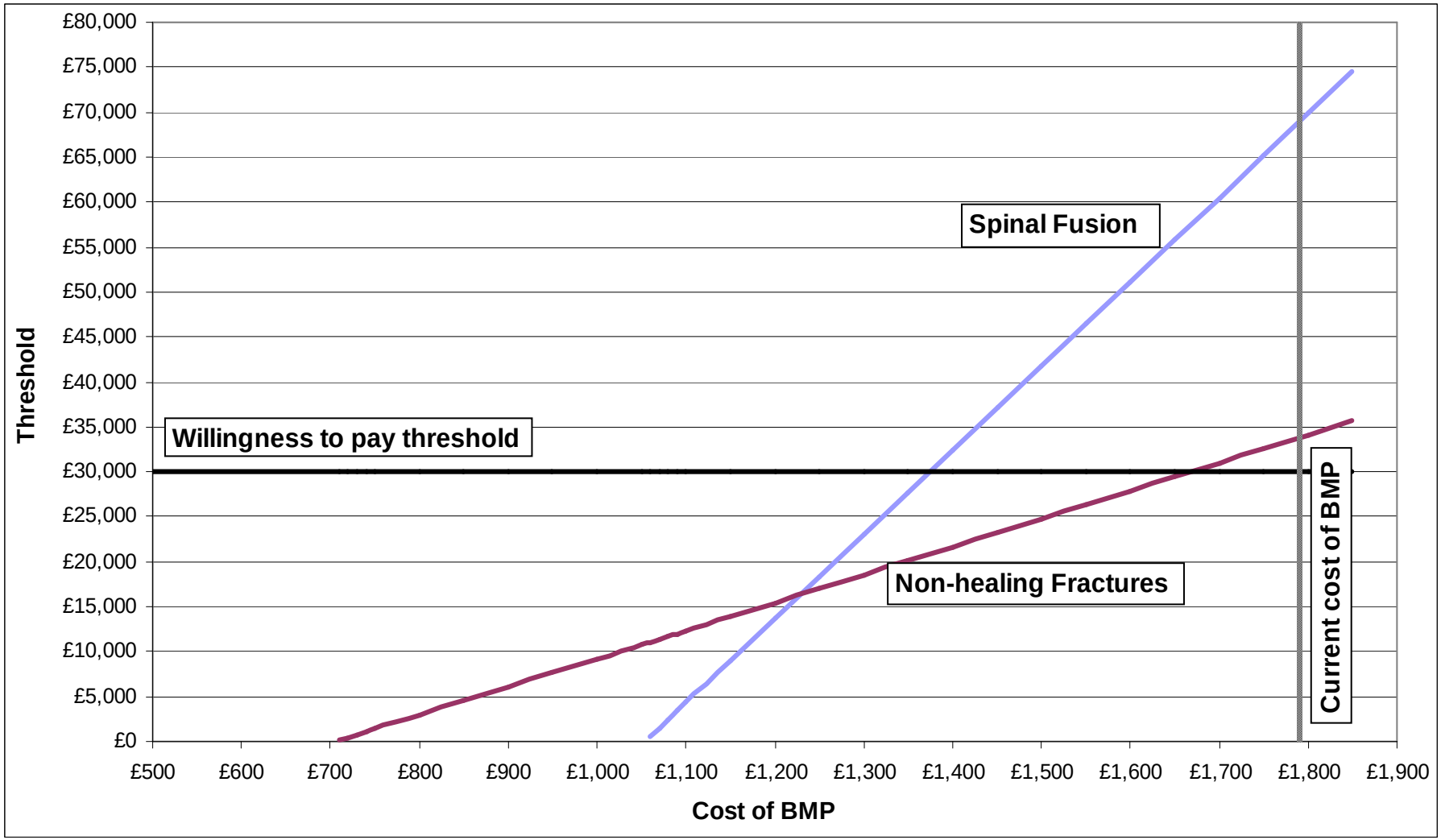
Equation 6.4: $ICER = \Delta cost / \Delta QALY$

For spinal fusion, the cost at which BMP would be cost-effective, at a threshold of £30,000, is £1,370 ($2,200, €1,500) (a 28% reduction in current price) and, at a threshold of £20,000, is £1,260 ($2,000, €1,400) (a 30% reduction in current price). For fracture repair the cost at which BMP would be cost-effective, at a threshold of £30,000, is £1,660 ($2,700, €2,000) (a 7% reduction in current price) and, at a threshold of £20,000, is £1,340 ($2,200, €1,500) (a 35% reduction in current price), after savings associated with infections and avoiding outpatient contact are taken into account. This analysis demonstrates that BMP is very nearly cost-effective, particularly for non-healing fracture repair, and a slight decrease in the price of BMP could make this product reimbursable in the UK NHS. The results are shown in table 6.15 and figure 6.5.

Table 6.15: Supply side analysis of BMP

Parameter	Spinal Fusion	Non-healing Fracture Repair
Initial cost impact per treatment	£1,790	£1,790
Costs offset by avoiding bone harvesting	£736	£639
Net cost per treatment	£1,054	£1,151
Cost of BMP to achieve cost-effectiveness at £30,000 threshold	£1,370	£1,660
Price reduction compared to current cost of BMP	23%	7%
Cost of BMP to achieve cost-effectiveness at £20,000 threshold	£1,260	£1,340
Price reduction compared to current cost of BMP	30%	25%

Figure 6.5: The cost at which BMP could be cost-effective at different thresholds of willingness-to-pay for healthcare interventions



This figure illustrates graphically the maximum cost for BMP to be determined cost-effective at different WTP thresholds

6.7.4 Cost-Minimisation Analysis

Current data suggests that BMP is slightly more effective than standard treatment. However, the effect to which these results translate into improved long term outcomes is very uncertain. What is certain is that operation time is reduced by use of BMP due to time saved by avoiding bone harvest. The difference in operating time between BMP and autograft was 0.41 hours (25 minutes), which results in a cost saving of £891 ($1,500, €1,000) (table 6.14, page 186). Since this is the case, I have performed a CMA on autograft versus BMP and have assumed that the effectiveness of the two treatments is the same, the only difference being operating time. I use the economic model used in the Garrison review. Firstly, I recalculate the incremental cost of BMP (∆cost). Secondly, using equation 6.5 (where WTP threshold is £30,000), I calculate the price at which BMP would be cost-effective by varying the price of BMP until the ∆QALY is equal to zero.

Equation 6.5: ∆QALY =∆cost/WTP threshold

For spinal fusion, the cost at which BMP would be cost-effective, if there was no difference in benefit, is £806 ($1,300, €900) (a 55% reduction in current price). For fracture repair the cost at which BMP would be cost-effective, if there was no difference in benefit, is £417 ($680, €500) (a 77% reduction in current price). This analysis demonstrates that a reduction in operation time is not sufficient to offset the incremental cost of using BMP and confirms that BMP needs to improve success rates and clinical outcomes including health-related quality of life, before it can be deemed cost-effective.

Table 6.16: Cost Minimisation Analysis of BMP

Parameter	Spinal Fusion	Non-healing Fracture Repair
Initial cost impact per treatment	£1,790	£1,790
Costs offset by avoiding bone harvesting	£806	£417
Net cost per treatment	£984	£1,374
Cost of BMP in order to achieve cost-effectiveness	£806	£417
Reduction compared to current cost of BMP	55%	77%

6.7.5 Headroom Analysis

Finally, I calculate the headroom - the maximum *incremental* cost of the new treatment over the comparator, which could still be deemed cost effective – for a new RM technology, either in vitro or in vivo, compared to the gold standard, autograft. This will determine whether it is worthwhile investing in the potentially more expensive *in vitro* technology.

As previously discussed, before calculating the headroom I must estimate the maximum potential change in effectiveness, measured using QALYs. For spinal fusion, I calculate the disutility associated with donor site morbidity as 0.003825 from table 6.10 (section 6.5.4, page 179). I assume the effects of avoiding donor site morbidity last a maximum of 12 months. Using equation 6.6, I determine a maximum change in effectiveness of 0.0038 QALY (equation 6.6).

Equation 6.6: Δ QALY = 1 x 0.0038 = 0.0038

Next, I calculate the headroom (maxΔCost). Based on a reimbursement level of £30,000 ($49,000, €34,000), the headroom is calculated as £114 ($180, €130) (equation 6.7). Finally, I take account of cost savings associated with reduced operating time from avoiding bone harvest (£819). This gives total headroom of £933 ($1,500, €1,000). If a new bone RM technology for spinal fusion is going to be deemed cost-effective, it needs to be marketed at a price that would keep the maxΔCost below £933 ($1,500, €1,000).

Equation 6.7: maxΔCost = 0.0038 x £30,000 = £114

For non-healing fractures, I will use the utility value identified through the TUFTs database, reported in section 6.5.4 (page 179). Here, I assume an optimistic maximum duration of this health state of nine months. Based on the classification of a nonunion fracture as failure to heal within six months, and assuming a period of three months before the patient receives a reoperation. Therefore, I calculate a maximum change in effectiveness of 0.5 QALY (equation 6.8).

Equation 6.8: Δ QALY = 0.75 x (1-0.5) = 0.375

Next, I calculate the headroom (max∆Cost). Based on a reimbursement level of £30,000 ($49,000, €34,000), the headroom is calculated as £11,250 ($18,400, €12,900) (equation 6.9). Finally, I take account of cost savings associated with reduced operating time from avoiding bone harvest (£283). This gives total headroom of £11,533 ($18,900, €13,200). If a new bone RM technology for nonunion fracture repair is going to be deemed cost-effective, it needs to be marketed at a price that would keep the max∆Cost below £12,000 ($19,600, €13,000).

Equation 6.9: max∆Cost = 0.375 x £30,000 = £11,250

However, as described above, changes in the duration of the negative effects of can have a large impact on the headroom. Furthermore, advances *in vivo* technology could make BMPs cost-effective and thus reduce the effectiveness gap, limiting the headroom further.

6.8 Discussion

6.8.1 Summary of Findings

When the natural healing properties of bone break down, intervention is required. Following careful analysis of the clinical problem, I discern there are three broad alternatives for the management of a moderate size bone defect. Firstly, autograft using bone graft harvested from the iliac crest (the current gold standard approach), secondly, *in vivo* bone production (via implantation of growth factors and/or uncultured cells on some form of matrix/scaffold) and thirdly, *in vitro* bone production using cells grown on a scaffold (with or without growth factors). The first method (autologous bone graft) is the current standard. However, this method has a number of limitations primarily that of donor site morbidity, which reduces health-related quality of life and increases recovery time, ultimately increasing the cost of treatment. The solution to these problems could rest in RM. This technology could avoid the time, pain, and complications associated with harvesting from the bone as well as having a higher rate of effectiveness i.e. lower rate of failed fusion. *In vivo* production uses the body as a factory and avoids the logistical difficulties and cost of culturing the patient's cells *in vitro*. Using the examples of spinal fusion and non-healing fracture repair, I have assessed the cost-effectiveness of

bone autograft versus *in vivo* bone production (illustrated using growth factor BMP) and made predictions about the headroom for improvement for *in vitro* bone production.

Although the studies are not perfect, BMP does appear to be slightly more effective than autograft, which is essential if it is to be cost-effective. At the current price BMP is borderline cost-effective in the UK for non-healing fractures (see figure 6.5). For spinal fusion, at the current price, the results are much less encouraging and BMP will probably not be cost-effective, even at a much higher WTP threshold. However, if the price of BMP is halved, or if the effectiveness of BMP can be improved, it could become extremely cost-effective in the UK. Currently the increase in effectiveness appears to be insufficient to offset the additional cost of BMP.

The headroom method has shown that under pessimistic assumptions of the side effects of the current treatment (i.e. donor site morbidity) there is large headroom for improvement. It is highly likely that an *in vivo* solution could be brought in at a price below the headroom. It is also possible that an *in vitro* solution could be brought to market within such a headroom. However, as I have said BMP saves the need for bone harvesting (contingent saving in cost and morbidities) without all the difficulties of *in vitro* production and is currently the favoured approach. Furthermore, the utility used here could be an overestimation of the true effects of donor site morbidity. For example, if the effects of donor site morbidity were to last 12 months rather than 24 months then the headroom would be reduced to around £12,000 ($19,600, €13,000) - a figure, which could be too low to support an *in vitro* approach.

6.8.2 Limitations

Going forward, utility estimates need to be improved if accurate estimates of cost-effectiveness are to be made. The utility estimates used in this analysis are heavily based on the data from the Garrison review and could very well be out of date with respect to bone repair using autograft. New RCTs conducted in this area should incorporate utility-based HRQL data collection into their studies. This will give a more accurate picture of the effectiveness of BMP and the headroom for more sophisticated technology.

6.8.3 Implications of this Work

This work has been of great interest to the tissue engineers with whom I collaborated. Interestingly when I started this work there were two camps of thought. There were those advocating the 'body as a factory' approach - using growth factors embedded in a scaffold, and those who wanted to make bone outside the body. Although the science of developing such a tissue as bone outside the body may be worthy of research, in terms of developing a product likely to be reimbursed, I have demonstrated that the 'body as the factory' approach will almost certainly win. As I have previously stated the use of BMP compared to autograft is very nearly cost-effective, therefore I suggest resources and time are best spent on improving this technology. Indeed, this work has convinced some partners within the STEPS consortium, to scale back work on developing bone per se and invest more resources on using the "body as a factory" approach i.e. scaffold plus growth factors.

Contradiction to my Findings

Despite the conclusions, that suggest BMP is not cost-effective at its current price and effectiveness, in the USA INFUSE (or BMP) is (allegedly) the best selling RM product, with sales currently at $700 million per year and growing rapidly (Lysaght et al., 2008). This contradicts my findings, so clearly in the US market other factors are at play. There are three possible explanations for this high sale volume in the US:

1. Purchasers could be negotiating a large reduction in cost;
2. The WTP threshold is higher (say £50,000 ($82,000, €57,000)) and purchasers negotiated a small reduction in cost (however, this would suggest that the system is based on evidence based medicine);
3. BMP has been brought in "under the radar" – that is to say, the opportunity cost of its use has been ignored – i.e. its use is not based on cost-effectiveness analysis.

My initial thought is that it is probably a combination of all three explanations. This however, may not be much use to the UK industry, who may hope to sell their products in the US. To inform the UK industry it would be helpful to know why this is the case. This was beyond the scope of this PhD but is something that is being investigated by another work package within the REMEDI consortium.

Pricing to a Threshold

Our supply-side analysis showed that to achieve cost-effectiveness BMP requires a reduction in price of 7% and 23% for non-healing fracture repair and spinal fusion, respectively (based on current levels of effectiveness and a WTP threshold of £30,000). If I also consider market size the returns could be greater for non-healing fracture repair than for spinal fusion, thus profitability could be maximised if the price of BMP is reduced to cover its application in non-healing fracture repair but not to cover spinal fusion. Alternatively, different prices could be set for different applications.

There are dangers for the industry in pricing to a threshold. Firstly, the industry might inadvertently over shoot and set too high a price – the health service may use different assumptions when coming to model cost-effectiveness moreover the cost-effectiveness threshold is allowed to vary to some extent – elsewhere the effect of uncertainties in the affordable price on optimised pricing strategy has been modelled (Girling et al., 2008). Secondly, industry may undershoot, especially if consumer pressures for the product are high or other emotional or political factions come into play to support the product. Thirdly, pricing in other countries may be deflated by prices in those with the lower thresholds. This is a rather weak argument because many manufacturers set different prices already. Moreover, a negative rationing decision in one country might exert deflationary pressures elsewhere to a greater degree than a price reduction.

There are also dangers to the health service, although, in England the government seems to have crossed this crucial point by introducing risk sharing schemes where costs are adjusted according to accumulating information over the years. There is a risk that the service might create a hostage to fortune by binding itself to a methodology that precludes negotiation of a lower price. This seems a weak argument for a patented medicine where rationing decisions apply. Once the patent has expired, other manufacturers are free to undercut the threshold price. Difficulties arise when a product has more than one application with different incremental cost-effectiveness ratios (as in this case). However, different approaches can be taken in this scenario, including different prices for different applications or weighted average prices across applications.

The issue of pricing to a threshold has been discussed by Claxton and colleagues in a recent paper (Claxton et al., 2008). The principles of value based pricing means that drugs will be approved for use only at prices that ensure that their expected health benefits exceed the health displaced. In the longer term this means prices based on value to the health service will provide incentives for manufacturers to develop technologies that are more likely to be of value i.e. cost-effective (Claxton et al, 2008). Price negotiation and guidance will then depend on the value of the technology and the responsibility for rejecting or restricting access to a new technology will be shared between the NHS, that cannot afford the cost-ineffective technology, and the manufacturer who is unwilling to accept a price that would make it cost-effective. Of course, for this to work, it requires NICE to signal, clearly, to the industry what is of value. It is then for manufacturer's to choose to invest in technologies they believe will be both cost-effective for the NHS and give satisfactory return on investment (Claxton et al, 2008). The industry is free to follow a mechanism of pricing to a threshold and does not need to have permission from a third party payer to do so. However, an iterative process, where by the price can be adjusted to accommodate outputs of independent models that have withstood challenge may be more efficient from an industry and societal perspective.

6.9 Conclusion

Here I have shown that health economics has a role in strengthening the supply side, not just the demand side of the health economy.

This application of the headroom method has been very different compared to the previous example given in chapters 4 and 5. The differences have arose due to the existence of an autograft substitute already on the market having already undergone CEA RM bone is further along the development process than visceral TE products. In this instance, supply side analysis, based on the premise of the headroom method, was conducted to find out the price at which the product would be cost-effective. This analysis has shown that BMP is very close to being cost-effective, which has been informative for the industry. It has indicated that small increases in effectiveness, such as changes in delivery

systems or BMP concentrations, could be sufficient to make BMP a cost-effective solution relative to autograft, and therefore it is likely to be worthwhile continuing to invest in this technology.

RM has the potential to revolutionise the treatment of bone conditions resulting in treatments, which are less invasive, more effective, and less expensive. Future RM research may move towards cell-based therapies, developing the ability to influence stem cells and direct their differentiation into cells that can be used directly for repairing defects, and developing appropriate biodegradable scaffolds for use in cell implantation into the body. The headroom analysis shows that there could be scope for these solutions to be a cost-effective alternative to autograft. However, the time between cell extraction, proliferation, and implantation must be reduced. Currently growth factors are the preferred option for a RM solution as they have the advantage over cells of being able to be used immediately. Furthermore, advances in the BMP delivery systems may prove to be more effective, and at lower concentrations, thus being less costly than current scaffolds.

In the following chapter, I consider the final clinical application for a RM solution; cartilage defects of the knee.

CHAPTER 7 COST EFFECTIVENESS ANALYSIS OF REGENERATIVE MEDICINE IN CARTILAGE DEFECTS OF THE KNEE

7.1 Introduction

Cartilage is connective tissue, more flexible than bone, but harder than muscle, which often serves as an early skeletal framework, becoming mineralised as the animal ages. Cartilage consists of chondrocytes; specialised cells, representing 10% of the volume of cartilage, essential for cartilage formation and functionality (L'Hermette et al., 2006;Lin et al., 2006). Unlike other connective tissues, cartilage does not contain blood vessels. The chondrocytes are fed by diffusion generated through a pumping action of the articular cartilage and, as a result, compared to other connective tissues, cartilage grows and repairs more slowly.

There are three main types of cartilage each with slightly different properties that make each type the most appropriate to fulfil its function (ICRS, 2009):

1. Elastic cartilage – contains large amounts of elastin and it is present in the ears and parts of the nose
2. Fibrocartilage – is characterised by the dense population of type I collagen and has a high tensile strength and it is found in areas exposed to frequent stress such as intervertebral discs
3. Hyaline cartilage – is hard and contains high amounts of type II collagen (collagen unique to cartilage) and it covers the end of bone to form the smooth articular surface of joints, such as the knee, which permits friction-free movement of the bony ends.

This chapter will focus on defects of hyaline cartilage of the knee joint (also referred to as articular cartilage). Articular cartilage is prone to injury from trauma or overuse, and from loss of blood supply to an area of subchondral bone. Cartilage damage can have immediate dramatic consequences on knee

function and detrimental long-term degenerative effects on the joint. Articular cartilage defects fail to heal spontaneously and left untreated the defects progressively enlarge with time and predispose to OA, a joint disease involving degeneration of hyaline cartilage. In the western world, OA is second only to cardiovascular disease as a cause of disability (Salaffi et al., 2005), representing a large socioeconomic burden. OA is the most prevalent disorder of the musculoskeletal system and leads to joint pain and tenderness, limitation of movement, occasional effusion and variable degrees of inflammation (Risbud et al., 2002).

The poor healing potential of hyaline cartilage makes cartilage defect repair a prime target for RM solutions. RM has the potential to enable the body to repair, replace, restore, and regenerate damaged or diseased cells, tissues, and organs. An ideal RM therapy for cartilage defects would prevent onset of OA altogether, but a delay in OA onset would be valuable and arguably a more plausible objective. Such a treatment would delay, if not prevent, the need for a total knee replacement (TKR) (or total knee arthroplasty (TKA)), which in turn should prevent the need for secondary knee replacements and further surgery.

The purpose of this chapter is to provide the RM industry and the clinical world with up to date information regarding the current state of research into RM treatments for cartilage defects and the likely cost-effectiveness of RM solutions.

7.2 Methods

7.2.1 Overview

I begin by summarising the natural progression of cartilage defects of the knee. I identify the existing and emerging treatment options proposed to repair a cartilage defect of the knee and go on to compare the clinical effectiveness and costs of the each. Next, I conduct CEA. This has two parts. First, I review previous cost-effectiveness analysis of RM solutions to treat cartilage defects of the knee. Second, I build on this analysis using the headroom method and estimate the maximum potential cost of an ideal RM solution.

7.2.2 Defining the Clinical Problem

I conducted a systematic literature review of the relative effects and costs of each cartilage repair treatment, using the search strings shown in appendix 12. I was aided by a HTA systematic review and economic analysis by Clar and colleagues (Clar et al., 2005), which I identified during the course of the literature search. A great deal of the literature found referred to knee and hip defects, OA, and replacement. However, it was decided from the outset that the focus of this work would be on defects of the knee and therefore only studies related to the knee were extracted. Finally, I identified the HRQL and utility associated with different health states:

a) Cartilage defect of the knee and its treatments – I was unable to identify a utility score from the literature associated with having a cartilage defect prior to any treatment. Utility gains associated with cartilage repair treatments are reported; however, the baseline values are not reported.

b) OA of the knee - Four prospective studies were identified that had each measured HRQL associated with knee OA using SF-36. The SF-36 sub-scores were converted into SF-6D and EQ-5D utility scores using two different algorithms described in the papers by Ara and Brazier (Ara et al., 2008a;Ara et al., 2008b). In addition, a cost benefit study was identified. This study described two hypothetical scenarios (based on EQ-5D domains); one related to mild-moderate knee OA (some problems with walking, no problems with self-care or performing usual activities, moderate pain or discomfort, not anxious or depressed), and one related to severe knee OA (problems with walking, self-care, performing usual activities, extreme pain or discomfort, and moderately depressed). Individuals indicated preferences for each state, elicited through VAS (visual analogue scale), TTO, and SG. The author also calculated WTP per QALY for each of the health states described. Utilities were also sourced from a report by Dong and colleagues (Dong et al, 2006) as part of the MATCH (multidisciplinary Assessment of Technology Centre for Health) collaboration. This study used a Markov model to assess cost-effectiveness of conventional TKR versus computer-assisted TKR. The utility scores associated with OA identified during the course of this work are reported here.

c) Primary and secondary knee replacement – Here, I report the utility gains identified from two systematic reviews (Clar et al, 2005;Ethgen et al., 2004) and a MATCH report by Dong and colleagues (Dong et al, 2006), discussed above. The Ethgen review reported HRQL scores following a TKR, measured using SF-36. As above I determined utility (SF-6D and EQ-5D) scores from the SF-36 scores using the algorithm described by Ara and Brazier (Ara et al, 2008a;Ara et al, 2008b).

7.2.3 Cost-Effectiveness

This section has two stages. Firstly, I review previous short- and long-term CEA of RM treatments. Secondly, I conduct my own supply side analysis, based on the headroom method described in chapter 3. Here, I ask two questions:

1. What is the minimum incremental effectiveness a competitive treatment should have in the short term to be more cost-effective than microfracture?
2. What is the maximum incremental cost a competitive treatment could be to be cost-effective in the long term?

7.3 Indication for a RM Solution

There are three main types of cartilage injury:

(a) *Matrix disruption* – damage to extra-cellular matrix, usually not extreme, and repair is via remaining viable chondrocytes;

(b) *Partial thickness defect* – is disruption of cartilage surface but not extending to subchondral bone. Nearby cells begin to proliferate but, for reasons unknown, discontinue proliferation before filling defect;

(c) *Full thickness defect* - traverses entire cartilage thickness, penetrating subchondral bone, resulting in exposure of progenitor cells from bone marrow, which migrate to fill defect. The lesion is filled with an intermediate tissue between fibrocartilage and hyaline cartilage, which is less stiff and more

permeable than native hyaline cartilage and which degrades over a period of years (Temenoff et al., 2000).

This chapter focuses on partial and full thickness cartilage damage in the knee, resulting from trauma in otherwise young, healthy patients. Cartilage defects become apparent many months or years after initial insult, making it difficult to calculate prevalence and incidence accurately. In the UK an estimated 10,000 patients per year - mostly young adults - suffer hyaline cartilage damage in knee joints of sufficient severity to cause symptoms (NICE, 2005b). Ultimately, these injuries can result in OA (figure 7.1). On average, patients who have suffered cartilage damage develop OA five to ten years earlier than patients who have not (Gelber et al., 2000;Hangody et al., 2006). When OA symptoms (pain, stiffness and swelling) become disabling, joint replacement surgery is necessary, the longer this can be delayed the better, for two reasons. Firstly, surgery carries risks (for example of osteomyelitis (inflammation of the bone)). Secondly, the earlier the joint replacement, the greater the chance of a secondary knee replacement (Bhosale et al., 2008). The current treatment strategy for OA in younger, active patients is to decrease symptoms and delay time to surgery. Since OA progression cannot be halted if early events are not prevented, the current challenge is to develop treatments that target cartilage repair to delay or even avoid surgical treatments for incapacitating OA (Goldring, 2006).

Figure 7.1: Diagram to illustrate the degeneration of cartilage in osteoarthritis

Image courtesy of Medical Multimedia Group LLC, www.eOrthopod.com
Source: http://www.eorthopod.com/public/patient_education/6516/osteoarthritis_of_the_knee.html

7.4 Treatment

There are several surgical therapies available for the treatment of cartilage damage of the knee but currently there is no truly effective strategy. The aim of these treatments is to restore normal, long-term, and pain free motion of the joint by promoting the formation of repair tissue with the structure and durability of natural hyaline articular cartilage (Saris et al., 2008). However, the quality of the tissue formed by each method is not always identical and has been reported as hyaline-like cartilage or fibrocartilage rather than regenerated hyaline articular cartilage (Simon et al., 2006;Williams et al., 2008).

7.4.1 Current Treatment

Current interventions include:

i. ***Conservative management*** - involves a combination of exercise and non-steroidal anti-inflammatory drugs.

ii. ***Arthroscopic debridement*** - a clean up process removing loose fragments of damaged tissue and trimming sharp margins.

iii. ***Microfracture*** *(or arthroscopic marrow stimulation)* - involves boring holes into subchondral plate bone to stimulate ingrowth and metaplasia (change in cells) of mesenchymal stem cells (MSCs) to repair cartilage damage. This technique is used in small defects (<2cm_2) (figure 7.2).

iv. ***Mosaicplasty*** *(or osteochondral autologous transfer (OATs)* – involves transfer of healthy mature cartilage and bone dowels from non-weight bearing joint areas to defective load bearing areas. This technique is associated with donor site morbidity and suited to small defects only (figure 7.2).

7.4.2 State of the Art in Regenerative Medicine

State of the art treatment involves the introduction of a defect-filling matrix, either containing cartilage precursor cells or signalling substances that will induce their local recruitment. The underlying principle

is that the cartilage precursor cells (transplanted or locally recruited) will differentiate into cartilage-producing chondrocytes (ICRS, 2009). These cartilage-engineering strategies are summarised below:

i. ***Autologous Chondrocyte Implantation (ACI)*** is a 2-step RM procedure. Firstly, autologous chondrocyte cells are harvested, via arthroscopy from a non-load bearing region of articular cartilage. Secondly, chondrocytes are cultured *in vitro* for 4-5 weeks and implanted, held in place under a membrane or mesh (Brittberg et al., 1994;Saris et al, 2008) (figure 7.2).

ii. ***Matrix-induced Autologous Chondrocyte Implantation (MACI)*** – used when chondral lesions are deep (>2 cm_2), to encourage further cell migration. Cells are harvested and cultured *in vitro* before implantation where they are held in place using a collagen or collagen-imitating membrane, which will degrade over time. The scaffold does not require stitching to cartilage and is a quicker procedure than ACI.

iii. ***Characterised Chondrocyte Implantation (CCI)*** (ChondroCelect, Tigenix) - is a variation on conventional ACI. The expansion of autologous cells in conventional ACI leads to dedifferentiation and loss of chondrogenic capacity (the ability to form cartilage). The basic premise of CCI is to improve articular regeneration leading to more durable joint surfaces. This is achieved by using a cell population capable of making stable hyaline-like cartilage in vivo (Saris et al, 2008).

iv. ***Osteochondral Scaffolding*** - a more recent addition to cartilage regenerative repair. The scaffold, made from a resorbable polymer plug mimics composition and structure of natural articular joints and can be used with current surgical procedures such as microfracture or mosaicplasty to improve outcomes (Simon et al, 2006;Williams et al, 2008).

Figure 7.2: Illustrations of microfracture, mosaicplasty, and ACI

Microfracture

Mosaicplasty

ACI

Images courtesy of Yorkshire Knee Clinic
Source:
http://www.yorkshirekneeclinic.co.uk/jointsurfaceinjuries.htm

7.5 Clinical Effectiveness of Treatment

7.5.1 Short-Term Results (based on clinical trials)

Eight RCTs have assessed short-term (<2 years) clinical effectiveness of RM therapies for articular cartilage defects of the knee. Three compare ACI with mosaicplasty (Bentley et al., 2003;Dozin et al., 2005;Horas et al., 2003). One compares ACI with microfracture (Knutsen et al., 2004); one compares MACI with microfracture (Basad et al., 2004). One compares CCI and microfracture (Saris et al, 2008). One compares ACI with MACI (Bartlett et al., 2005) and finally one compares two different approaches of ACI (Gooding et al., 2006). The results are summarised below and in table 7.1 to 7.3 (page 208-

211). Four of these trials (Basad et al, 2004;Bentley et al, 2003;Horas et al, 2003;Knutsen et al, 2004) were included in a Cochrane review (Wasiak et al., 2006), which found there is no evidence of significant difference between ACI and other cartilage repair treatments but concluded there is a requirement for high quality RCTs with long-term follow-up. No past or current trial or study has compared ACI or MACI with conservative management. In all trials, the main clinical outcome measure is knee function, but each trial uses different specific outcome measures. Therefore, a quantitative meta-analysis of clinical outcome results is not possible.

Bentley and colleagues reported statistically significant results in favour of ACI over mosaicplasty, with improved outcomes on the International Cartilage Repair Society (ICRS) arthroscopic grading system at 12 months. However, only 30% of patients underwent 12-month arthroscopic follow-up. The improved arthroscopic appearance did not translate to a statistically significant difference in knee function on the Cincinnati scale, except in the (retrospectively defined) subgroup of patients with lesions of the medial femoral condyle (rounded articular surface at the extremity of a bone). Dozin and colleagues randomised 47 patients to ACI or mosaicplasty 6 months after initial arthroscopic debridement of the lesion. However, nearly a third of patients did not receive the allocated treatment due to sufficient improvement following debridement alone. A further 7 patients were lost to follow-up leaving just 23 patients for evaluation of treatment effect. Complete recovery was reported in 88% of mosaicplasty group and 68% of ACI group (P=0.093) (measured using Lysholm knee scoring scale 90-100). Horas and colleagues reported a statistically significant difference in function in favour of the mosaicplasty group compared to the ACI group, using the Lysholm scores at 6, 12 and 24 months, but significance disappears using Meyers or Tegner scores.

Knutsen and colleagues found a difference at 2 years favouring microfracture, using the SF-36 physical component ($P<0.05$), the Lysholm score ($P>0.05$) and in need for further surgery (25 % of ACI group versus 10% of microfracture group). Basad and colleagues rendered improved results for MACI compared to microfracture based on the Lysholm-Gillquist score ($P<0.05$) at 24 months, the Meyers score ($P<0.05$) at an undefined period and the Tegner-Lysholm score ($P>0.05$) at 24 months. Saris and colleagues found a statistically significant difference in terms of quality of tissue restoration

in favour of CCI compared with microfracture, at 18 months. However, clinical outcome using KOOS (Knee injury and Osteoarthritis Outcome Score) was similar for both groups. The authors conclude that CCI is not demonstrably inferior to microfracture in the short-term and hypothesise that clinical benefit of CCI may not be observed until mid to long term follow-up. Bartlett and colleagues compared ACI with MACI in 91 patients. Both treatments showed improvement at 12 months, measured using modified Cincinnati knee score (ACI, 41.1 to 59.0 (P=0.01) and MACI, 44.5 to 64.1 (P=0.002)).

Finally, one trial compared different ACI approaches. Gooding and colleagues compared periosteum (connective tissue) -covered ACI to type I/II collagen covered ACI over 2 years. There is debate about whether the periosteum cover acts simply as a watertight seal or whether it secretes growth factors essential for development of hyaline cartilage (Gooding et al, 2006). There is no significant difference in clinical or arthroscopic outcomes. This study supports previous findings that a periosteum cover is not essential to development and maturation of hyaline cartilage. The only difference found was a greater incidence of graft hypertrophy (enlargement) in the periosteum-covered group, a result of increased morbidity due to longer surgery required to harvest the patch of periosteum.

Many of these trials are head-to-head comparisons of *in vivo* methods to stimulate cartilage production (e.g. mosaicplasty with or without scaffolding) with *in vitro* methods (e.g. ACI). There may be some evidence favouring the latter in arthroscopic appearances but, if anything, the *in vivo* methods are associated with improved functional performance. The ‘acid-test’ lies in longer-term outcomes.

Table 7.1: Short-term results of RCTs comparing ACI to mosaicplasty

Study		Bentley et al. 2003		Horas et al. 2003		Dozin et al. 2005	
RCT characteristics	**Trial**	ACI vs. Mosaicplasty		ACI vs. Mosaicplasty		ACI vs. Mosaicplasty	
	Mean follow-up	19 months		24 months			
	N	100		40		47	
	Mean Age (years)	31.3 (range: 16 - 49)		33.4 (range: 18 - 44)		28.7 (range: 21 - 36)	
	Mean defect Size (cm^2)	4.66		3.75		1.9	
	Aetiology of defect	trauma 46%, unknown 21%, osteochodritis dissecans 19%, chondromalacia patellae 14%		100% from trauma and all full thickness		Femoral condyle 71%, medial 84%, lateral 16%, patella 30%. Grade III 23%, grade IV 78%.	
	Mean duration of symptoms	7.2 years		None reported		None reported	
	Previous surgery	94% (excluding Arthroscopy)		Overall 40% (abrasion 20%, incomplete resection of the medial meniscus 7.5%, extraction of osteochondral bodies 5%, arthroscopy alone 5%, incomplete resection of the medial meniscus 7.5%, drilling 2.5%)		None	
Clinical Outcome		**Cincinnati Rating System**		**Modified Lysholm Score**		**Lysholm Knee Scoring Scale**	
		ACI n=58	**Mosaicplasty n=42**	**ACI n=20**	**Mosaicplasty n=20**	**ACI n = 19**	**Mosaicplasty n = 18**
		poor 0%	poor 17%	baseline 24.9	baseline 28.4	<60 4.5%	<60 0%
		fair 12%	fair 14%	3 months 27.5	3 months 27.9	60-90 23%	60-90 9%
		good 48%	good 48%	6 months 45.7	6 months 53.4	90-100 45%	90-100 63%
		excellent 40%	excellent 21%	12 months 57.5	12 months 68.2		
		Excellent + good 88%	Excellent + good 69%	24 months 66.7*	24 months 72.7*	subjective improvement 14%	subjective improvement 5%
		medial femoral condoyle defects		**Meyers Score**			
		ACI n=24	**Mosaicplasty n=29**	baseline 24.9	baseline 7.8		
		poor 0%	poor 14%	3 months 8.5	3 months 7.8		
		fair 12%	fair 14%	6 months 12.0	6 months 13.7		
		good 42%	good 52%	12 months 14.1	12 months 15.9		
		excellent 46%	excellent 21%	24 months 15.9	24 months 16.7		
		Excellent + good 88%*	Excellent + good 74%*				
		lateral femoral condyle defects					

	ACI n=13	**Mosaicplasty n=5**				
	poor 0%	poor 20%				
	fair 8%	fair 40%				
	good 38%	good 0%				
	excellent 54%	excellent 40%				
	excellent+good 92%	excellent+good 74%				
	patellar defects					
	ACI n=20	**Mosaicplasty n=5**				
	poor 0%	poor 40%				
	fair 15%	fair 0%				
	good 60%	good 60%				
	excellent 25%	excellent 0%				
	excellent+good 85%	excellent+good 60%				
Complication	3% low to mobilise required manipulation under anaesthesia; 1 arthroscopy and artrolysis to mobilise knee; 1 calf-vein thrombosis, required anticoagulants; 1 superficial infection.		ACI - 12; Mosaicplasty - 12		None reported	
Failure of treatment	None reported		None reported		None reported	
Need for further surgery	None reported		ACI - 8; Mosaicplasty - 9		None reported	

**P<0.05*

Table 7.2: Short-term results of RCTs comparing ACI to microfracture

Study		Basad et al. 2004		Knutsen et al. 2004		Saris et al 2008	
RCT characteristics	**Trial**	MACI vs. microfracture		ACI vs. microfracture		CCI vs. Microfracture	
	Mean follow-up	12 months		2 years		18 month	
	N	46		80		118	
	Age (years)	33		32.2 (range: 18-45)		18 - 50	
	Mean defect Size (cm^2)	2-10		4.8		1 - 5	
	Aetiology of defect			full thickness 96%, trauma 65%, OCD 28%, other 7%, partial thickness 4%		symptomatic cartilage lesion of the femoral condoyle	
	Mean duration of symptoms			36 months		CCI 1.97 years; Microfracture 1.57 years	
	Previous surgery			Overall 94% (arthroscopic lavage and debridement 36%, anterior cruiciate ligament reconstruction 19%, meniscal surgery 18%, drilling or fixation of a fragment 16%, pridie drilling 4%)		CCI 50%; microfracture 47% (greater than 2 previous surgeries: CCI 21%; microfracture 13%)	
Clinical Outcome		**MACI n=10**	**Microfracture n=9**	**ACI n=40**	**Microfracture n=40**	**Knee injury and osteoarthritis outcome score**	
		Meyers Score Improvement		**Lysholm Score**		**CCI n=51**	**Microfracture n=61**
		12 months 6.5	12 months 1.9	baseline 57	baseline 55	baseline 56.30	baseline 59.53
				12 months 68	12 months 77	6 months 70.56	6 months 72.63
		Lysholm-Gillquist Score Improvement		24 months 70	24 months 75	12 months 73.26	12 months 73.10
		12 months 27.4	12 months 4.1	**Pain (VAS, 0 to 100)**		18 months 74.73	18 months 75.04
				baseline 54	baseline 53		
		Tegner -Lysholm Score Improvement		12 months 40	12 months 35		
		12 months 32.6	12 months 15.3	24 months 35	24 months 31		
				Short form-36: physical component			
				baseline 41	baseline 37		
				12 months 42.5	12 months 41		
				24 months 42*	24 months 46*		
Complications		None reported		ACI group: symptomatic tissue hypertrophy; Microfracture group: 1 patient had arthrofibrosis, 3 patients had minor debridement's; No serious complications such as deep infection		mild or moderate: CCI 88% vs. microfracture 82%; Severe: CCI 12% vs. microfracture 13%	
Failure of treatment				ACI 5%; Microfracture 2.5%		None reported	
Need for further surgery				ACI: Biopsy 80%, Arthroscopic debridement 25%; Microfracture Biopsy 88%, Arthroscopic debridement 10%		None reported	

Table 7.3: Short -term results of RCTs comparing ACI to MACI and ACI

Study		Bartlett et al. 2005		Gooding et al. 2006	
RCT characteristics	**Trial**	ACI vs. MACI		ACI - Periosteum vs. ACI - Collagen	
	Mean follow-up	12 months		24 months	
	N	91		46	
	Age (years)	33.4 years		31.6	
	Mean defect Size (cm^2)	6.0		4.66	
	Aetiology of defect			disabling pain associated with an isolated full thickness chondral defect	
	Mean duration of symptoms	9.87 years		7.09 years (range: 1-27 years)	
	Previous surgery	ACI 2.3; MACI 2.1		2.09	
Clinical Outcome		**Modified Cincinnati Rating System**		**Modified Cincinnati Rating System**	
		ACI n = 44	**MACI n = 47**	**ACI-perisoteum n=33**	**ACI-collagen n=35**
		Poor 18.2%	Poor 12.8%	Poor 27.3%	Poor 23%
		Fair 22.7%	Fair 14.9%	Fair 33.3%	Fair 43%
		Good 36.4%	Good 40.4%	Good 39.4%	Good 34%
		Excellent 22.7%	Excellent 31.9%		
				International Cartilage Research Society	
		International Cartilage Research Society		**12 months**	
		poor 0%	poor 5.6%	Poor 3.2%	poor 3.4%
		Fair 20.8%	Fair 27.8%	Fair 16%	Fair 17.2%
		Good 62.5%	Good 44.4%	Good 71%	Good 69%
		Excellent 16.7%	Excellent 22.2%	Excellent 9.7%	Excellent 10.3%
				International Cartilage Research Society	
		Type of cartilage		**24 months**	
		hyaline like 28.6%	hyaline like 27.3%	poor 0%	poor 11.1%
		hyaline/fibrocartilage 14.3%	hyaline/fibrocartilage 9.1%	Fair 18%	Fair 33.3%
		fibrocartilage 57.1	fibrocartilage 63.6%	Good 73%	Good 55.5%
				Excellent 9%	Excellent 0%
Complications		hypertrophy (n=4)	hypertrophy (n=3)	1 major (Deep vein thrombosis); 12 minor	
Failure of treatment					2
Need for further surgery					

7.5.2 Medium-Term Results

Clinical Trials

Medium-term (5-15 years) clinical effectiveness of RM therapies has been reported in one RCT (Knutsen et al., 2007) comparing ACI with microfracture (table 7.4). After five years, there is no statistically significant difference in knee function using the Lysholm score, the Tegner score or Visual Analogue Scale (VAS). There was a difference favouring microfracture using SF-36 physical component, but this was not significant. Major complications such as complete treatment failure (defined as lack of healing of primary treated defect) and need for TKR were not statistically different.

Observational Studies

Longer-term follow-up (10 years) has been assessed in several observational studies (Blevins et al., 1998;Hangody et al., 2003;Hangody et al., 2004;Hangody et al., 2008;Peterson et al., 2000;Peterson et al., 2002;Peterson et al., 2003;Steadman et al., 2003;Szerb et al., 2005) (table 7.4). These studies have been reviewed by the HTA (Clar et al, 2005) and NICE (NICE, 2005b). They conclude that longer-term defects require hyaline cartilage for lasting benefit as fibrocartilage will eventually crumble.

Several other observational studies, not included in NICE and HTA reviews (Brittberg et al., 2003;Erggelet et al., 2003;Gillogly et al., 2006;Lohmander, 2003;Marcacci et al., 2002) have also assessed the effectiveness of ACI and found success regarding total number of improved patients (detailed results not reported). The criticism of these studies is the lack of head-to-head studies comparing ACI to other cartilage repair techniques, and the lack of sufficiently long-term follow up.

More recently, there have been two prospective studies published (table 7.4). Asik and colleagues (Asik et al., 2008) found microfracture is effective with regard to improvement in daily activities and pain relief after 5 years. Zaslav and colleagues (Zaslav et al., 2009) assessed ACI in patients with failed prior treatment and found ACI can provide sustained and clinically meaningful improvement in pain and function. There was a higher than normally reported rate of subsequent surgical procedures (49% overall with 40% related to ACI). However, the authors stated that a need for subsequent surgical procedure was not a predictor of failure.

Table 7.4: Medium-term results of observational studies of ACI and alternative treatments

Study		Knutsen et al. 2007		Zaslav et al. 2009	Asik et al. 2008	Steadman et al. 2003	Blevin et al. 1998	Hangody et al. 2001, 2003, 2004, 2008, Szerb et l. 2005	Peterson et al. 2000, 2002, 2003
RCT characteristics	**Type of study**	RCT: ACI vs. microfracture		ACI	Microfracture	Microfracture	Microfracture	Mosaicplasty	ACI
	Mean follow-up	5 years		4 years	5 years (range: 2 - 9)	2-11 years	2-5 years	1-15 years	2 - 11 years
	N	80 (ACI = 40; Microfracture = 40)		154	90	72	178		58 - 101
	Age (years)	32.2 (range: 18-45)		34.5	34.5 (range: 20-58)	13-45	13-68	27 (range: 16-47)	
	Mean defect Size (cm^2)	4.8		5.74	68 < $2cm^2$; 22 > 2 cm^2			1 - 4 cm^2	
	Aetiology of defect	full thickness 96%, trauma 65%, OCD 28%, other 7%, partial thickness 4%		chondral defect > $4cm^2$	Grade IV full thickness lesions			66% - grade III or IV lesion, 33% - OCD	moderate to large full thickness defects
	Mean duration of symptoms	36 months							
	Previous surgery	94%		100%					
	Type of previous surgery	arthroscopic lavage and debridement 36%, anterior cruiciate liagment reconstruction 19%, meniscal surgery 18%, drilling or fixation of a fragment 16%, pridie drilling 4%		48% debridement, 27% microfracture, 10% drilling, 6% arthroscopy, 5% osteochondral autograft, 2% chondroplasty, 1% marrow stimulation					
Clinical Outcome		**Lysholm Score**		**Modified Cincinati score**	**Lysholm Score**	80% rated themselves as improved at 7 years. Patients younger than 35 years had greater improvement	77% of high level athletes returned to competition, 71% reported to be equal or superior to preinjury level	**overall results**	Good and excellent results recorded in 82% at 2 years, 84% at 5-11 years (92% isolated femoral condyle, 67% multiple lesions, 89% OCD, 65% patella, 75% femoral condyle with anterior cruiciate
		ACI	**Microfracture**	baseline 3.26	baseline 52.4			good-to-excellent results were achieved in 92% of the patients treated with femoral condylar implantations, 87% of those treated with tibial resurfacing, 79% of those treated with	
		baseline 57	baseline 55	6 months 4.99	68 months 84.6*				
		12 months 68	12 months 77	12 months 5.58	**Tegner Score**				
		24 months 70	24 months 75	24 months 5.90	baseline 2.6				
		5years 78*	5years 80*	36 months 5.84	68 months 5.2*				

	Pain (VAS, 0 to 100)		48 months 6.31	**Oxford Knee questionnaire**			patellar and/or trochlear mosaicplasties, and 94% of those treated with talar procedures. 83% had good gliding surface	ligament reconstruction).
	ACI	**Microfracture**	**Global VAS**					
	baseline 54	baseline 53	baseline 28.8	baseline 23.1				
	12 months 40	12 months 35	6 months 60.1	68 months 44.8*				
	24 months 35	24 months 31	12 months 64.4					
	5 years 25*	5 years 24*	24 months 68.2					
	Short form-36: physical component		36 months 64.4					
	ACI	**Microfracture**	48 months 69.9					
	baseline 41	baseline 37	**Knee-related HRQL**					
	12 months 42.5	12 months 41	baseline 20.9					
	24 months 42*	24 months 46*	12 months 38.6				**Talar Implantations n=36**	
	5 years 48	5 years 47	24 months 44.6				**Hannover scoring system**	
			36 months 44.9				excellent 28	
			48 months 52.2				good 6	
			SF-36 overall health				moderate 2	
			baseline 33.0				**competitive sports athletes n=93**	
			12 months 39.8					
			24 months 42.0				64% returned to same level, 19% returned to lower level, 17% had to discontinue	
			36 months 42.5					
			48 months 44.4					
Complications	None reported		84% overall (14.9% hypertrophy, 12.3% arthrofibrosis, 11% cartilage injury)	None reported	None reported	None reported	3% donor site morbidity; 4 deep infections; 36 haemarthroses; 2 thromboembolic complications	50% (3 wound infections, 1 fever, 2 haematomas, 10 intrarticular adhesions, 26 Periosteal hypertrophies and 7 graft failures)
Failure	23%	23%	39% of those with complication					
Need for further surgery	TKR, and repeat microfracture.	Repeat microfracture, mosaicplasty, & ACI						

7.5.3 Long-Term Results

The findings from medium term observational studies suggest that even in the longer term, there is no clear advantage in terms of clinical effectiveness of using ACI or MACI over other treatments. However, there are several trials underway with large numbers and long-term follow-up (>15 years) comparing ACI or MACI with alternative treatments. One of the largest trials is a Medical Research Council funded multicentre RCT, the ACTIVE trial, led by Professor James Richardson of Keele University. This trial includes 24 hospitals and started in March 2004. Patient randomisation is in a one-to-one ratio to receive ACI or non-ACI treatment. Non-ACI treatments include debridement, abrasion, microfracture, and mosaicplasty and clinical preference determines treatment selection. Preliminary results are expected after 2010 but follow-up is to continue until at least 2017. Health economics is an integral part of the study, which will determine an incremental cost per QALY for each intervention from a societal perspective. Additional information, including the trial protocol, can be found at http://www.active-trial.org.uk (last accessed 9 October 2009). Wasiak and colleagues (Wasiak et al, 2006) list another nine ongoing studies, which unfortunately do not offer public access to their protocol or any trial detail.

It is possible RM solutions are better than non-RM solutions. In that case, the most interesting comparison would not be ACI against 'all common' treatments but *in vitro* versus *in vivo* RM solutions. The latter are cheaper and do not involve two taxing procedures. Although the Keele based study will provide interesting results, it may leave the most interesting questions unanswered.

7.6 Health-related quality of life and Utilities

For economic analysis, I need a utility-based HRQL score. As discussed, the main health economic gains/losses from treatment of cartilage defects lie in the longer term where OA develops. To conduct long-term analysis first I need to identify the utility associated with cartilage defects, OA, TKR, and revisions. Table 7.5 (page 219) shows the utility scores identified for each of the health states, which will be used later in my economic analysis.

7.6.1 Utility of Cartilage Damage

I have been unable to identify a utility score from the literature associated with a having a cartilage defect prior to any treatment. Although, as you will see, when utility gains associated with cartilage repair treatment are reported the baseline values are not reported. The implications of this are discussed further in 7.9.2 (page 229).

7.6.2 Utility of a Repaired Cartilage Defect

Clar and colleagues (Clar et al, 2005) report a short-term (1-2 years) annual utility gain of 0.1 QALY in the first two years after surgery. This value was based on the findings of a report by Jobanputra and colleagues (Jobanputra et al., 2001), which stated (based on expert opinion) that ACI was associated with a HRQL improvement of 0.107. This finding was similar to that from an earlier observational study (Minas, 1998), where 44 ACI patients were assessed over 24 months and a HRQL improvement of 0.11 associated with ACI was reported (elicited indirectly using SF-36 questionnaires, no methodological details given).

Derrett and colleagues conducted a cost and health status two year retrospective analysis of ACI versus mosaicplasty and calculated utility gains using EQ-5D (in principle this should elicit more reliable estimates than those based on expert opinion). A QALY gain of 0.23 following ACI and 0.06 following mosaicplasty was reported. These values were based on a mean preoperative score of 0.41 (elicited using EQ-5D from a third group of patients whom were waiting for ACI). The postoperative EQ-5D score for ACI (0.64, n=41) was higher than for mosaicplasty (0.47, n=11) but this difference was not statistically significant. I note the QALY gain following ACI reported in this study is double that of the QALY gain reported by Clar et al. I would like to remind the reader that the baseline results are from a different group of patients than the group whom received either ACI or mosaicplasty; therefore, I feel these results are extremely suspect. Furthermore, the difference in total QALY gain between ACI and mosaicplasty is rather large, once again casting further doubt on this study. For these reasons, I have decided not to use the results of this study in my CEA.

7.6.3 Utility Associated with Osteoarthritis of the Knee

As previously discussed, longer-term benefits, are found in avoiding OA and TKR. The next two sections aim to identify the utility associated with OA of the knee and a TKR. Here, I report the utility values associated with OA of the knee, identified from four prospective studies (Boutron et al., 2008;McHugh et al., 2008;Salaffi et al, 2005;Yilmaz et al., 2008); a cost benefit analysis (Byrne et al., 2005); and a report by Dong and colleagues (Dong et al, 2006), produced as part of the MATCH collaboration.

All four prospective observational studies assessed HRQL associated with knee OA using SF-36. Overall, as might be expected, the physical components of the measure had lower scores than the emotional, mental, or general health components. I divided the studies into mild and severe OA based on the mean duration of OA symptoms in the cohort of patients for each study. The overall average age of the patients is 64.8, with an average of 63.8 years for mild OA and 68.0 years for severe OA. I converted the SF-36 scores into SF-6D and EQ-5D utility scores using the algorithms described by Ara and Brazier (Ara et al, 2008a;Ara et al, 2008b). The overall average utility is 0.60 (using SF-6D) and 0.47 (using EQ-5D). For mild OA, the average utility is 0.61 (using SF-6D) and 0.51 (using EQ-5D). For severe OA, the average utility is 0.56 (using SF-6D) and 0.37 (using EQ-5D). These scores are summarised in table 7.5 (page 219) and I will use both scores in subsequent analysis.

Byrne and colleagues reported utility values (table 7.5, page 219) associated with mild and severe OA, elicited using VAS (0.73 vs. 0.46), TTO (0.81 vs. 0.66), SG (0.73 vs. (0.61). The authors also reported a WTP per QALY for each measure. Using VAS, the WTP/QALY for mild and severe OA was $2,019 and $1,221, respectively; using TTO, the WTP/QALY was $4,040 and $3,802, respectively; and for SG, the WTP/QALY was $2,844 and $3,020, respectively. TTO consistently elicits a higher preference, whilst VAS elicits the lowest. Finally, the MATCH report gives a utility of 0.72 associated with OA of the knee.

7.6.4 Utility following Total Knee Replacement (TKR)

Here, I report the utility gains associated with a TKR, identified from two systematic reviews (Clar et al, 2005;Ethgen et al, 2004) the report by MATCH (Dong et al, 2006), discussed above.

The Clar review reported that TKR gives a utility gain of 0.1 QALY. This was obtained from an average of the HRQL gains reported from three studies. i) Drewett and colleagues (Drewett et al., 1992), using the Rosser scale, observed a HRQL increase of 0.064; ii) James and colleagues (James et al., 1996) used two different measures (EQ-5D and Rosser scale) on patient's and consultants. EQ-5D gave an average HRQL gain of 0.201 among patients and 0.40 among consultants. Rosser gave a HRQL gain of 0.044 among patients and 0.069 among consultants; iii) Lavernia and colleagues (Lavernia et al., 1997), using the Quality Well Being scale, calculated that TKR results in a HRQL improvement of 0.0702 at 1 year and 0.055 at 4 years. Note the wide spread of values (0.04 to 0.4) in the study by James and colleagues, and the rather implausible gains obtained using EQ-5D, particularly those from consultants, which imply a patient would be willing to sacrifice nearly half their remaining life expectancy in order to undergo a TKR. Interestingly, if I take out the scores elicited using EQ-5D the average HRQL gain is 0.06, which seems more plausible.

The Ethgen review reported HRQL scores following a TKR, measured using SF-36, from eight prospective studies (Bennett et al., 1997;Brazier et al., 1999;Dawson et al., 1998;Heck et al., 1998;Lingard et al., 2001;Sharma et al., 1996;van Essen et al., 1998). Once again the utility scores were calculated using the algorithm described by Ara and Brazier (Ara et al, 2008a;Ara et al, 2008b). Two of the eight studies (Lingard et al, 2001;Sharma et al, 1996) did not report scores for all eight subgroups of the SF-36, necessary to calculate utility, and these studies were discarded. The average preoperative utility is 0.531 (using EQ-5D) and 0.617 (using SF-6D). The average postoperative utility is 0.695 (using EQ-5D) and 0.702 (using (SF-6D). The total QALY gain at 2 years following TKR is 0.09 (using the SF-6D approach) and 0.16 (using the EQ-5D approach). Finally, the MATCH report gives a utility value of 0.78 associated with TKR at 24 months (assuming no problems).

7.6.5 Utility following Secondary Knee Replacement

I have been unable to identify a utility score from the literature that is associated with a secondary TKR. The Ethgen review (Ethgen et al, 2004) reports physical function of hip replacement was significantly higher for those following primary surgery compared to those who had a revision. However, the review does not give any data on secondary knee replacements.

7.6.6 Summary

Table 7.5 shows the average utility scores associated with OA and TKR. I combined the results for severe OA with the pre-op scores of patients who received TKR; an indication for TKR is severe OA so I would expect all preoperative patients to be classified as having severe OA of the knee. I will use these scores in my subsequent CEA. The utility elicited by EQ-5D will be referred to as model 1 and the SF-6D as model 2 and the utility from the MATCH report as model 3. The VAS, TTO and SG results from Byrne and colleagues are shown for comparison however, these will not be used in subsequent analysis as this study only assessed OA and not TKR. The utility scores taken from the MATCH report are higher than those calculated using the algorithm by Ara and Brazier.

Table 7.5: Average utility associated with osteoarthritis and total knee replacement

state		Utility					Utility (Model 3)
		EQ-5D (Model 1)	SF-36 (Model 2)	VAS	TTO	SG	
Source		*Calculated from literature**		*Byrne et al. 2005*			*Dong et al. 2006*
OA	mild	0.51	0.61	0.73	0.81	0.73	0.72
	severe	0.46	0.59	0.46	0.66	0.61	
TKR	3 mth	0.71	0.69				
	6 mth	0.65	0.68				
	12 mth	0.72	0.72				
	24 mth	0.70	0.70				0.78

**The number of studies used to calculate the utility scores were as follows: mild OA – 3; severe OA – 7; Total Knee Replacement (TKR) – 6.*

7.7 Costs of Treatment

The total surgical costs for cartilage defect repair including days as an inpatient and follow-up physiotherapy rehabilitation sessions are given in the HTA monograph (obtained from the Aberdeen Royal Infirmary) (Clar et al, 2005) and summarised below and in table 7.6. These were updated where possible using the NHS national schedule of reference costs (Department of Health, 2006b).

Mosaicplasty has a cost of £3,710 ($6,000, €4,200), an operation time of 120 minutes, a length of stay of 2.5 days and requires 15-20 physiotherapy sessions. Microfracture has a cost of £2,348 ($3,800, €2,700), an operation time of 60 minutes, a length of stay of 2 days and requires 15-20 physiotherapy sessions. Arthroscopic ACI has a cost of £3,184 ($5,200, €3,600), and operation time of 90 minutes, a length of stay of 1.5 days and requires 12 (2 inpatient and 10 outpatient) physiotherapy sessions. Open knee ACI has a cost of £5,446 ($8,900, €6,200), an operation time of 90 minutes, a length of stay of 7.5 days and requires 18 (8 inpatient and 10 outpatient) physiotherapy sessions. In addition to these procedure costs, ACI has an additional cost of £3,200 ($5,200, €3,600) for cell culturing. Microfracture is associated with a cost saving of £1,362 ($2,200, €1,500) over mosaicplasty and microfracture is associated with a cost saving over ACI of £4,036 ($6,600, €4,600) or £6,298 ($10,300, €7,200), depending on the type of ACI used (arthroscopic versus open knee) (Clar et al, 2005).

The burden of TKR is considerable. In England and Wales in 2005/06 there were around 52,000 primary TKRs (HRG code H04) at a cost of £5,843 ($9,500, €6,700) (Department of Health, 2006b). A TKR has an operation time of around 150 minutes (Clar et al, 2005), an average length of stay of 7 days (Department of Health, 2006b) and requires 9 rehabilitation sessions (6 inpatient and 3 outpatients) (Clar et al, 2005). On average patients can expect no more than 15-20 years before their joint replacements fail. For patients in their 70's or 80's this remaining life expectancy is generally sufficient to live out their life pain free. Patients in their 50's or 60's will generally out live their replacement and require further surgery. In England and Wales in 2005/06 there were 4,639 revisional procedures to the knees (HRG code H72) at a unit cost of £7,245 ($11,800, €8,300) (Department of Health, 2006b). A revisional knee procedure has an operation time of 270 minutes (Clar et al, 2005),

an average length of stay of 9 days (Department of Health, 2006b) and requires 17 physiotherapy sessions (12 inpatient and 5 outpatients) (Clar et al, 2005).

Table 7.6: Procedure costs and resource usage associated with cartilage defect repair and knee replacement

procedure	Total cost	operation time (minutes)	length of stay (days)	Rehabilitation (days)	Cell Culture Cost
Arthroscopy (day case)*	£1,458	20	0	0	
Mosaicplasty	£3,710	120	2.5	15-20	
Microfracture	£2,348	60	2	15-20	
ACI arthroscopic	£6,384	90	1.5	2 IP, 10 OP	£3,200
ACI open knee	£8,646	90	7.5	8 IP, 10 OP	£3,200
First Knee Replacement*	£5,843	150	7	6 IP, 3 OP	
Second Knee Replacement*	£7,245	270	9	12 IP, 5 OP	

*Adapted from Clar et al 2005; * 2006 NHS reference costs (Department of Health, 2006b)*

7.8 Cost-Effectiveness

7.8.1 Review of Previous Cost-Effectiveness Analysis

I identified two cost-effectiveness studies of ACI (Clar et al, 2005;Derrett et al., 2005). The first (Clar et al, 2005), used clinical outcome data from four RCTs and observational studies backed up by expert opinion. Short-term (1-2 years) and long-term (10-20 years) modelling was conducted. Note this CEA was conducted before publication of the five-year follow up results of Knutsen's RCT. The lack of long-term follow up clinical outcomes (such as later OA and knee replacement) made it impossible for the researchers to calculate the ICER with any accuracy. Illustrative modelling compared ACI with microfracture, mosaicplasty, and arthroscopic debridement. The researchers needed to formulate a broad range of assumptions concerning effectiveness and costs of each treatment. Sensitivity analysis was undertaken for several parameters, including the cost of ACI, the average time to TKR, the long-term HRQL gains from all interventions (including TKR), and the discount rate. The latter (Derrett et al, 2005), also conducted in 2005, is a two year retrospective comparison of costs and effectiveness of ACI and mosaicplasty. Some participants had previously been involved in the RCT that compared ACI

with mosaicplasty in 2003 (Bentley et al, 2003). This assessment is less ambitious than the Clar review, comparing just two treatments, and there was no long-term modelling. The results give QALY gains based on utilities obtained using EQ-5D.

Short-Term Modelling

Clar and colleagues assume all treatments provide a utility gain of 0.1. The health economic exercise becomes a CMA and, because it entails the lower costs, microfracture dominates all treatments. Sensitivity analysis assumes ACI gives an additional 0.1 QALY over microfracture per year. However, this gain is not sufficient for ACI to be cost-effective relative to microfracture. To be cost-effective at 2 years, the gain from ACI would have to be 0.17 to 0.20 additional QALYs over microfracture; however, over 10 years the gain from ACI would have to be 0.11 to 0.12 additional QALYs over microfracture (given the £20,000 to £30,000 per QALY threshold recommended by NICE).

Derrett and colleagues observe average higher costs and improved clinical outcomes (P>0.05) for ACI relative to mosaicplasty. Given the point estimate for utility differences of 0.17, the authors calculate an ICER for ACI relative to mosaicplasty of £16,349 ($26,700, €18,700). This falls beneath the implicit funding threshold for the UK NHS of £30,000 ($49,000, €34,000). Table 7.7 summarises the costs, utility gains and short term results of the two CE studies reviewed here.

Table 7.7: Short-term cost-effectiveness results for different surgical treatments

study	treatment	Average cost per patient[(a)]	QALY gain over lavage and debridement	ICER of ACI over alternative treatment
Clar et al (HTA, 2005)	ACI (arthroscopic)	£6,384	0.30[(b)]	
	Microfracture	£2,348	0.20	£40,360
	Mosaicplasty	£3,710	0.10	
Derrett el al (2005)	ACI (arthroscopic)	£10,600	0.23[(d)]	
	Mosaicplasty	£7,948	0.06[(d)]	£16,349

Adapted from Clar et al 2005

[a] *All average costs include immediate preoperative care, surgery, and cell culture. Derrett et. al. also includes costs of follow up to two years.*

[b] *Assuming ACI gives an additional 0.1 QALY over microfracture and microfracture gives an additional 0.1 QALY over mosaicplasty (based on expert opinion).*

[c] *Not calculated because mosaicplasty is fully dominated by microfracture.*

[d] *Calculated using EQ-5D.*

Long-Term Modelling

The only long term modelling identified is reported in the HTA study (Clar et al, 2005). Assuming principal long-term benefits are avoidance of OA and TKR, and TKR gives a utility gain of 0.1 QALY, the long-term modelling (20-30 years) shows mosaicplasty performs consistently poorly in terms of cost-effectiveness while ACI falls in second place behind microfracture the most cost-effective treatment.

Assuming that among a cohort of 100 patients, all those offered a TKR accept it, the move from microfracture to ACI would reduce the number of patients requiring a TKR. However, this reduction would not be sufficient to outweigh the higher costs of ACI, making ACI roughly as cost effective as mosaicplasty and somewhat less cost effective than microfracture. The lack of long-term data and the fact that key data on which the model was constructed is subject to considerable uncertainty makes us question the soundness of these results.

In summary, there is no evidence at present to say ACI is cost-effective compared to microfracture and mosaicplasty (Clar et al, 2005;NICE, 2005b). These results seem to be further supported by the latest evidence from Knutsen et al (2007), which compares ACI to microfracture after five years. Given that no significant differences in utility gain or failure of treatment between the procedures are found, and given the relatively high cost of ACI, currently microfracture is the most cost-effective treatment.

ACI has great promise as a treatment for chondral lesions, and could be cost-effective in the future provided the technology fulfils expectations regarding the production of hyaline cartilage in the longer term (Clar et al, 2005). However, based on current evidence, NICE does not recommend ACI or MACI for treatment of articular cartilage defects on the knee, except in the context of ongoing or new clinical studies designed to generate relevant clinical outcome data (NICE, 2005b).

7.8.2 My Cost Effectiveness Analysis

Here I perform an extension on the CEA just reviewed. Microfracture is the current treatment of choice – the comparator for any new treatment. Firstly, I assess the headroom based on short term effectiveness. As a RM technology is already developed and the cost is known, the conventional use of the headroom method – to determine the maximum change in cost is not of much use, instead I use the headroom method, to find the minimum change in effectiveness, rather than cost, for a RM technology to be cost-effective. Secondly, I assess the headroom based on long-term effectiveness. Here I use the headroom method, to calculate the maximum change in cost of a RM technology.

Short-Term Modelling

This modelling takes account of short term changes in clinical outcome between different cartilage defect repair treatments only; it assumes no change in long term clinical outcome. Here I ask:

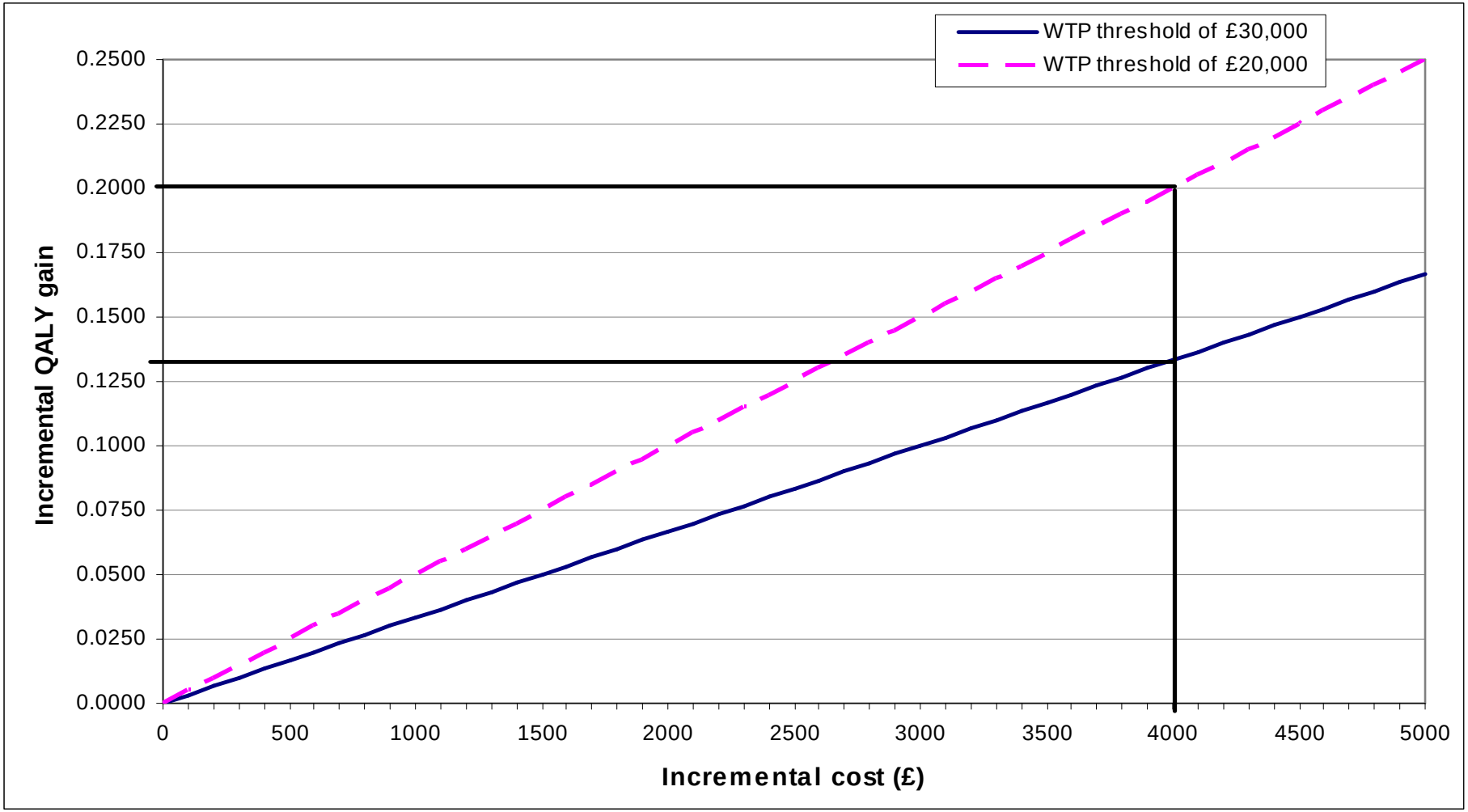
"What is the minimum incremental effectiveness a competitive treatment should have in the short term to be more cost-effective than microfracture?"

If the incremental cost (∆Cost) of the new technology is known, the minimum required incremental benefit (∆Effectiveness) can be calculated. I rearrange equation 1.3 (page 40) and calculate ∆Effectiveness (equation 7.1).

Equation 7.1: ∆Effectiveness = ∆Cost / WTP threshold

I assume the ∆Cost of ACI over microfracture is £4,000 ($6,500, €4,500) (table 7.6, page 221). Using £30,000 ($49,000, €34,000) as the WTP threshold, I populate equation 7.1, and calculate that for ACI to be cost effective it needs to provide a gain of 0.13 QALYs relative to microfracture. If the WTP threshold is £20,000 ($33,000, €23,000) ACI would need to yield 0.2 QALYs more than microfracture to be cost-effective. Figure 7.3 illustrates the necessary total QALY gain required for different incremental costs.

Figure 7.3: Minimum incremental benefit for a new treatment based on different incremental costs of that same treatment



Assuming you know how much extra your new treatment/technology will cost, the minimum incremental QALY gain of required by the new treatment/technology compared to the current gold standard can be calculated. This figure illustrates the relationship between incremental QALY gain and incremental cost (up to an incremental cost of £5000).

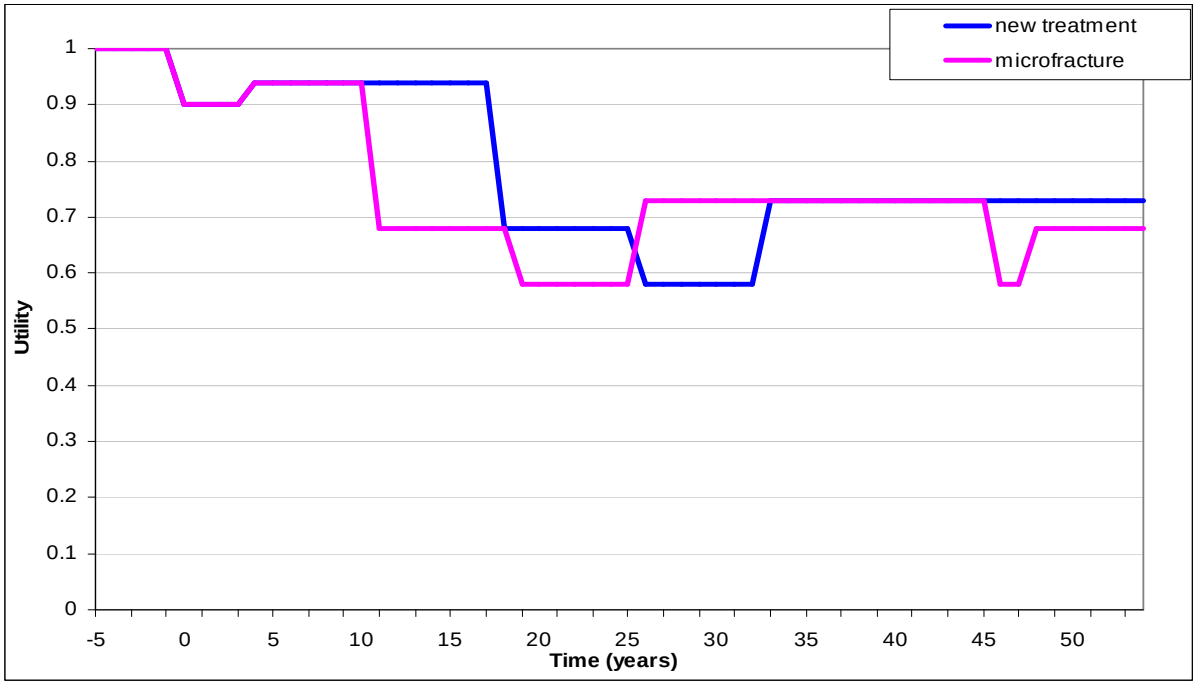
Long-Term Modelling

As previously discussed, the ideal RM solution would prevent or at least delay the onset of OA and ultimately abolish the need for a TKR. Here I endeavour to take account of long term changes in clinical outcome i.e. changes in the onset time of OA and need for a TKR, using the headroom method. All studies to date only measure effectiveness of cartilage repair treatment in the short term and the potential gains i.e. the effectiveness group, for a new treatment appears to be limited. Therefore, if expensive treatments are to be cost-effective their gain needs to be in the long term, in maintaining a pain free knee for the patient and delaying the onset of OA. Here I ask:

"What is the maximum incremental cost a competitive treatment could be to be cost-effective in the long term?"

Figure 7.4 illustrates the estimated disease progression over the long-term for different treatments. I illustrate the disease progression following microfracture (the current gold standard) and a new RM treatment as effective as microfracture in the short-term but with longer-term effects.

Figure 7.4: Natural progression of disease for treatments with differing effectiveness



Estimating the Change in Effectiveness (ΔQALY)

Firstly, I use the utility values identified in section 7.7 (summarised in table 7.5, page 219) to calculate the disutility. I propose three models to account for varying utility scores. Model 1 illustrates the most optimistic scenario and model 3 illustrates the most pessimistic scenario. Secondly, I estimate the duration of the clinical effects of OA and TKR from the same studies, identified in section 7.7, which reported utility. Using this information, I estimate the maximum incremental QALY gain for the new treatment (table 7.8).

Table 7.8: The maximum incremental QALY gains for a new RM treatment

MODEL	State	Utility	Disutility (1-Utility)	Duration (yrs)	Total QALY gain
MODEL 1	**mild OA**	0.51	0.49	7.5	3.7
	Severe OA	0.46	0.54	7.5	4.0
	TKR	0.70	0.30	15	4.6
	Total			**30**	**12.3**
MODEL 2	**mild OA**	0.61	0.39	7.5	2.9
	Severe OA	0.59	0.41	7.5	3.1
	TKR	0.70	0.30	15	4.5
	Total			**30**	**10.5**
MODEL 3	**mild OA**	0.70	0.30	15	4.5
	Severe OA				
	TKR	0.78	0.22	15	3.3
	Total			**30**	**7.8**

These tables show the total QALY gains possible over the duration of disease (assumed to be 30 years) when compared to no treatment. Model 1 refers to utility values elicited from EQ-5D questionnaires. Model 2 refers to utility values elicited from SF-36 scores. Model 3 is utility data obtained from the literature (Dong et al, 2006).

Calculating Headroom

I calculate the headroom using equation 3.1 (page 76). Using the information given in table 7.8, I calculated the total number of QALYs saved per year; for model 1, this was 0.41, for model 2, this was 0.35, and for model 3, this was 0.26. I created different scenarios for the effectiveness of the new treatment. At one extreme, I imagine the new treatment is so effective OA and TKR are avoided for the duration of remaining life of the patient (30 years), however, if possible the question would be a no

brainer but included for completeness. At the other extreme, I imagine the new treatment delays onset of OA by just 1 month. The results are shown in table 7.9. QALY gain is discounted by 1.5% per year and headroom (maximum change in cost) is discounted by 3.5% per year. In general, the results using model 3 (the least optimistic model), are £200 - £300 less for each given scenario than those using model 1 or 2.

Table 7.9: The headroom for new treatment when compared to no treatment

Model	Scenario	QALYs gained per 30 years	Headroom	
			£30,000 threshold	£20,000 threshold
Model 1	avoid OA and TKR	11.85	£355,646	£237,097
	delay onset of OA for 10 years	3.95	£118,549	£79,032
	delay onset of OA for 5years	1.98	£59,274	£39,516
	delay onset of OA for 4 years	1.60	£47,869	£31,913
	delay onset of OA for 3 years	1.19	£35,565	£23,710
	delay onset of OA for 2 years	0.79	£23,710	£15,806
	delay onset of OA for 1 years	0.40	£11,855	£7,903
	delay onset of OA for 6 months	0.20	£5,927	£3,952
	delay onset of OA for 3 months	0.09	£2,841	£1,894
Model 2	avoid OA and TKR	10.02	£314,041	£209,360
	delay onset of OA for 10 years	3.34	£104,680	£69,787
	delay onset of OA for 5years	1.67	£52,340	£34,893
	delay onset of OA for 4 years	1.35	£41,872	£27,915
	delay onset of OA for 3 years	1.00	£31,404	£20,936
	delay onset of OA for 2 years	0.67	£20,936	£13,957
	delay onset of OA for 1 years	0.33	£10,468	£6,979
	delay onset of OA for 6 months	0.17	£5,234	£3,489
	delay onset of OA for 3 months	0.08	£2,512	£1,675
Model 3	avoid OA and TKR	7.35	£220,499	£146,999
	delay onset of OA for 10 years	2.45	£73,500	£49,000
	delay onset of OA for 5years	1.23	£36,750	£24,500
	delay onset of OA for 4 years	1.00	£29,850	£19,900
	delay onset of OA for 3 years	0.74	£22,050	£14,700
	delay onset of OA for 2 years	0.49	£14,700	£9,800
	delay onset of OA for 1 years	0.25	£7,350	£4,900
	delay onset of OA for 6 months	0.12	£3,675	£2,450
	delay onset of OA for 3 months	0.06	£1,759	£1,173

Model 1 refers to utility values elicited from EQ-5D questionnaires. Model 2 refers to utility values elicited from SF-36 scores. Model 3 is utility data obtained from the literature (Dong et al, 2006).

If the treatment is successful in delaying the onset of OA by 5 years then the headroom for the cost of the new treatment is £36,750 ($60,000, €42,000) (based on model 3 in table 7.9). Table 7.9 can be interpreted another way and if the new treatment was expected to have an incremental cost of £1,000 then commensurate benefit is an additional 0.04 QALYs over 30 years (based on equation 7.1, page 224), equivalent to a delay in onset of OA by 2 months (based on model 3).

7.9 Discussion

7.9.1 Summary of Findings

Studies conducted to evaluate the efficacy of microfracture, mosaicplasty and ACI have been of poor quality and the results conflicting. Currently no evidence base consensus has emerged regarding the best treatment option, for this reason NICE only recommends ACI and MACI for use in clinical trials. All existing CEA has found microfracture to be the current most cost-effective cartilage repair treatment. Using the headroom method, I have found that in the short term, based on an incremental cost similar to that currently held by ACI, a new RM treatment would need to provide an incremental gain of 0.13 QALYs. However, there is sufficient headroom for a new RM treatment, which is associated with long-term benefits i.e. delay in the onset of OA.

7.9.2 Limitations

The quality of the data is very poor with very few RCTs and no systematic reviews comparing cartilage repair treatments to each other or to no treatment. However, it would be difficult to conduct a systematic review until there is more consistency in measuring outcomes used to measure knee function and utility, following cartilage repair. Current studies use too many different specific measures, which cannot be compared in a meta-analysis. This is illustrated in tables 7.10 and 7.11. Essentially, until this issue is addressed, the evidence base in this area will be limited.

Only one of the RCTs discussed (Knutsen et al, 2007) used a clinical outcome measure, which could be used to elicit utility. However, the author only gave results for the physical component score and at

present, all eight sub-scores of the SF-36 system are required to calculate utility. I contacted the author to request the data for the unpublished sub-groups but unfortunately this data was not available and therefore, I could not elicit a utility associated with having a cartilage defect and following cartilage repair treatments.

The literature identified no utility values associated with having a cartilage defect prior to treatment. Either the studies have not reported this information, presumably because it was never collected, or the HRQL has been measured using a clinical outcome measure, which cannot be used to elicit a utility.

The utility value associated with OA and TKR were calculated from SF-36 clinical outcome measures. However, this measure was used in a limited number of observational studies and no clinical trials. In addition there were variations between the utility scores calculated using the two methodologies by Ara and Brazier (Ara et al, 2008a;Ara et al, 2008b). These variations are due to differences in the importance of certain attributes for the two systems used; for example, SF-6D takes account of vitality whereas EQ-5D does not. Finally, I feel that the utility associated with OA and TKR are very low, and therefore may have overestimated the disutility of the clinical effects and consequently overestimated the headroom - the maximum incremental cost.

Table 7.10: Illustrates the number of clinical outcome measures used in short term RCTs

Study	RCT characteristics			Clinical outcome scoring system								
	Type	Mean follow-up (months)	N	Cincinnati rating scale	Modified Lysholm Score	Lysholm Score	Meyers Score	Lysholm-Gillquist Score	Tegner-Lysholm Score	Pain (VAS)	SF-36 (PC)	KIOO
Bentley et al. 2003	ACI vs. Mosaicplasty	19	100	✓								
Horas et al. 2003	ACI vs. Mosaicplasty	24	40		✓		✓					
Dozin et al. 2005	ACI vs. Mosaicplasty	NR	47			✓						
Basad et al. 2004	MACI vs. microfracture	12	46				✓	✓	✓			
Knutsen et al. 2004	ACI vs. microfracture	24	80			✓				✓	✓	
Saris et al 2008	CCI vs. Microfracture	18	118									✓
Bartlett et al. 2005	ACI vs. MACI	12	91	✓								
Gooding et al. 2006	ACI - Periosteum vs. ACI - Collagen	24	46	✓								

Table 7.11: Illustrate the number of clinical outcome measures used in medium term RCTs

Study	RCT characteristics			Clinical outcome scoring system								
	Type	Mean follow-up (years)	N	Modified Cincinnati rating scale	Lysholm Score	Tegner Score	Pain (VAS)	Global VAS	SF-36 (PC)	SF-36 (overall)	Oxford knee score	Hannover score
Knutsen et al. 2007	ACI vs. microfracture	5	80		✓		✓		✓			
Zaslav et al. 2009	ACI	4	154	✓				✓		✓		
Peterson et al. 2003	ACI	11	101									
Asik et al. 2008	Microfracture	5.5	90		✓	✓					✓	
Hangody et al. 2003	Mosaicplasty	6	578									✓

7.9.3 Future Work

To assess accurately the cost-effectiveness of ACI relative to other treatments, it is essential to have medium to long-term outcome data on durability of different types of cartilage repair and the utility associated to them (Clar et al, 2005;NICE, 2005b). Without these data evidence based modelling is impossible. It is also highly desirable that future studies on ACI provide comparable outcome scales, to facilitate the conduction of a meta-analysis. Research comparing accuracy and robustness of different scales relative to measurement of knee functionality is necessary. There is also a need for basic research into the genes and molecules that influence stem cells to become chondrocytes and to produce high-quality cartilage (Clar et al, 2005).

7.10 Conclusion

ACI is an RM technology already on the market, but which has been unable to get reimbursement (in the UK) due to its high cost for the incremental benefit gained. However, this is a rapidly changing field and there is a great deal of interest in developing cartilage repair technologies. As I have shown, if these technologies can sustain benefits for the long term, the technology has the potential to be a blockbuster. However, the difficulty is that trials with very long follow-up are required to prove effectiveness in the long-term. Currently no trial has produced such results although there are a number of ongoing trials, the results of which are eagerly awaited.

Here the application of the headroom method has shown how it can be used to provide evidence for a business case. The supply side analysis has been used to calculate the incremental benefit required if the technology is to cost the same as ACI. On the other hand, if manufacturers believe their technology could generate effectiveness equal to that of ACI but for a fraction of the cost then they can demonstrate to investors they have increased probability of obtaining reimbursement.

CHAPTER 8 AN ALTERNATIVE APPROACH TO THE CHALLENGE OF ELICITING UTILITIES

8.1 Introduction

One of the main advantages of the headroom method is that it is a relatively simple approach of obtaining the 'headroom', which can be applied by SME's. When utilities are available in the literature they can be easily incorporated in the method. However, when they are not available separate studies are needed as described in the examples in chapters 4 and 5. However, the demand of formal elicitation of public preferences undermines the idea behind the Headroom Method, which is to provide a quick and simple thinking tool for the busy industrialist. A more pragmatic approach is required for this method to be routinely applied in practice. SMEs need to be able to make common-sense estimates of a utility value for a given health state based on information already available. In the following section, I describe a new approach I have developed, which aims to address the issues above.

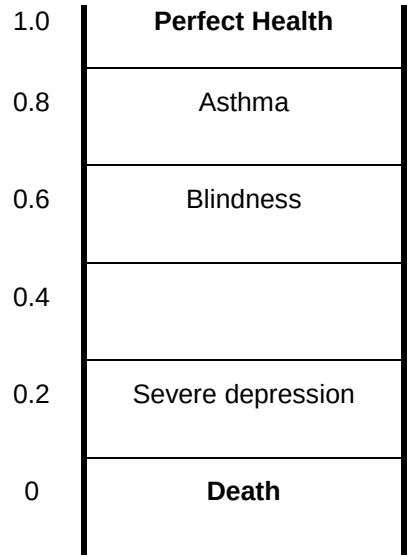
The forgoing discussion highlights an issue for the headroom method. On the one hand, eliciting utilities is a complicated process that is prone to error and beset with conceptual difficulties that have not been solved, many of which are underpinned by methodological challenges which may prove enduring. Furthermore, it is not the case that these problems can be resolved by a measurement of benefit, such as that obtained from WTP exercises. While such an approach may have many advantages over other methods, many of the same methodological issues remain. The point I am trying to make is that utilities are ephemeral in a way parameter estimates are not. In the case of parameter estimates there is broad agreement on what it is that is being measured, and how this should be done. In the case of utilities, however, there is much less agreement on the optimal methodology.

Faced with these issues, what is the manufacturer to do? On the one hand, expensive exercises to elicit utilities both violate the sprit of the headroom method and are likely to yield results of questionable value. On the other hand, utility (or benefit) values are necessary for economic modelling. The conundrum can therefore be simply stated as follows: utilities (or some other measure of benefit) are a requirement for headroom calculations. Yet primary studies to elicit these utilities are unlikely to be cost effective within this method. My approach to this problem is to provide manufacturers with a simple toolkit to obtaining utilities themselves. The method is based on using a 'ladder' of utility scores for well-known conditions to assist the user to assign a utility score to a condition for which no such score can be gleaned from the literature.

8.2 Methodology

My approach to this problem is to use 'example' utility values from the literature. My method relies on the decision makers' judgements, prompted by a simple ladder of utilities, such as that illustrated in figure 8.1, which provides the range of utility estimates over a set of well-known disease states that cover a wide range of disability and distress. The idea is to provide a frame of reference against which decision makers can form a judgement concerning the disutility of/ utility of, states that have not yet been studied from the point of view of human preferences.

Figure 8.1. Ladder of utilities scores



The second problem was to find a source of these utilities. The obvious place to start was the TUFTs database of utilities (Tufts Medical Centre, 2009). The TUFTS database consists, of a large matrix (7874 utility values, across 1654 studies and 68 disease classifications) and it can be quite difficult to select a limited number of values from a somewhat bewildering array of different values obtained from similar but not necessarily identical health states, elicited by one of eight different utility measurements. I tried to address this issue by grouping the utilities by method of elicitation, which to an extent was successful. However, this did not help overcome the issue that the descriptions of the health states were vague and often overlapping, such that it was difficult to summarise utilities across different diseases. I tried to overcome this problem by referring back to the relevant publication in an attempt to define the health state more precisely, but this was not as straightforward as I had originally hoped it would be. It was time consuming and raised issues around the quality of the utility values reported in the literature and subsequently reported in the database. Appendix 12 summarises the information gathered from the TUFTS database.

An alternative source of utilities was required. I considered other sources of utilities where I could borrow strengths from previous work and identified NICE appraisals as one such source. The advantage of NICE appraisals was that i) the health states are reasonably tightly defined, and ii) NICE committees review the quality of the appraisals. Therefore, I decided it would be reasonable to assume that these utilities would offer the best estimates currently available in the literature.

My first task was to identify the NICE appraisals and assign a disease topic to each of the appraisals. I identified 191 appraisals up to June 2010. Many of these were updates of an earlier appraisal so I removed any that had been superseded by a more recent review. I ended up with 138 appraisals, which covered 78 disease topics (see appendix 13). My second task was to identify the utility values. I did not intend to look through all 138 NICE appraisals. Rather, I surveyed the list to pick out conditions that on the face of it would cover a wide range of diseases/ sub-diseases, varying from psoriasis to motor neurone disease for example. This was

still a time consuming process as not all the NICE appraisals state the baseline utility score, (they frequently state only the QALY gain between the comparative treatments/ interventions). In these cases, I sourced the corresponding NICE Evidence Review Group (ERG) report and/or the NICE Technology Assessment Report (TAR) to gather the required information. Both the ERG report and TAR can be found via the advanced search function under published HTA report (http://www.hta.ac.uk/project/htapubs.asp), from here, there is a link to the corresponding NICE report and access to the ERG report and TAR.

8.3 Results

From the 138 appraisals identified I selected a range of diseases, which I thought would cover the spectrum of the utility scale (from 0 to 1) to be used to create a hierarchy or 'ladder' of utilities. This gave me 47 appraisals to scrutinise.

For my first task, I collated the utility values from NICE TAR, ERG, or HTA reports. Where more than one utility value for a given health state was reported I selected the utility value based on the following hierarchy: TAR, ERG, and HTA. If this did not result in one utility for one health state, I then selected the most recent NICE appraisal, as was the case for psoriasis. In 23 of the appraisals, I could not identify a utility value. Thus, 24 appraisals were reviewed, resulting in 61 utility values. The results are shown in table 8.1 below.

Next, I constructed a utility hierarchy or 'ladder' using the selected utilities (shown in yellow in table 8.1) to provide a frame of reference against which decision makers can form a judgement concerning the disutility/ utility of health states that have not yet been studied from the point of view of human preferences. Not all the information in table 8.1 was illustrated graphically. There were two reasons for this i) some utilities are too unrealistic. For example, a utility of 0.86 was reported for inguinal hernia repair 3 months postoperative, implying a person would risk a 14% risk of death or give up 14% of there remaining life to escape from this state, and ii) some health states are too diffuse to be meaningful. For example, non-fatal stroke/ myocardial infarction. The

reader must be able to envisage the impact of the health state being described in order to make a sensible judgement about where the health state to be defined may lie.

Finally, I chose to convey the selected utilities from table 8.1 across three utility **'**ladders' (illustrated in figures 8.2 through to figure 8.4). There was an unmanageably large number of utilities reported in table 8.1, which could not all be presented clearly in one graph. Using figures 8.2 through to 8.4, the industrialist can estimate the utility value required to conduct the Headroom Method by making a judgement based on the utility values stated for given disease states.

Table 8.1. Summary of Utility values gathered from NICE Technology Appraisals across a range of disease topics and health states

NICE reference	Disease Topic	Health state	Definition	Utility	NICE TA Utility	ERG Utility	HTA Utility
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 8.5-9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow	-0.19		-0.19	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 8.5-9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow	-0.15		-0.15	
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 7.5-8	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms	-0.05		-0.05	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 7.5-8	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms	-0.01		-0.01	
TA59	Depression & Anxiety	Severe depression	Severely depressed, receiving inpatient treatment	0.09			0.09
TA111	Alzheimer's Disease	Alzheimer's Disease patients - Full time care		0.30	0.3		
TA146	Psoriasis	Severe psoriasis	DLQI > 10 and PASI > 10	0.31		0.31	
TA59	Depression & Anxiety	Moderate depression	Relapsed from maintenance therapy	0.32			0.32
TA97	Depression & Anxiety	Severe depression		0.38	0.38		
TA186	Rheumatoid Arthritis	Severe active rheumatoid arthritis for more than 6 months	disease has responded inadequately to conventional disease-modifying anti-rheumatic drugs	0.38	0.38		
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 6.5-7	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day	0.39		0.39	
TA134	Psoriasis	severe psoriasis	DLQI > 10 and PASI > 20	0.41		0.41	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 6.5-7	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day	0.44		0.44	
TA20	Motor Neurone Disease	Terminal Motor Neurone Disease	Non-functional use of at least two regions and/or moderate or non-functional use of the third region	0.45			0.45

NICE reference	Disease Topic	Health state	Definition	Utility	NICE TA Utility	ERG Utility	HTA Utility
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 5.5-6	intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting	0.45		0.45	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 5.5-6	intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting	0.49		0.49	
TA152	Coronary Artery Disease	Severe angina		0.50			0.502
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 4.5-5	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)	0.51		0.51	
TA155	Macular Degeneration	Blindness	visual acuity < 20/400	0.52	0.518		
TA68	Macular Degeneration	Blindness	visual acuity 20/200 - 20/400	0.52			0.52
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 4.5-5	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)	0.56		0.56	
TA68	Macular Degeneration	Severe visual acuity	visual acuity 20/60 - 20/100	0.57			0.57
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 2.5-3	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory	0.57		0.57	
TA97	Depression & Anxiety	Moderate to severe depression		0.58	0.58		
TA97	Depression & Anxiety	Depression in symptomatic phase		0.59	0.59		
TA59	Depression & Anxiety	Mild depression		0.59			0.59
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 2.5-3	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory	0.61		0.61	
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 3.5-4	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters	0.61		0.61	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 3.5-4		0.65		0.65	

NICE reference	Disease Topic	Health state	Definition	Utility	NICE TA Utility	ERG Utility	HTA Utility
TA152	Coronary Artery Disease	Coronary Artery Disease Post-revascularisation		0.66			0.66
TA48	Renal Failure	End-stage renal failure patients on hospital haemodialysis	Usually specialist units. A renal physician and a team of specialised nursing staff are on call at all times	0.66			0.66
TA73	Angina and Myocardial Infarction	Angina patients following diagnosis for coronary artery disease with a high risk myocardial infarction	3VD and poor left ventricular function or left main vessel disease	0.67			0.67
TA20	Motor Neurone Disease	Moderate Motor Neurone Disease	Mild deficit in all three regions Moderate to severe deficit in one region while the other two regions are normal or mildly affected	0.67			0.67
TA111	Alzheimer's Disease	Alzheimer's Disease patients - pre-full-time care		0.69	0.69		
TA184	Lung Cancer	Relapsed lung cancer		0.70	0.7		
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 1.5-2	Mild disability in one FS	0.70		0.7	
TA79	Epilepsy	Child with epilepsy and learning disabilities		0.71			0.707
TA20	Motor Neurone Disease	Severe Motor Neurone Disease	Needs assistance in two or three regions Speech is dysarythric and/or patient needs assistance to walk and/or needs assistance with upper extremity functions and activities of daily living	0.71			0.71
TA157	Venous Thromboembolism	Deep Vein Thrombosis acute phase		0.73		0.73	
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 1.5-2	Mild disability in one FS	0.74		0.74	
TA98	ADHD	Children with ADHD who do not respond to drug treatment	Outcome was the same regardless of treatment (drug) type	0.77	0.773		
TA97	Depression & Anxiety	Mild to moderate depression		0.78	0.78		
TA20	Motor Neurone Disease	Mild Motor Neurone Disease	Recently diagnosed. Mild deficit only in one of the three regions (speech, arm, leg). Functionally independent in speech, upper extremity, activities of daily living and ambulation	0.79			0.79

NICE reference	Disease Topic	Health state	Definition	Utility	NICE TA Utility	ERG Utility	HTA Utility
TA59	Depression & Anxiety	Depression in remission	Responded to treatment, receiving maintenance therapy	0.79			0.79
TA97	Depression & Anxiety	OCD patients not responding to computerised cognitive behaviour therapy	they have a Y-BOCS equivalent to the mean treatment score assumed to be 25	0.80	0.8		
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 0.5-1	No disability, minimal signs in one functional system	0.80		0.8	
TA73	Angina and Myocardial Infarction	Angina patients following diagnosis for coronary artery disease with a moderate risk of myocardial infarction	single or two vessel disease	0.81			0.81
TA68	Macular Degeneration	Moderate Visual Impairment	visual acuity20/30 - 20/50	0.81			0.81
TA48	Renal Failure	End-stage renal failure patients on satellite haemodialysis	Centres tend to be in smaller district general hospitals and have a reduced level of medical cover compared with specialist units.	0.81			0.81
TA98	ADHD	Children with ADHD who respond to drug treatment		0.84	0.837		
TA76	Epilepsy	Adult epilepsy poorly controlled		0.84			0.84
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 0.5-1	No disability, minimal signs in one functional system	0.84		0.84	
TA79	Epilepsy	Child with epilepsy		0.85			0.846
TA131	Asthma	Asthma patients - poorly controlled		0.85	0.85		
TA138	Asthma	Asthma patients - poorly controlled		0.85			0.85
TA83	Hernia	Inguinal hernia repair 3 months postoperative period		0.86			0.855
TA73	Angina and Myocardial Infarction	Angina patients following diagnosis for coronary artery disease with a low risk of myocardial infarction	No significant heart disease present	0.87			0.87
TA127	Multiple Sclerosis	Relapsing remitting multiple sclerosis EDSS 0	Normal neurological examination	0.87		0.87	
TA68	Macular Degeneration	Normal Vision	visual acuity 20/20 - 20/25	0.89			0.89

NICE reference	Disease Topic	Health state	Definition	Utility	NICE TA Utility	ERG Utility	HTA Utility
TA155	Macular Degeneration	Normal vision	visual acuity > 20/40	0.90	0.9		
TA127	Multiple Sclerosis	Secondary progressive multiple sclerosis EDSS 0	Normal neurological examination	0.91		0.91	
TA97	Depression & Anxiety	OCD patients responding to computerised cognitive behaviour therapy	they have a Y-BOCS equivalent to a post treatment score of 6	0.92	0.92		
TA48	Renal Failure	End-stage renal failure patients on home haemodialysis	the same equipment and consumables are used in the home as are used for hospital haemodialysis	0.92			0.92
TA76	Epilepsy	Adult with epilepsy – well controlled		0.94			0.94
TA182	Acute Coronary Syndrome	Non fatal stroke / Myocardial Infarction		0.95	0.9476		
TA182	Acute Coronary Syndrome	Acute coronary syndrome		0.96	0.9591		
TA131	Asthma	Asthma patents 'symptom free'		0.97	0.97		
TA138	Asthma	Asthma patents 'symptom free'		0.97			0.97
TA97	Depression & Anxiety	Depression free period		1.00	1		

Key: DLQI - Dermatology Life Quality Index, EDSS – Expanded Disability Status Scale, PASI – Psoriasis Area Severity Index , RRMS – Relapsing remitting Multiple Sclerosis, SPMS – Secondary progressive multiple sclerosis, Y-BOCS – Yale-Brown Obsessive Compulsive Scale

Figure 8.2. Hierarchy of utility values: range of conditions spread between 0 and 1.0

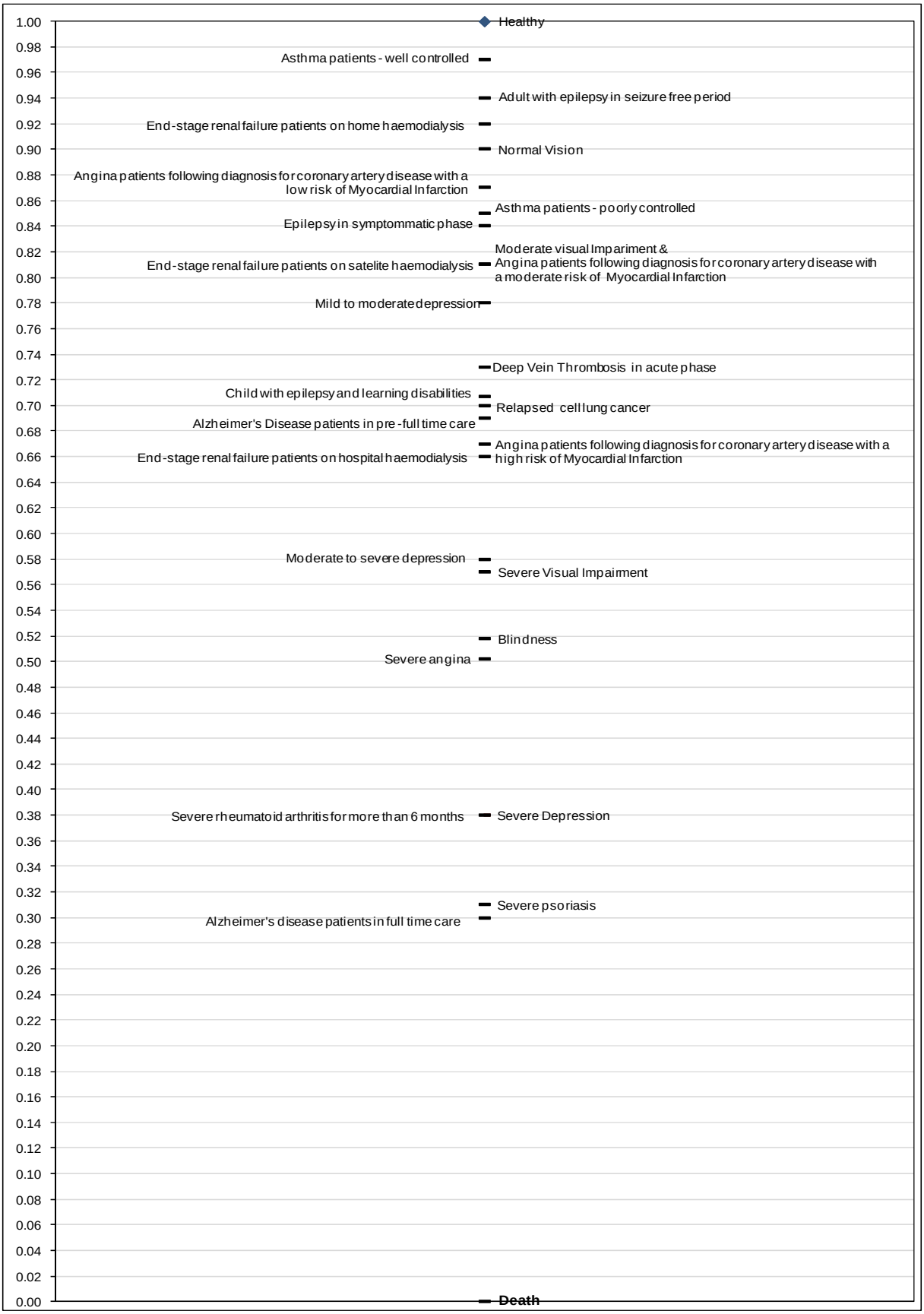


Figure 8.3. Hierarchy of utilities: focus on utilities between 0.5 and 1.0

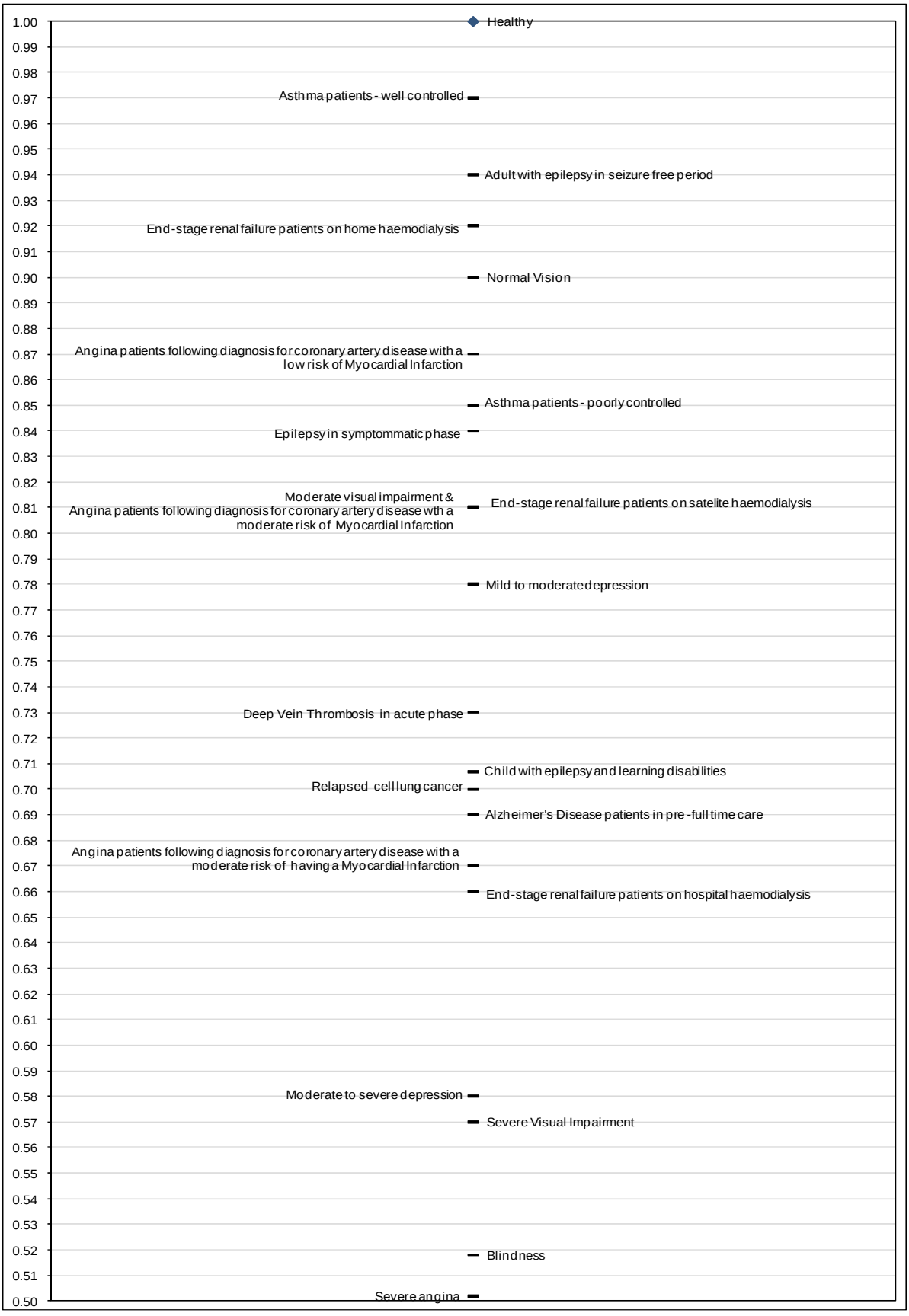
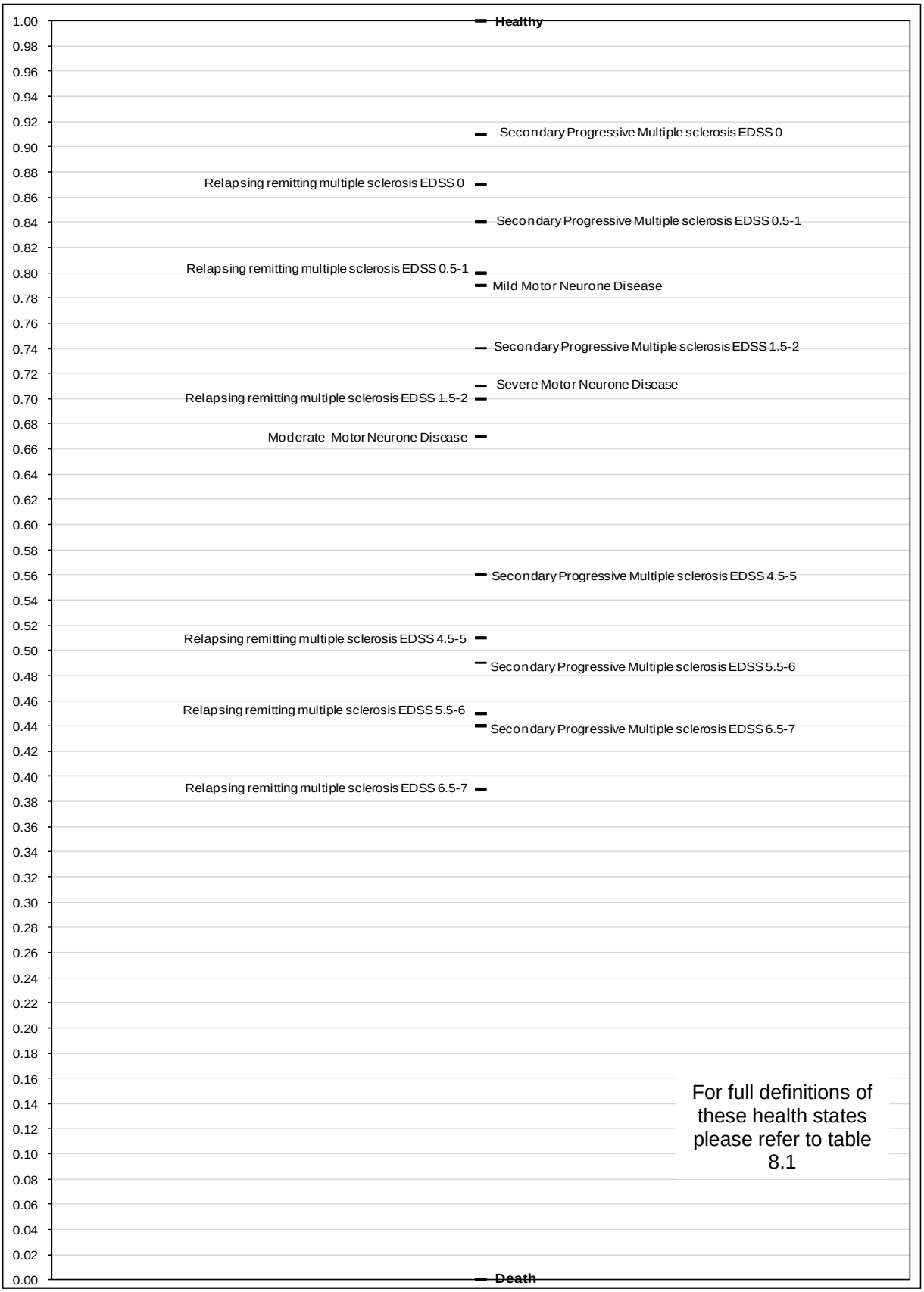


Figure 8.4. Hierarchy of utilities: utilities for neurological disorders



8.4 Discussion

The work in this chapter is designed to overcome one of the pitfalls of the headroom method, as applied in chapters 4-7. A measure of utility is a requirement for headroom calculations. If this utility value cannot be sourced from the literature, several complex methods of eliciting the required utilities exist. This formal approach to the elicitation of utilities goes against the premise of the headroom method, which is to provide a simple approach for use by manufacturer's (or those with little prior health economic knowledge and experience), to guide them through the challenge of conducting early economic evaluation.

My approach to this problem was to provide manufacturers with a practical approach that would assist with the estimation of utilities for the relevant health state. For this, I needed to identify 'example' utility values from the literature, which could form a hierarchy of utilities upon which judgments about other, currently unidentified, utility values could be made.

The main challenge I encountered here was identifying a suitable source of utilities. I first sought to source the utilities from the TUFTs database but this proved unsuccessful for the purposes of this work. The description of the health states were too vague and often overlapping, the range of values for a given health state were vast, and the quality of the utility values reported was unknown without further exploration. The TUFTs database provides useful information, such as the types of measure used but due to the difficultly in making comparisons across health states and determining what the 'true' utility values were I could no longer continue with this option (see appendix 12). For this reason, I sought an alternative source and identified NICE appraisals as one such source. I felt it was relevant and appropriate to use these values as part of the Headroom Method, particularly as the headroom method has been demonstrated in the context of the NHS in this thesis. The advantage of NICE appraisals was that i) the health states are reasonably tightly defined, and ii) NICE committees review the quality of the appraisals.

The second problem I encountered concerned the production of a visual scale that would be functional from the point of view of the manufacturer. The scale needed enough health states to be useful but not

so many that it was impossible to read. The presentation of the utility ladder has been an evolutionary process that has resulted in the production of three utility ladders to be used either alone or in conjunction with each other to aid utility estimation. In the end, I believe I have selected a suitable array of health states, which reflect a range of morbidities. The only criticism perhaps is that there are no health states corresponding to values between 0 – 0.3 on the utility scale. Although, this does reflect the fewer heath states that report such low utility-based QoL scores as well as the well known 'ceiling effect' of the EQ-5D measure (utility estimation instrument recommended by NICE) (Bharmal et al., 2006).

8.5 Conclusion

Utilities are a requirement for headroom calculations. Yet, if utilities are not available in the literature, several complex methods of eliciting the utilities exist. Primary studies to elicit these utilities undermine the premise of the Headroom Method and are unlikely to be a cost effective use of resources within this method. I set out to devise a quick and easy solution to this problem and believe I have achieved this. The solution is based on the manufacturer being able to make common-sense estimates of a utility value for a given health state based on information already available. The existing information is provided in the form of a utility ladder (or utility hierarchy) and is designed to provide a frame of reference against which a manufacturer can make a judgement concerning the utility of a health state not yet studied from the point of view of human preferences. This pragmatic solution is consistent with the "back of the envelope" nature of the headroom method.

CHAPTER 9 DISCUSSION

9.1 Overview

RM is an emerging multidisplinary field of medicine which focuses on the replacement or regeneration of human cells, tissues or organs, to restore or establish normal function (Mason et al, 2008). Despite a rapid proliferation of start up companies in the 1990's as well as many scientific advances, RM has had few products make the transition from laboratory bench to large-scale production and ultimately patient bedside. The failed attempts have been due largely to insufficient marginal effectiveness delivered for marginal costs incurred. The aim of this work was to demonstrate to the RM industry how using health economics, the tools used to assess the most efficient (i.e. best value for money) use of available resources in the allocation of health and healthcare, could help the industry assess the economic potential of their products early in development.

Economic evaluation is used to assess if increased costs of a new technology are justified by a sufficient increase in effectiveness. This CEA is usually performed after a product has been developed, i.e. from the demand side, and is used to provide compelling evidence to healthcare purchasers for its adoption within the healthcare systems. As a result, CEA is now considered the fourth hurdle to market. If, at the final product development stage, prior to market launch, a product is deemed not cost-effective and not appropriate for reimbursement the risk of commercial failure is high. Therefore, to effectively aid the RM industry CEA needs to be conducted before the product is developed (i.e. from the supply side). Over the last decade, interest in early economic evaluation has grown in all sectors of the healthcare industry. As explained in detail in chapter 2, the benefits of early economic evaluation extend beyond the assessment of future reimbursement and include, at the earliest stages helping to rationalise product development decisions (DiMasi et al, 2001) and further downstream to inform price determination (Brown et al, 2007).

As previously discussed, to effectively aid the RM industry, to reduce the risk of investment and secure future commercial success, economic evaluation needs to be conducted earlier in the product development cycle. However, a judgement of cost-effectiveness must start with effectiveness. This is all very well for conventional CEA but what if effectiveness is unknown – what if the product is yet to be developed? Chapter 2 details various methodologies that have been suggested for conducting economic evaluation earlier in product development. However, a number of limitations have been reported. Firstly, manufacturers are unfamiliar with some of the suggested methodologies and decision makers are reluctant to base decisions on them (Hartz et al, 2008). Secondly, manufacturers may not have the resources to conduct such complex modelling, particularly the case in the small companies that make up the RM industry. Based on these findings I propose a simple approach, termed the headroom method, which can be used to help healthcare industries avoid investing in a technology that is unlikely to be cost-effective. This methodology provides an alternative, at least in the first instance, to complex health economic modelling.

The headroom method is useful as a barrier to misguidedly investing in those technologies that are unlikley to be cost-effective and reimbursed by the healthcare providers. This approach provides a framework to support investment decisions, which illuminates a situation that may otherwise be hard to fathom. I have focused on two key stages of this framework; defining the clinical problem – I have done this where others previously had not - and the headroom analysis itself. Firstly, after defining the clinical problem an effectiveness gap can be established – the room for improvement between the current treatment and the new treatment, this is an essential but not always a straightforward aspect. Secondly, the headroom can be calculated – the maximum additional cost, compared to the current best treatment, that a technology can be brought to market and still be considered cost-effective. If there is, little or no chance the technology could be marketed at a price that would keep the maximum incremental cost below the threshold (i.e. maximum change in cost) then the technology should not attract further investment.

In chapters 4 through to 7, I demonstrated the headroom method with real examples from the RM industry. The technologies discussed had all passed strategic consideration stage and are under

active consideration for development. For each application, my first task was to define the clinical problem; this is essential risk assessment for anyone considering investing their time or money in a RM technology. This differentiated those applications with small headroom for improvement from those where the headroom is larger. My second task was to identify the most propitious applications for a RM technology and compare clinical effectiveness, with special emphasis on HRQL and utility, and costs of current treatment. Finally, I calculated the disutility of the clinical effects of the current treatment and conducted the headroom analysis to find the maximum additional cost of the new technology, which would still be considered cost-effective. The clinical applications considered included defects of the bladder, urethra, abdominal wall, bone, and cartilage. The specific findings relating to each application are discussed in the following section.

9.2 Overall Findings

9.2.1 Introduction

The aim of this thesis has to help the RM industry reduce the risk of investing in a new technology that once developed is unlikely to be reimbursed by the healthcare providers. The objectives of this thesis were:

i. To assess whether headroom method can be used, before the development process begins, to understand the scale of the market and clinical opportunity
ii. To develop a novel method using health economic principles that can be used early in healthcare technology development and that is simple enough to be used by Small and Medium enterprises (SME's)
iii. To demonstrate to the RM industry how this method can be used to assess the economic potential of their products at early stage product development

9.2.2 The Headroom Method

The headroom method is an approach which has been demonstrated in this thesis to be a simple and rigorous way to make a preliminary conclusion as to the cost-effectiveness of a new treatment, even

when some of the parameters are extremely uncertain, without having to build a complex model with very wide parameter uncertainty.

The Headroom Method arose from work on the use of economics to inform supply side decisions and had an intellectual and practical provenance. From the practical point of view, the purpose of the headroom method was to assist manufacturers and investors to assess the health economic value of proposed healthcare technology developments. From the intellectual point of view, the task proposed the challenge of performing a CEA in the absence of effectiveness parameter values. Both the practical and intellectual problem could be addressed by reversing the question that usually motivates a CEA, thus to establish the cost effectiveness gap, or the “headroom”, within which the technology could prove cost-effective. This methodology recognises that the limiting case is defined by the epidemiology of the condition, most notably the effectiveness of the current best treatment and an optimistic assumption concerning the effectiveness of the new technology.

This thesis concentrated on the clinical definition and headroom analysis stages of the headroom method framework. However, each part of the framework plays a role in supporting decision-making. The key to successful exploitation is to know which tools to use and when.

9.2.3 The Clinical Applications

I illustrated the headroom method using five real clinical examples taken from the nascent RM industry. The main findings are summarised in table 8.1. In chapter 4, I investigated the potential for a TE technology in the repair of urethral strictures and bladder resection following cancer. The current treatment for urethral strictures is urethroplasty using buccal mucosa, which reports good effectiveness and therefore the headroom is unlikely to be large enough to support a TE tissue product populated with cells. Following bladder cancer, the current treatment is bladder augmentation cystoplasty using bowel. In this case, the headroom was more viable but this application has a limited market size, which reduces potential profitability. These findings were reported to a TE company who, at the time, were investing in TE bladders. Based on the findings they decided to reduce investment,

but not completely cease development, in TE bladders and channel the extra resources to more potentially profitable areas.

In chapter 5, I investigated the application with the greatest potential for a TE solution for the repair of abdominal wall defects. Current treatment of abdominal wall defects is via tension free repair using a synthetic mesh. The headroom analysis found that the greatest room for improvement in effectiveness is when a defect is large and infected. I focused the headroom analysis on incisional hernias, specifically infected incisional hernias, those undergoing non-primary repair. In this case, the headroom was sufficient to support a new generation acellular mesh and it may be sufficient to support a cellular TE mesh, in other words, at this stage, the headroom was not too low to rule out supporting further investment, and further economic analysis could be conducted as development continues.

In chapter 6, I demonstrated supply side analysis using an example based on a RM alternative to bone for use in bony defects. The current best treatment of a bony defect is to use autograft, usually taken from the iliac crest. The greatest potential for a RM bone product is in moderate to large defects and I focused on spinal fusion repair for degenerative disc disease (DDD), and on non-healing fracture repair for fracture nonunions and segmental defects. I discerned three broad alternatives for treatment, autograft harvested from the iliac crest (the current best treatment), *in vivo* bone production, via implantation of growth factors (i.e. using the body as a factory), and *in vitro* bone production (i.e. making bone outside the body). The body as a factory approach, specifically the growth factor BMP has gathered a lot of interest in the literature. However, recent cost-effectiveness analysis in the UK has found that this approach is not cost-effective compared to using autograft. Therefore, I decided to ask the question *'What would the price of BMP need to be to become cost-effective?'* I found that BMP is very close to being cost-effective but currently the increase in effectiveness is insufficient to offset the additional cost of BMP. However, with a small decrease in the price or an improvement in effectiveness, it could be extremely cost-effective in the UK. Finally, in this chapter I conducted the headroom analysis based on pessimistic assumptions of the clinical effects of autograft. For both applications, the headroom was sufficient to support an *in vivo* approach of RM solution and possibly

for an *in vitro* solution. However, advances in *in vivo* approaches could mean that compared to *in vivo*, there would be insufficient headroom for an *in vitro* approach.

In chapter 7, I focused on articular cartilage defects of the knee. There are several surgical approaches available but currently there is no truly effective strategy. There are already RM solutions on the market but they have not yet proved to be cost-effective compared with microfracture, the current best non-RM solution. Here I conducted supply side analysis similar to that used in chapter 6. Firstly, I asked *'What is the minimum incremental effectiveness a new treatment should have in the short term to be more cost-effective than microfracture?'* and I found that a new RM treatment needs to provide an incremental gain of 0.13 QALYs, based on a cost similar to that held by the current RM products on the market. Secondly, I used the headroom analysis to answer the following question, *'What is the maximum incremental cost a new treatment could be to be cost-effective in the long term?'* Here, I used different scenarios based on delaying the onset of OA. In the long term if a new treatment was successful in delaying the onset of OA the cost-effectiveness issue is a bit of no brainer, however, by modelling the expected headroom based on different scenarios I can make predications about the expected headroom. For example if a new treatment could delay the onset of OA for 5 years, the headroom is approximately £36,000 ($60,000, €41,000).

Above and in table 9.1 I have summarised the main findings from this work. However, there were a number of limitations and assumptions associated with this work, which one must be aware of when interpreting the findings. These are summarised in the following section.

Table 9.1: Summary of the main findings from the application of the headroom method

Clinical Area	Urogenital		Abdominal Wall	Bone		Cartilage
Indication for an RM solution	Bladder Carcinoma	Urethral Strictures	Recurrent Incisional Hernia	Spinal fusion	Nonunion of Fractures & Segmental Defects	Articular Defects of the Knee
Current Treatment	Bladder Cystoplasty using bowel	Urethroplasty using buccal mucosa	Tension free synthetic mesh repair	Autograft	Autograft	Microfracture
Disutility of Clinical Effects of Current Treatment	0.04	0.06	0.15	0.0038	0.5	Osteoarthritis: 0.3 Total knee replacement: 0.22
Duration of Clinical Effects (yrs)	10	0.1	1	1	0.75	30
Max∆QALY	0.4	0.006	0.075	0.0038	0.375	7.8
Headroom (WTP threshold £30,000)	£12,000	£180	£2,250	£114	£11,250	£234,000
Additional Cost Savings	£1,268	£225	Early complications: £840 Late complications: £668	£819	£283	Costs discounted at 3.5%, benefit discounted at 1.5%
Max∆Cost	£13,268	£405	Early complications: £3,090 Late complications: £3,758	£933	£11,533	£220,500
Conclusion	Viable headroom but a limited market size reduces potential profitability	Insufficient headroom	Sufficient to support new generation acellular mesh and likely to be sufficient for a cellular TE mesh	Headroom is sufficient to support an *in vivo* approach and likely to be sufficient for an *in vitro* solution. Advances in *in vivo* approaches could mean that compared to *in vivo*, there would be insufficient headroom for an *in vitro* approach.		There is sufficient headroom for a new RM treatment if it can produce long-term benefits - delay the onset of OA and TKR

9.3 Limitations of the Headroom Method

As previously described, the headroom method is based on a number of assumptions: the most pessimistic scenario for the current treatment along with the most optimistic scenario for the new treatment. The reason for this is that, if under this scenario the new treatment is unlikely to

be cost-effective then, if the current is more effective than was thought and the new treatment less effective than hoped for, the new treatment will certainly not be cost-effective.

The headroom method is designed to give a crude estimation of the potential cost-effectiveness of a new technology. Therefore, it is probably not necessary and would not be a good use of time and resources to try to calculate the parameters within a high level of accuracy. In fact, this would be difficult, given that the technology is not yet developed and there is no evidence of effectiveness from direct studies. However, with the presence of many assumptions comes a high level of uncertainty around the parameter estimates. Uncertainty in economic evaluations is usually explored using sensitivity analysis (described in chapter 1). Sensitivity analysis examines the effect on the result of using different assumptions around the parameter estimates. I have dealt with uncertainty within the analysis for each of the applications I describe (chapters 4-7). In all cases, I have calculated the headroom based on both a £20,000 and £30,000 threshold limit, to assess the impact of threshold limit on the headroom. In chapter 6 (page 189), I illustrated the effect of threshold variation on the cost of the new technology. In addition, I have examined the impact on the headroom of varying the utility estimate or survival time (chapter 4, pages 106 & 107) and using utility values elicited from a number of methods (chapter 7) as it is well-known that method of elicitation impacts on the utility value obtained.

The headroom has been calculated based on the threshold values applicable to a UK setting i.e. £30,000 ($49,000, €34,000) and £20,000 ($33,000, €23,000). These threshold values were selected because the UK has been more transparent than most other countries in clarifying a range where the threshold limit lies. However, any threshold value deemed to be appropriate by the manufacturers and investors can be applied. Thus, the headroom method is not restricted to use in a UK setting only. In fact, it could be regarded as a strength of the headroom method that the impact on cost-effectiveness for a range of threshold limits could be evaluated relatively quickly. Although, it should be noted that the value of applying these methods at the supply side is dependent on the planned technologies being aimed at the third party payer (an organisation other than the patient (first party) or health care provider (second party)).

Finally, I would say that the biggest limitation of the headroom method has been surrounding the elicitation of the health utilities. Ideally, these values would be sought from patients every time but this is not always practical which means other methods must be employed. I discuss the issue of health utilities including their limitations and impact on the headroom analysis in more detail in the following section.

9.4 Health Utilities

9.4.1 Introduction

The headroom method is based on the health economic concepts used by NICE i.e. cost-utility analysis (CUA). As previously described (chapter 1, page 30), CUA is a particular kind of CEA where the benefits are measured on a utility scale, and QALYs are such a scale. Measured on a cardinal scale, from 0 to 1, health utilities measure the strength of an individual's preference for a particular health state. Preferences can be measured using formal methods, of which there are a number of approaches, described in further detail elsewhere (section 1.2., page 30). Alternatively, a health utility may be identified in the literature. A health utility score is required in order to conduct the headroom analysis. Throughout the course of this work, I have used both approaches to identify a health utility. The methods used are described briefly below, followed by a summary of the limitations of the methods used.

9.4.2 Summary of Methods

Here I summarise the methods used to elicit utilities in chapters 4 through to 7 of this thesis. In chapter 4 and 5, there were no values reported in the literature so I elicited the utility values using formal methods, TTO and WTP. For TTO, each interviewee was asked what amount of time they would be willing to sacrifice from 10 years of remaining life, to avoid the negative side effects of the condition described to them. In WTP, participants were asked how much they would be willing to pay for a treatment that would relieve them of the described health state.

Combining the responses from both the WTP and TTO questions allowed me to calculate each individual's WTP per QALY.

Two of the three questionnaires used in chapter 4 and 5 were completed by specialist clinicians and the other was completed by a sample of the general public, selected at random from the public health building at the University of Birmingham and from two locations within Birmingham city centre. The urologists contacted as part of chapter 4 were identified from hospitals within the Birmingham area through the NHS website. Here the urologists were emailed the questionnaire. On the other hand, for chapter 5 I arranged to attend the conference of the Association of Coloprotology of Great Britain and Ireland and asked the attending clinicians. This decision was made in an attempt to achieve a larger sample size than was obtained through the emailing of questionnaires, yet to complete as many questionnaires as possible in a short time period.

In chapters 6 and 7, I used the alterative approach to identify the health utilities; I sourced them from the literature. In chapter 6, I identified the utility associated with spinal fusion using autograft in a HTA report and the utility associated with nonunion fractures through a search of the database held by TUFTS (Tufts Medical Centre, 2009). In chapter 7, I needed to identify several utility values for different health states. For OA of the knee I identified four prospective studies, which had measured HRQL using SF-36. Using an algorithm described by Ara and Brazier (Ara et al, 2008a;Ara et al, 2008b) I was able to covert the sub-scores of SF-36 data into SF-6D and EQ-5D utility scores, from which I took the average to use in my analysis. I also identified a report by Dong and colleagues (Dong et al, 2006) which stated health utilities for OA and TKR. Health utilities associated with TKR were also identified from two systematic reviews (Clar 2005; Ethgen 2004). The Ethgen review reported HRQL scores measured using SF-36 so the same algorithms referred to earlier were used to calculate the utility values.

9.4.3 Limitations

The analysis of the headroom for a TE bladder was limited by the small sample size used to elicit the health utility associated with cystoplasty using the bowel. Sixteen urologists were contacted but only four completed the questionnaire. I feel the failure to obtain a greater sample of clinicians was due to the emailing of the questionnaire. With high numbers of emails received everyday, it is easy to see how a questionnaire from an unknown individual could simply be missed. The success of this approach could have been improved by posting the questionnaires or arranging a telephone interview, or through increasing the sample of urologists who were initially contacted. Despite the low sample size I do believe that the utility value (0.96) elicited is acceptable and reliable. In comparison, the limitation of the utility values elicited for urethroplasty using buccal mucosa was concerned with a potentially unrepresentative sample of the general population. Those interviewed from the university were more familiar with both the health state under investigation and the methods of measuring preferences. Although, the sample size was larger than that for the previous questionnaire, I have reservations about whether this questionnaire was fully understood and feel the resulting utility value is slightly unrealistic. I offer three explanations for this. Firstly, a misinterpretation of the health states being described, secondly, a big error, and finally, a natural occurrence. It has been reported that the general public tend to exaggerate the impact of disease on HRQL (Ubel et al, 2003). In chapter 7, the health utility associated with OA and TKR were elicited from SF-36 scores using algorithms for SF6D and EQ-5D. There were two limitations here. Firstly, the SF-36 measure was only used in a small number of observational studies and no RCTs. Secondly, there were variations in the utility values calculated due to the variations in the importance of different attributes between SF-6D and EQ-5D.

One of the main advantages of the headroom method is in its simplicity. However, when utility values are not available from the literature, several complex methods exist to obtain utilities using formal methods. This violates the spirit of the headroom method. Eliciting utilities is a complicated process, beset with conceptual difficulties that have not been solved. In addition to the complexity, these formal methods can be costly to conduct and therefore unlikely to cost-

effective within this method. So faced with these issues, what is the manufacturer to do? Utilities are a requirement for headroom calculations. In the following section, I summarise my solution to this problem of utility elicitation in the context of the headroom method.

9.4.4 An alternative approach to the challenge of eliciting utilities

As discussed above, the current approaches to estimating the utility value of a given health state not previously reported in the literature go against the premise of the headroom method and a more pragmatic approach is required if the headroom method is to be routinely used in practice. A quick and easy approach, akin to the headroom method itself is required. A manufacturer needs to be able to make a common-sense estimate of a utility value for a given health state based on information already available. My approach was to provide a 'toolkit' for this purpose. For this, I needed to identify 'example' utility values from the literature, which could form a hierarchy or 'ladder' of utilities upon which judgements about other, currently unidentified, utility values could be made.

The main challenge I encountered was identifying a suitable source of predefined utility values. My first idea was to use the TUFTS database of utilities but this proved unsuccessful for the purposes of this work. The descriptions of the health states were too vague and often overlapping, the range of values for a given health state were vast and the quality of the utilities reported were questionable without further exploration. For these reasons, I sought an alternative and hit upon the idea of using utility values reported in NICE appraisals. The advantages of the NICE appraisals were that i) the health states are reasonably tightly defined, and ii) NICE committees review the quality of the appraisals. I concluded that it was reasonable to assume these utilities would offer the best estimates currently available in the literature.

Having selected an array of health states to reflect a range of morbidities, I created a hierarchy of utilities. This is shown in figures 8.2 through to 8.4 (page 242) and is accompanied by table 8.1 (page 237) which proves further detail of the definition of each health state. Together this information provides a frame of reference against which a manufacturer can make a judgement

concerning the utility of a health state not yet studied from the point of view of human preferences. This solution is consistent with the 'back of the envelope' nature of the headroom method.

9.4.5 Discussion

The quickest and easiest way to elicit health utilities is from the literature. However, there are two limitations here. Firstly, utilities have not been measured for all conditions, and therefore there may be no utility values reported at all, as was the case in chapter 6 for example. Secondly, the utility values reported in the literature vary in quality, or may be out-of-date. This makes it difficult to assess the accuracy and reliability of the health utility values reported. Overall, there needs to be an increase in the number of RCTs incorporating utility-based HRQL data collection.

In the case where the literature did not report the utility values I required, (I believed) I had no option but to elicit this value myself. Therefore, I had to make a decision about which formal methods to employ, who to ask and how to ask them. I believe the approach I took in chapter 5 was favourable over the approach used in chapter 4. In chapter 5,I took a more direct approach to the completion of the TTO questionnaires, and spoke directly with the clinicians. Obviously, it may not always be possible to attend a conference but I feel this experience taught me that a face-to-face interview is much more effective than an email or postal questionnaire where there is no contact with the interviewee. I also believe that a telephone interview approach would be preferable to a postal approach. However, I appreciate that arranging to call or meet with people is more time consuming to coordinate and conduct and therefore not always practical. In these cases, however, I acknowledge that it would have been ideal to elicit utilities directly from patients receiving the healthcare, but this is not always possible. I believe that clinicians are a better proxy for patients than the general public. Although, I do not disagree with the point that the general public are those who pay for healthcare and who represent public opinion, but I do not believe that the general public always have a full understanding of the condition being described to them. The disadvantage with asking clinicians, however, is around WTP as the

income between a clinician and the general public could be vastly different and therefore be unrepresentative. Despite this, I would still favour the clinician as a proxy due the reasons already outlined above.

However on reflection after applying the headroom method to the examples given in chapters 4 through to 7, I believe the concept of the headroom method is floored if a manufacturer is required to elicit the utility-based QoL measures directly (or indirectly) themselves, in order to calculate the headroom. One of the main advantages of the headroom method is in its simplicity and the use of complex formal methods goes against this premise. Chapter 8 is dedicated to a search to addressing this challenge and I believe I have achieved a solution that is quick and easy to use, akin to the nature of headroom method itself. This solution is by no means designed to replace the use of formal methods to eliciting utility values, but to be used as guide to estimate the potential headroom in effectiveness that may be available.

9.5 Barriers to Innovation of RM Technologies

As development progresses and nears market, further difficulties may arise. Some of these further barriers to innovation are discussed briefly below.

i. **Uncertainties** – a major barrier to the adoption of technology is the requirement to provide sufficient evidence of effectiveness. Evidence on the effectiveness of a technology should ideally come from RCTs.

ii. **Silo budgets** – silo budgeting is a major barrier to the adoption of technology. The segmentation of the delivery of healthcare by departments means you have to provide an economic argument for a single department. This is often very difficult, because while the cost may lie in one department, the benefit is accrued in another. For example, less invasive surgery may increase cost in the operating theatre, yet the benefit and cost saving is made on the ward. Ultimately a more joined-up system is required (Mark Sansom, 2005). Silo budgeting is a concern for manufacturers developing treatments that will benefit the long term but incur large up front costs.

iii. **Business strategy** – some products will aim at more than one application e.g. bone morphogenic proteins (BMPs). Each application may have a different ICER and headroom. Furthermore, the first application might not necessarily be the 'big one'.

9.6 Final Conclusion

This thesis is inspired by the idea that health economics could reduce the risk of commercial failure and is concerned with the adoption of health economics in decision making at the supply side. The underlying idea is that the adoption of new technologies is determined (at least in part) by its cost-effectiveness and manufacturers and investors would be well advised to take a view on how their projects are likely to be assessed in the procurement of healthcare.

The headroom method is an approach to the challenge of conducting supply side analysis. It is designed to help industry avoid misguidedly investing in those technologies that will never be cost-effective. It is intended for use in the first instance before substantial investments are made to inform investment decisions and indicate which products have the greatest potential. My thesis has demonstrated the headroom method in the context of the RM industry, which has had difficulties translating RM products from laboratory bench to patient bedside, due largely to insufficient marginal effectiveness delivered for marginal costs incurred.

The advantage of the headroom method is in its simplicity. Designed to allow a manufacturer to conduct their own early economic evaluation and assess the potential for investment in their product. In addition, the headroom method, compared to full health economic modelling, is relatively cheap to conduct. During the early stages of product development, it is probably not a cost-effective use of a researcher's time and resources to conduct a full health economic model. However, as I have already discussed, as development continues it is important to repeat the economic evaluation as further evidence becomes available. More sophisticated health economic tools will be required at this stage.

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APPENDICES

Appendix 1: The Headroom Method User Guide

Investing in Medical Technologies:

The Headroom Method

The headroom method is an approach to help avoid misguidedly investing in those technologies that will never be cost-effective. This is a step-by-step guide for industry which will take you through conducting your own headroom analysis.

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Introduction

The changing face of health care purchasing

Health economics manages the scarcity of resources. It provides the tools necessary to assess the most efficient use of available resources in the allocation of health and health care. Cost-effectiveness analysis, defined in terms of costs and consequences, is the comparative analysis of alternative courses of action. It tries to identify where more benefit can be produced at the same cost, or lower cost can be achieved for equal benefit[*].

Cost-effectiveness of a technology is compelling evidence for its adoption by healthcare providers. Healthcare markets are increasingly competitive. Health services are using cost-effectiveness analysis to a greater extent to guide purchasing and reimbursement decisions.

Cost-effectiveness analysis tells us the cost of achieving a particular goal. Assessment of whether this is worthwhile is made through reference to an external standard (e.g. specified budget or threshold limit). In the UK, the National Institute for Health and Clinical Excellence (NICE) is the body which assesses the evidence of clinical and cost-effectiveness of a particular technology and gives recommendations about whether and in what circumstances the technology should be used. NICE uses this approach to assesses the incremental cost-effectiveness ratio (ICER) of the technology. This is the extra cost per extra unit of benefit achieved when comparing one technology against another. It determines whether an increase in cost is justified by a sufficient increase in effectiveness. Decisions are made based on a threshold level for an ICER[†]. Our purpose was to adapt cost-effectiveness analysis to inform investments and development decisions.

Applying Health Economics Early in the Development Cycle

Cost-effectiveness analysis is typically conducted from the demand side i.e. after the product has been developed and parameter estimates made available from direct studies. In the case of a technology yet to be developed, or in early stages of development, the very nature of the product is uncertain and no effectiveness studies have been conducted. We argue for the adoption of health economic principles at the supply side i.e. early stage development when

[*] A useful source of further information on health economics and cost-effectiveness analysis can be found in Drummond et al. 2006. Methods for the economic evaluation of health care programmes, 3rd Edition(1)

[†] NICE is an independent organisation responsible for providing guidance on promoting good health and preventing and treating ill health. NICE produced guidance on its threshold level in 2004(2). For technologies with an ICER below £20,000 per QALY this should be sufficient to obtain acceptance. For technologies with an ICER between £20,000 and £30,000 per QALY other factors need to be present to favour acceptance of the technology. For technologies with an ICER above £30,000 per QALY these additional arguments favouring treatments need to be strong. For more information on NICE see www.nice.org.uk

effectiveness is unknown. This will help inform investment decisions and indicate which products have greatest potential.

We describe a method of cost-effectiveness analysis to be used at the supply side. We have called this the **Headroom Method**[3]. This is a simple threshold approach, which estimates the maximum cost that a technology can be brought to market and still be considered cost-effective. This document is a step-by-step guide of how to conduct your own headroom analysis. We illustrate the method using examples from the field of regenerative medicine.

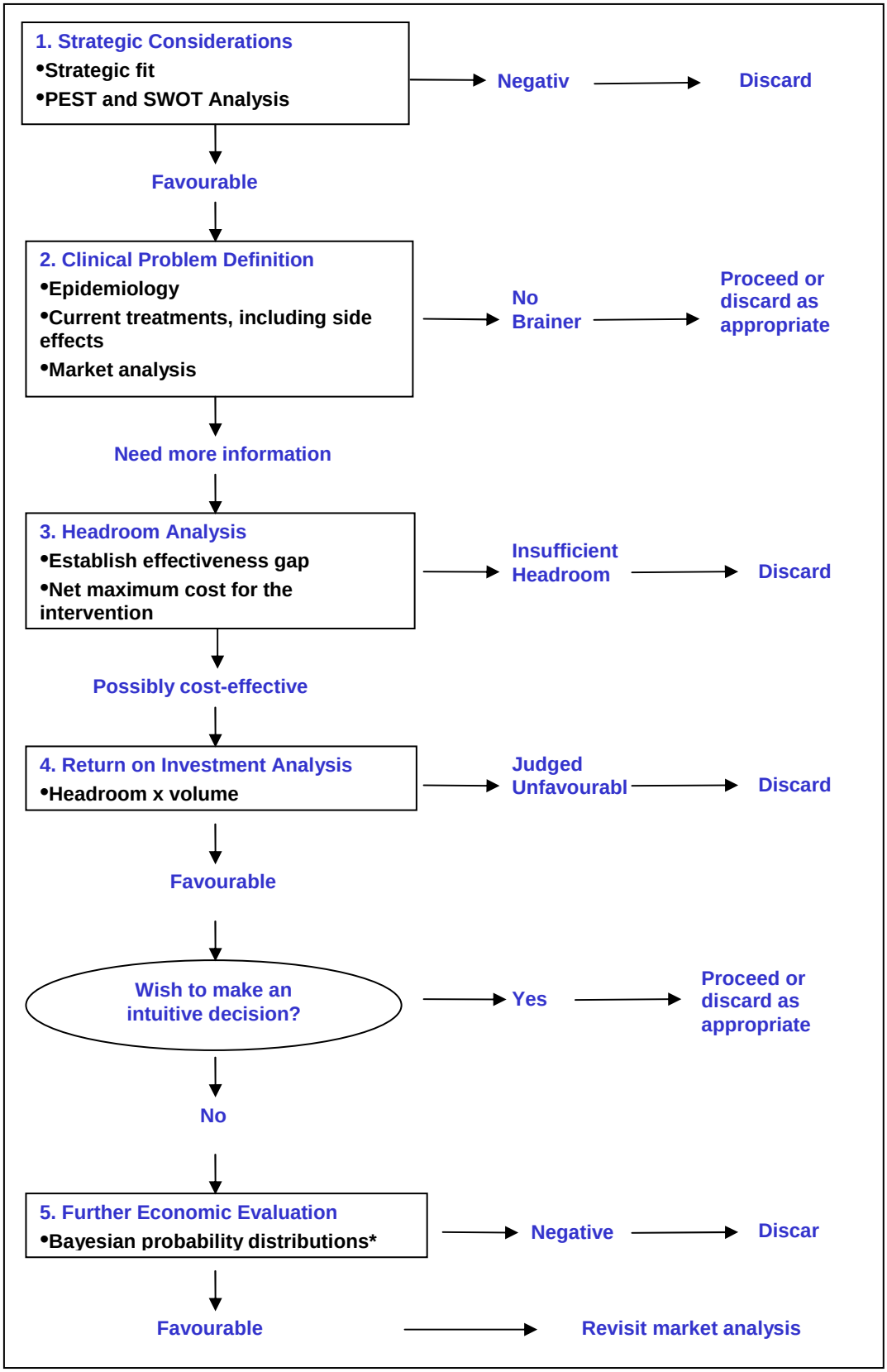
The Headroom Method

The headroom method simply looks at the potential of a clinically defined market. Instead of asking, *"How cost-effective will the technology be?*" - The question for conventional cost-effectiveness analysis of a technology already developed - we ask, *"Would it be cost-effective if it works as well as one would hope?"* In other words, optimistic assumptions are made about the incremental effectiveness of the proposed treatment over the best alternative. We then ask, *"At what cost would this new technology be cost-effective?*" This gives the maximum potential cost of the new treatment (including development costs), factoring in any health service savings.

If this cost [the headroom] is too low - if the incremental cost of the product could not realistically be held below this level - then investment funds should be channelled elsewhere. Of course, the reverse is not true - the new technology might still fail despite adequate headroom. For example, it might turn out to be less effective or more expensive than hoped or novel competing alternatives may emerge. However, the headroom method can lower the risk of embarking on an investment that is doomed from the outset.

The headroom analysis fits into a broader decision framework, illustrated in figure 1 below. In this guide, we will discuss stages 1-4 of the framework. We focus primarily on the aspects directly involved with understanding and undertaking the headroom method – stages 2 and 3 – defining the clinical problem and the headroom analysis.

Figure 1: Algorithm for investment Decisions for new Technologies[4]



* Discussed in a publication[5]

Stages in the Decision Algorithm

1. Strategic Considerations

You will be fully aware that an organisation needs to begin by addressing strategic fit issues and that management tools, such as PEST (political, economic, social, technology) and SWOT (strength, weaknesses, opportunities, threats) analysis, exist for structuring and defining a business problem situation. This process may do no more than formalise existing knowledge. It will however provide rigour to the decision and exclude obviously futile schemes. At the very least it reduces the risk that some important considerations will be accidentally omitted from the deliberations. In regenerative medicine there is an additional specific question you must ask yourself, *"What changes to the regulations are in the pipeline?"* If the technology is not ruled out by strategic considerations, then the investigation should move to the next stage; a study of the clinical problem and an analysis of how the technology may help.

2. Defining the Clinical Problem

In some circumstances, the decision to invest in a technology can be made without the need of any formal method of evaluation. If an unmet clinical need can be identified and resolved - such as curing a common, chronic disease at low cost – then the decision makes itself. These blockbuster discoveries come along only seldom. The cost-effectiveness of most proposed new technologies is much more difficult to predict. In such cases, it is important not to be carried away by enthusiasm for the technology or to over estimate the size of the potential market.

There is always a limit on how cost effective a new technology may be. The epidemiology and clinical features of the condition in question limit the potential benefit. This is *the effectiveness gap* – the room for improvement in effectiveness between the current best treatment and that which the new technology might plausibly achieve.

All the conditions where a new technology may have an application need to be examined in turn; at least to the point where it is clear there is a material clinical problem to be solved. It is important to be as specific as possible about the clinical problem. A clearly defined clinical need based on a good understanding of the strengths and weaknesses of current treatment, including side effects is crucial to the uptake of a new technology. It is essential to complete this prior to conducting the headroom analysis.

This point may sound obvious but, in our experience, investors and even inventors typically have a very vague, even naïve, understanding of the clinical problem. Table 1 below outlines the questions to aid you to establish a clear definition of the clinical problem.

Table 1: Defining the clinical problem

Questions	Definition
What is the technology?	A precise description of new technology being considered, including a description of any uncertainties. For example, in the field of regenerative medicine it is uncertain whether a tissue-engineered bladder will become re-innervated with nerves.
What is the disease/condition?	A precise description of disease and natural history. This includes analysis of disease sub-groups where the new technology may be more or less applicable. For example, there may be a greater need for tissue-engineered bone for fracture nonunion repair than for spinal fusion surgery to treat degenerative disc disease.
What is the prevalence and incidence of the disease/condition?	This information can be obtained through a literature search of published studies. Hospital episode statistics (www.**hes**online.nhs.uk/) can be a useful source of data on incidence. This data will need to be broken down by relevant sub-groups, since the effectiveness gap may vary widely by sub-group, as it does, for example in hernia repair.
What are the current treatments?	The current gold standard is the comparator for the new technology. However, new developments must also be reviewed as this may change the shape of the market. For example, the availability of bone morphogenic proteins is replacing the need for complicated bone scaffolds, especially those populated by living cells in vitro.
What is the effectiveness of current treatments?	The effectiveness, including any side effects and complications of the current gold standard treatment must be clearly described. Any side effects or complications, which could potentially be avoided by the new treatment, must be identified. For example, a tissue-engineered solution to repair complex hernias would avoid adhesions and infections, which result from current treatment.

The vast majority of this information can be obtained through a systematic review of the literature. The sources that follow will be useful[*], but it is important to back up this information with clinical opinion and experts in the industry.

- NICE guidance (http://www.nice.org.uk/guidance/index.jsp) – is there any current NICE guidance regarding the treatment of the condition/disease you wish to target?
- The Cochrane library (http://www.cochrane.org/) or clinicalTrials.gov (www.clinicaltrials.gov) – will contain any systematic reviews or economic evaluations that have been performed on

[*] Note that these sources are focused on UK information only.

the topic in question. It may also give you information on any ongoing clinical trials and when are the results due to be published.

- PubMed *(*www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.co.uk/), and EMBASE *(*www.embase.com/) – can be used to search for clinical trials (and observational studies). It is important to search for trials, which may have been published since the most recent systematic reviews, economic evaluations or NICE guidance.
- Hospital episode statistics (HES), available from the NHS information centre, *(*www.hesonline.nhs.uk/) – contains information regarding admission numbers, defined by diagnoses and main operations, for England and Wales.
- Department of health NHS reference costs (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/index.htm) - contains information on cost of treatment/procedures in England and Wales.

3. Headroom Analysis

The headroom method involves two key aspects:

1. **Establishing the 'headroom' in effectiveness –** the effectiveness gap i.e. the room for improvement in effectiveness between the current best treatment and that which the new technology might plausibly achieve.
2. **Calculating the headroom -** the maximum incremental cost (maximum additional cost compared to the current best treatment) of the new technology which could still be considered cost effective. This is based on optimistic but plausible estimates of effectiveness of the technology being assessed.

Before we can do the calculation, we must go over some basic health economics principles:

1. Incremental Cost-Effectiveness Ratio (ICER)

Cost-effectiveness analysis aims to quantify the incremental cost-effectiveness ratio (ICER). This is the extra cost per extra unit of benefit when comparing one technology against another. This is most often done on a cost per quality adjusted life year (QALY)[*] basis[†] (QALYs are discussed below).

[*] For a quick and easy introduction to QALYs see 'what is a QALY' by Phillips et al.[6]

[†] There are different types of economic evaluation each using different measures of effectiveness: i) cost-minimisation analysis (CMA) – a comparison of costs; ii) cost-effectiveness analysis (CEA) – effectiveness measured in natural units e.g. life years gained; iii) cost-benefit analysis (CBA) – effectiveness and costs measured in monetary units; iv) cost-utility analysis (CUA) – effectiveness measured on a utility scale e.g. QALY. More information can be found in any health economics textbook, such as Drummond et al. 2006. Methods for the economic evaluation of health care programmes, 3rd Edition[1]

The comparator for the new technology should always be the current gold standard treatment. Only an improvement on this performance, in terms of cost-effectiveness, will support the reimbursement of a new technology. The current gold standard treatment should have been identified during stage 2 - defining the clinical problem.

An ICER is calculated as in equation 1, using the incremental cost (change in cost from treatment A to treatment B (ΔC)) and the incremental effectiveness (change in effectiveness from treatment A to treatment B (ΔE)). This gives a cost per additional unit of effectiveness, or an incremental cost per QALY (see box 1).

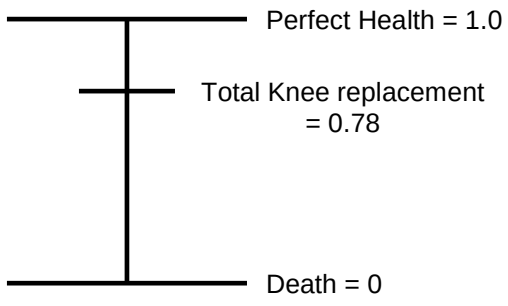
Equation 1: ICER = $\Delta C / \Delta E$

2. Quality Adjusted Life Year (QALY)

A QALY is a measure that takes into account both the *quantity* and the *quality* of life generated by healthcare. Quantity is expressed in years, in terms of survival or remaining life expectancy. Quality is measured by health utilities*.

A health utility measures the strength of an individuals' preference for a particular health outcome. It is measured on a scale from 0, death, to 1, perfect health (see figure 2). A greater preference for a particular health outcome will result in a greater utility for that health outcome. A year of perfect health is worth 1 i.e. 1 QALY is equal to 1 year of perfect health.

Figure 2: Health utility Scale



A health utility is expressed on a scale from 0 to 1. For example, a total knee replacement gives an average utility of 0.78. The quality of life is 0.78. A 50-year-old patient with a life expectancy of 80 years has a quantity of life of 20 years. The QALY gain would be 0.78 x 20 = 15.6

Total incremental QALY (ΔQALY) for a technology is calculated as in equation 2. It is a function of improvement in health utility (Δutility) and the duration over which this improvement is sustained (see Box 2), when the new technology is compared to the current gold standard.

Equation 2: ΔQALY = ΔUtility x duration of time (years) with that health state

* Utilities place a value on a particular health state and are used to calculate QALYs, unlike quality of life scores which directly measure the impact of a disease or treatment on people's ability to function in life and which cannot be used to calculate QALYs. For a quick and easy introduction to health utilities see 'what is a utility' by Petrou[7].

Box 1: Calculating an Incremental Cost Effectiveness Ratio (ICER)

1. ∆C = cost of Treatment B – cost of Treatment A
2. ∆E = benefit of Treatment B – benefit of Treatment A
3. ICER = ∆C / ∆E

Where,

∆C is the difference in cost between the new treatment and the gold standard comparator,

∆E is the difference in effectiveness between the new treatments and the gold standard comparator

Note: ∆E can be measured in different terms, in the UK, this is most frequently the QALY, calculated using the formula in box 2. ∆QALY becomes the measure of the change in effectiveness between the two treatment options thus, ICER = ∆C / ∆QALY

Example:

Treatment A is current gold standard it costs £50,000 and gives 9 QALYs. Treatment B is the new treatment it costs £100,000 and gives 16 QALYs.

1. ∆C = £100,000 – £50,000 = £50,000
2. ∆QALY = 16 – 9 = 7 QALYs
3. ICER = ∆C / ∆QALY = 50,000 / 7 = **£7,142 per QALY**

Treatment B costs an additional £7,142 per QALY compared to Treatment A. The healthcare provider must now decide whether this is an acceptable cost per QALY.

Box 2: Calculating incremental QALY gain

∆QALY = (utility score of treatment B x duration (years) of that health state)
- (utility score of treatment A x duration (years) of that health state)

Where,

QALY is Quality adjusted life year (measure of effectiveness).

Example:

Treatment A is current gold standard. Following treatment A, the patient lives for 15 years with a health state of 0.6. Treatment B is the new treatment. Following treatment, B the patient lives for 15 years with a health state of 0.8.

∆QALY = (0.8-0.6) x 15) = 0.2 x 15 = **3 QALYs**

Thus, treatment B results in 3 additional QALYs compared to treatment A. in other words, treatment B results in the equivalent of 3 additional years of perfect health compared to treatment A.

3. Cost Effectiveness Plane

New technologies can be represented graphically according to their cost and effectiveness on a cost-effectiveness plane (figure 3)[8]. This can determine which interventions are cost-effective and which are not i.e. which technologies may be eligible for reimbursement by the healthcare system.

In figure 3, a straight line passes through the origin, where cost is equal to benefit. The gradient of this line is dependent on the threshold limit of the ICER. This is the maximum cost a healthcare provider will pay for 1 QALY. It is also referred to as the maximum willingness to pay (WTP) threshold i.e. the maximum WTP for 1 QALY. This will vary from country to country.

The line divides the plane into cost-effective (right half) and non-cost-effective (left half) sections. The ICER for the technology can then be plotted on the plane. Depending on their position, the technology may either be accepted or rejected for reimbursement by the healthcare provider.

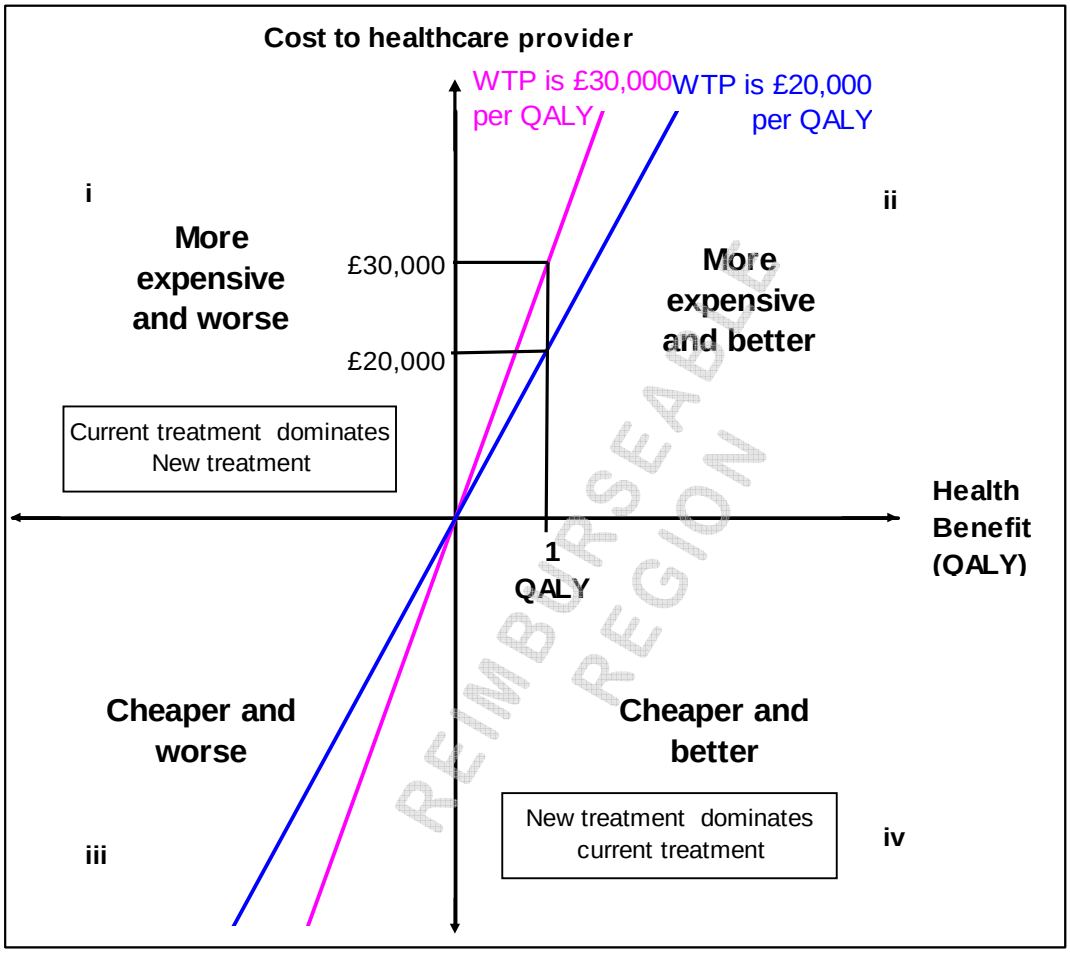
As stated earlier, assessment of cost-effectiveness needs to be compared to an external standard. In the UK, NICE carries out this assessment and uses a WTP threshold limit of £20,000 to £30,000 per QALY. In other words, the healthcare provider in the UK is willing to pay £30,000 for 1 QALY.

ICER
***Incremental cost-effectiveness ratio* - the extra cost per extra unit of benefit when comparing one technology against another - most often done on a cost per QALY basis (pg 8).**

QALY
***Quality adjusted life year* – takes into account both *quantity* and *quality* of life generated by healthcare (pg 8).**

The ICER of a regenerative medicine technology is mostly likely to be in quadrant ii (better but more expensive). You need to make sure the additional costs of the technology are equal to the additional benefits. This will bring the ICER of the new technology below the WTP threshold, making it more likely to receive reimbursement.

Figure 3: Cost effectiveness Plane illustrating reimbursable region



Calculating Headroom

Now we know how to calculate an ICER we can work out how to calculate the headroom. We rearrange equation 1 into equation 3 below. We substitute 'ICER' with 'WTP threshold'. We assume the WTP threshold is £30,000 - the most optimistic scenario for the UK NHS. Next, we need to estimate the maximum ΔQALY.

Equation 3: max ΔCost = WTP threshold x max ΔQALY

maxΔcost is the *headroom* – the maximum additional cost of new treatment over the comparator (current gold standard) for the new treatment to be deemed cost-effective. It is important to note that maxΔCost is the net difference in cost [to the health service] of the proposed new technology. It includes any net savings or costs to the health service along with the costs of the product itself.

WTP threshold is *maximum threshold for the incremental cost effectiveness ratio*. In the UK, we assume this to be £30,000 per QALY. Equation 3 can also be expressed as: max ΔCost = £30,000 x max ΔQALY.

maxΔQALY is the *effectiveness gap* - the maximum additional benefit that could be obtained from the new treatment, this must be estimated before we calculate the headroom (see below).

Estimating the Maximum ΔQALY – the Effectiveness Gap

When the current treatment is sub-optimal, an effectiveness gap can be estimated. For those conditions with treatments, which are ineffective for large proportions of patients or have significant side effects, the maximum potential increase in effectiveness over current treatment may be used as the optimistic assumption. Specifically we are looking for those side effects that could be eliminated by the new treatment – these should have been identified during stage 2 (defining the clinical problem).

There are two steps required to calculate the effectiveness gap (maxΔQALY):

1. Health utility associated with the current treatment

Having defined the clinical problem and existing treatment, it is possible to identify the clinical outcome that the new treatment should improve – in the simplest case, there will be one target outcome. Next, it is necessary to identify the health utility value associated with that clinical outcome. Health utilities can often be identified in the literature or in the database of utilities [9] held by TUFTS. If not, the utility values will have to be established by conducting a primary survey. Methods of utility estimation are summarised in the box 3.

Finally, we define the effectiveness gap. We subtract the utility value we have identified from 1 (perfect health). Since we do not know the true effectiveness of our new technology, we assume the most optimistic scenario. This would be for the new technology to return the patient to perfect health (health utility = 1).

For example, the current gold standard treatment for people with severe osteoarthritis is total knee replacement. This treatment has an average utility of 0.78[10]. The effectiveness gap for the new treatment would be 0.22.

Maximum potential health utility of new technology = 1 (perfect health).
Health utility of current treatment (total knee replacement) = 0.78.
Maximum potential effectiveness gap for a new technology = 1 – 0.78 = 0.22

Box 3: Measuring Utilities

Measuring utilities involves three stages:

1. define a set of health states of interest (e.g. side-effects of current treatment);
2. identify individuals to obtain utilities from (e.g. patients, clinicians, general public);
3. total across the individuals to determine average values for each health state

There are formal methods for measuring utilities:

- Firstly, those elicited from general population (recommended by NICE), such as rating scale, standard gamble and time trade-off. The most common approach is time trade-off (TTO). The subject is offered two alternatives: a) health outcome *U* for time *t* (life expectancy of an individual with chronic condition, e.g. 10 years) followed by death; b) healthy for time $x < t$ followed by death. Time *x* is varied until subject is indifferent between the two alternatives at which point the required preference score for health outcome *U* is given.

- Secondly, those elicited from patients directly who are using the technology. These are pre-scored multi-attribute health classification systems such as EuroQol (EQ-5D – www.euroqol.org).

For more information on these techniques, refer to a standard health economics textbook, such as Drummond et al. 2006. Methods for the economic evaluation of health care programmes, 3rd Edition, Oxford [(1)].

2. Estimation of duration of the improvement in effectiveness

We have defined the maximum potential effectiveness gap for the new technology compared to the current treatment. The next step is to identify the maximum potential duration of the clinical benefit expected from the new treatment. If there is no difference in life expectancy, it is necessary only to consider the period of time during which the health utility values differ. If there is likely to be a difference in life expectancy with your new treatment then this must be included in the calculation.

For instance, a new generation alternative to total knee replacement would be unlikely to increase life, but it is likely to improve the health utility of the patient. As there is no extension in life, only the duration of the improvement in clinical benefit is taken into account, i.e. the duration of the side effects of the current treatment that would be abolished by the new treatment.

For example, a patient receives a total knee replacement at an average age of 55 years and has an average life expectancy of 70 years. The improvement in clinical benefit associated with the new generation alternative to total knee replacement would have duration of 15 years. We now calculate the incremental QALY gain as illustrated in box 2. This gives a maximum incremental QALY (**max ∆QALY**) gain of 3.3 QALYs.

Maximum potential effectiveness gap for a new technology = 1 – 0.78 = 0.22
Maximum potential duration of effectiveness gap = 70-55 = 15
Maximum incremental QALY gain = 0.22x15 = 3.3

Now we have all the necessary parameters to populate equation 3 we can calculate the headroom (max∆cost). For example, the headroom (max ∆Cost) for a new generation alternative to total knee replacement is calculated as £99,000.

Maximum incremental QALY gain (max ∆QALY) = 0.22x15 = 3.3
Headroom (max ∆Cost) = WTP threshold x max ∆QALY = £30,000 x 3.3 = £99,000

The headroom tells us that a new generation alternative to total knee replacement could be cost-effective if it costs under £99,000. This is based on an assumption that it restores perfect health to the patient and lasts for the remainder of the patient's life.

Two examples of the headroom method from the field of regenerative medicine are given in the boxes below. Both have "passed" the strategic considerations stage and are under active consideration for development in industry. More detailed accounts of this work can be found in a publication by McAteer et al.[11].

Box 4: Regenerative Medicine for Urethral Stricture

1. Defining Clinical Problem

An urethroplasty is the current treatment option for long or complicated urethral strictures. A urethral stricture is an abnormal narrowing of the urethra, which adversely affects the passage of urine. In an urethroplasty, the narrowed section of the urethra is surgically opened or removed, and the urethra repaired with a tissue graft. Buccal mucosa (tissue making up the lining of the cheek) is the gold standard urethral substitute. Like urethral tissue, it is a mucous membrane, with similar physical properties, although it has disadvantages relating to morbidity at the donor site. TE aims to replace the use of tissue grafts in this procedure.

2. Estimation of Parameters

We assume that a tissue-engineered substitute would avoid donor site morbidity and perform as well as natural autologous tissue with no difference in mortality. Estimates will be required for the utility of avoiding donor site morbidity and the time over which the utilities for the treatments would differ.

A systematic review of the literature revealed no utility values for patients following an urethroplasty using buccal mucosa. Instead, the quantity was obtained from the general public using the time trade-off (TTO) method (see box 3). The utility associated with side effects of buccal mucosa was 0.94. After consultation with clinicians, the duration of the side effects was estimated as 0.1 years.

The effectiveness gap is: 1 - 0.94 = 0.06, and maxΔQALY is: 0.1 x 0.06 = 0.006

3. Headroom Analysis

The headroom is calculated using: max ΔCost = WTP threshold x max ΔQALY. Thus, £30,000 x 0.006 = £180 per patient treated.

However, this does not take into account the saving in operation time resulting from avoiding the harvesting of tissue. There is a saving of about 40 minutes in operating time. This is calculated as £225 per patient (based on a total operation cost of £3480 (HRG code L33, Department of Health reference costs) and a total operation time of 75 minutes). Thus, total headroom is £405.

4. Conclusion

The headroom for tissue-engineered urethral tissue has been optimistically estimated to be £411 over and above the current cost of a tissue grafting operation. It is unlikely that this is large enough to support the launch of a cell-bearing TE product, according to consultations with the industry.

Box 5: Regenerative Medicine for Surgical Treatment of Bladder Cancer

1. Defining the Clinical Problem

When bladder capacity or function has been substantially reduced current best surgical intervention is by means of an augmentation cystoplasty procedure (bladder reconstruction surgery). This increases the bladder capacity by directly increasing the volume of the bladder by stitching a section of small intestine into the bladder. A tissue-engineered bladder would most likely be used as an alternative to bowel in cystoplasty following bladder removal for cancer. Other indications (dysfunctional bladder and bilharzia) are not favourable due to the existence of non-invasive treatments and market forces, respectively.

2. Estimation of Parameters

We assume that a tissue-engineered bladder would avoid complications relating to the use of bowel and there would be no difference in mortality. Estimates will be required for the utility of avoiding use of bowel and the time over which the utilities for the treatments would differ.

A systematic review of the literature revealed no utility values for patients following a cystoplasty using bowel. Due to the complex nature of the problem, we obtained the health utility from urologists using the time trade-off (TTO) method (see box 3). The utility value relating to the use of bowel in cystoplasty was 0.95. We assume the improvement in clinical benefit will last for the remainder of the patient's life. The average age of presentation of this condition is 72 years. We assume that the duration of the improvement to be an average of 10 years.

The effectiveness gap was: 1 – 0.96 = 0.04, and the maxΔ QALY of: 10 x 0.04 = 0.4

3. Headroom Analysis

The headroom is calculated using: maxΔCost = WTP threshold x maxΔQALY. Thus, £30,000 x 0.4 = £12,000 per patient treated.

However, this does not take into account savings in hospital bed days by avoiding bowel surgery of £1,268 per patient (based on a hospital bed day cost of £317 (Department of Health national average cost of excess bed day) and a mean saving of 4 hospital bed days).
Headroom is hence £13,268 per patient treated.

4. Conclusion

The headroom for TE bladders has been optimistically estimated at around £16,000 over and above the cost of ileocystoplasty. The industry experts we consulted were optimistic that this was a potentially viable price. However, profit would be volume dependent and in this case, market size may not be large enough.

4. Return on Investment

For technologies that appear to have headroom, continuing development and investment would appear to be justified. At this stage we focus on whether or not the technology has the potential to succeed once brought to market. Return on investment may be affected by the rarity of a condition or because it occurs, only in economies unable to support high cost remedies.

The revenue that can be generated is a function of the headroom, the likely cost and volumes (see equation 4). The expected profit should also be discounted over a time horizon chosen to reflect the company strategy.

Equation 4: Revenue = (max ΔCost – C') x Volume

Where, max ΔCost is the headroom, C' is the expected cost of goods and volume is expected sales.

For example, in the case of tissue-engineered bladder, the return on investment is estimated as £4 million. This is assuming each device costs £8,000 and there are 500 cases per year.

R = (£16,000 – £8,000) x 500 = £4,000,000

Conclusion

The framework discussed here provides a structure for investment decisions. The headroom analysis is useful as a barrier to misguidedly investing in those devices, which can never be cost- effective. If there is little or no chance the technology could be marketed at a price that would keep the maximum incremental cost below the threshold (i.e. at the maxΔcost or below) then the technology should not attract further investment.

Following the headroom analysis, two further possibilities exist:

1. The investor can make an intuitive decision to invest based on the outcome of the headroom method.

2. The investor can perform more formal value of investment analysis (see figure 1, involving the testing of Bayesian probability (discussed in another paper[5]).

As research and development progresses, it is important to update estimates of costs and effectiveness and recalculate the headroom. Continual economic assessment at various stages of the development cycle will enable more accurate predictions of a product's cost-effectiveness and hence of its market potential[12;13]. It should be noted that the value of applying these methods at the supply

side is dependent on the planned technologies being aimed at the third party payer (an organisation other than the patient (first party) or health care provider (second party) involved in the financing of personal health services).

As development progresses and nears market, further difficulties can arise. Some of these are discussed briefly below.

i. Uncertainties – a major barrier to the adoption of technology is the requirement to provide sufficient evidence of effectiveness. Evidence on the effectiveness of a technology should ideally come from randomised control trials.

ii. Silo budgets – silo budgeting is a major barrier to the adoption of technology. The segmentation of the delivery of healthcare by departments means you have to provide an economic argument for a single department. This is often very difficult, because while the cost may lie in one department, the benefit is accrued in another. For example, less invasive surgery may increase cost in the operating theatre, yet the benefit and cost saving is made on the ward. Ultimately a more joined-up system is required[14].

iii. Business strategy – some products will aim at more than on application e.g. bone morphogenic proteins. Each application may have a different ICER and headroom. Furthermore, the first application might not necessarily be the 'big one'.

Related Articles

It is worth mentioning that there is another tool[15], devised by the MATCH group at University of Nottingham (www.nottingham.ac.uk/match), which has been developed for the assessment of cost effectiveness of medical devices. This tool is a software model based on a decision tree. The aim is to give a quick estimation of cost-effectiveness and to preserve core data while reducing the burden of data collection. The decision tree does not aim to capture every possible outcome. It is a simplified representation of the treatment pathways being considered so is based on several assumptions (as is the headroom method). For further information see the website above or contact the team at match@nottingham.ac.uk.

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Appendix 2: Search Strings used in Chapter 4

2.1 Urethral Applications

Search	Database	Term	Yield
1	Medline	Common conditions of the urethra	6
2	Medline	Urethral strictures	180
3	Medline	Problems buccal mucosa in urethra	8
4	Medline	Hypospadias Problems	151
5	Medline	Hypospadias surgery	2167
6	Medline	Epispadias buccal mucosa	10
7	Medline	Epispadias surgery techniques	95
8	Medline	Quality of life economics urethra	2
9	Medline	Quality of Life urethra	2
10	Medline	Quality of life urethral strictures	18
11	Medline	Health economics urethra	2
12	Medline	Health economics urethral strictures	1
13	Medline	Health economic urethra	17
14	Medline	Health economic hypospadias	3
15	Medline	Economic hypospadias	10
16	Medline	Quality of life Hypospadias	4
17	Medline	QoL hypospadias	0
18	Medline	Epispadias Quality of life	7
19	Medline	Cost of urethra	182
20	Medline	cost of stricture	144
21	Google Scholar	Quality of life economics urethral strictures	34
22	Google Scholar	Quality of life urethral strictures	788
23	Medline	Quality of life lower urinary tract	459
24	Medline	Quality of life urethroplasty	5
25	Medline	Quality of life free graft	0
26	Medline	Cost of hypospadias	15
27	Medline	cost of epispadias	0
28	Google Scholar	cost of epispadias	124
29	Google Scholar	economic cost of epispadias	27
30	Google Scholar	Health economic urethra	1280
31	Medline	Economic cost of epispadias	0
32	Google Scholar	health economics urethral strictures	43
33	Google Scholar	health economics hypospadias	73
34	Google Scholar	quality of life hypospadias	1140
35	Google Scholar	QoL hypospadias	36
36	Google Scholar	Epispadias Quality of life	243
37	Google Scholar	Cost of urethra	3990
38	Google Scholar	cost of stricture	5450
39	Google Scholar	Quality of life urethroplasty	217
40	Google Scholar	Quality of life urethra free graft	482
41	Google Scholar	Cost of hypospadias	644
42	Google Scholar	Quality of life buccal mucosa	1600
43	Medline	Quality of life buccal mucosa	83
44	Medline	Quality of life economics urethra	2

45	Medline	Quality of Life urethra	2
46	Medline	Quality of life urethral strictures	18
47	Medline	Health economics urethra	2
48	Medline	Health economics urethral strictures	1
49	Medline	Health economic urethra	17
50	Medline	Health economic hypospadias	3
51	Medline	Economic hypospadias	10
52	Medline	Quality of life Hypospadias	4
53	Medline	QoL hypospadias	0
54	Medline	Epispadias Quality of life	7
55	Medline	Cost of urethra	182
56	Medline	cost of stricture	144
57	Google Scholar	Quality of life economics urethral strictures	34
58	Google Scholar	Quality of life urethral strictures	788
59	Medline	Quality of life lower urinary tract	459
60	Medline	Quality of life urethroplasty	5
61	Medline	Quality of life free graft	0
62	Medline	Cost of hypospadias	15
63	Medline	cost of epispadias	0
64	Google Scholar	cost of epispadias	124
65	Google Scholar	economic cost of epispadias	27
66	Google Scholar	Health economic urethra	1280
67	Medline	Economic cost of epispadias	0
68	Google Scholar	health economics urethral strictures	43
69	Google Scholar	health economics hypospadias	73
70	Google Scholar	quality of life hypospadias	1140
71	Google Scholar	QoL hypospadias	36
72	Google Scholar	Epispadias Quality of life	243
73	Google Scholar	Cost of urethra	3990
74	Google Scholar	cost of stricture	5450
75	Google Scholar	Quality of life urethroplasty	217
76	Google Scholar	Quality of life urethra free graft	482
77	Google Scholar	Cost of hypospadias	644
78	Google Scholar	Quality of life buccal mucosa	1600
79	Medline	Quality of life buccal mucosa	83

2.2 Bladder Applications

Search	Database	Term	Yield
1	Medline	Bladder cancer epidemiology	4424
2	Google scholar	Radical cystectomy	5640
3	Medline	Radical cystectomy (reviews only)	318
4	Medline	Partial cystectomy	936
5	Google scholar	Bladder cancer	237000
6	Google scholar	Bladder augmentation	6520
7	Medline	Bladder augmentation	1098
8	Medline	Ileocystoplasty (reviews only)	13
9	Medline	crab ileocystoplasty	0
10	Medline	Irritable bladder number (reviews only)	14
11	Google scholar	Irritable bladder "bladder augmentation"	24
12	Medline	Irritable bladder "bladder augmentation"	0
13	Google scholar	Post "bladder cancer" "bladder augmentation"	93
14	Google scholar	"Irritable bladder"	305
15	Medline	"Irritable bladder"	74
16	Medline	Overactive bladder symptoms and treatment	930
17	Medline	Overactive bladder calm cystoplasty	12
18	Medline	Cystoplasty overactive bladder	12
19	Google scholar	Neurologic bladder "bladder augmentation"	126
20	Google scholar	Cloacal exstrophy "bladder augmentation"	161
21	Medline	Cloacal exstrophy "bladder augmentation"	26
22	Google scholar	Post Irritable bladder "bladder augmentation"	13
23	Medline	Complications AND cystoplasty	304
24	Medline	Complications AND cystectomy	280
25	Google scholar	Complications AND cystectomy AND Partial cystectomy	1700

Appendix 3: Quality of Life Elicitation Questionnaire for Cystoplasty and Urethroplasty

Questionnaire 1: Cystoplasty using Bowel

Augmentation ileocystoplasty is a surgical procedure that seeks to increase the capacity of the bladder by suturing a folded segment of the patient's bowel around an incision of the bladder. It is used after an excision of the bladder, especially when the trigone has been spared.

We would appreciate your help in estimating what quality of life people associate with the complications arising from this procedure. We are working on a tissue-engineering project and need this information in order to estimate the potential benefit from such an approach. This in turn will help us work out whether such an approach could ever be a cost-effective solution. To do this analysis we require the quantity of life-years and amount of money that an informed person would be willing to trade in order to avoid having to suffer the complications.

The side effects of the operation are:

Stones – these can be painful and require surgical treatment before they become too large

Mucus – the bowel naturally produces mucus, which in the bladder can lead to Urinary Tract Infection (UTI). This can cause a frequent urge to urinate and a painful, burning feeling in the area of the bladder or urethra during urination

Metabolic disturbance – serum acidosis can develop, leading to weakness, fatigue and thirst

Diarrhoea

We would like you to imagine that you were about to have the procedure. Taking into account your knowledge of how likely, these problems are and how seriously they affect patients on average, we would like your estimation of how much you would be prepared to forgo in order to avoid experiencing the morbidity arising from an ileocystoplasty.

The Questionnaire

How familiar were you with the augmentation cystoplasty operation described, where 1 is “not at all”, and 5 is “extremely well”?

1 2 3 4 5

Question 1: The Time Trade-Off Method

In the Time Trade-Off (TTO) method, you are asked the maximum amount of life you would be willing to trade, as a patient, out of your remaining lifespan, in return for avoiding the restrictions and effects of a condition. The trade off can be any period of time up to the maximum, e.g. no time, 1-day or 1 year. For example, your maximum life span might be a further 10 years, but during that time you would be suffering from blindness. You might therefore be willing to trade 9 of those years to live a perfectly healthy life for the time remaining, in this case 1 year.

Were you already familiar with the TTO method, where 1 is “not at all”, and 5 is “extremely well”?

1 2 3 4 5

Now assume that your remaining life span is 10 years. You can either have the condition described in scenario 1 for all those 10 years, or perfect health for a shorter period of time.

What is the maximum amount of time you would be willing to trade of those 10 years to have a perfect quality of life, instead of suffering from the complications outlined on the explanation sheet? Please specify in days, weeks, months, or years. _____

You may optionally provide us with any comments you have on why you responded thus.

Question 2: The Cost-Benefit Method

In this method, you must consider the benefits of using an alternative treatment and decide how much you would pay to receive those benefits. For example, in the case of avoiding blindness for a remaining lifespan of 10 years, you might be willing to pay £25,000.

Were you already familiar with the Cost-Benefit method, where 1 is “not at all”, and 5 is “extremely well”.

1 2 3 4 5

Now assume you are suffering from the symptoms described on the explanation sheet. You can either have the condition described on the explanation sheet for six months, or perfect health for six months.

How much money would you be willing to pay to have a perfect quality of life, instead of the condition outlined? _____

You may optionally provide us with any comments you have on why you responded thus.

Please select the category from below into which your personal (not household) yearly income falls. This is to assist us with the analysis of your response to question 5.

Under £10 000

£10 000 to £27 000

£ 27 000 to £40 000

£ 40 000 to £100 000

£100 000 or over

This is the end of the questionnaire. Thank you very much for your time.

Results: Cystoplasty using Bowel

The questionnaire was completed by urologists, working within the hospitals close to Birmingham University (identified through the NHS website). Four out of sixteen (25%) completed questionnaires were returned from the urologists. Two surgeons stated they did not wish to take part and although the others were followed up with phone calls, no other responses were received. As urologists were asked to complete the questionnaire it should be safe to assume that they would be familiar with the augmentation cystoplasty procedure and this was the case, with 3 out of 4 (75%) indicating '5' (extremely well) on the 5 point Lycart scale and the other indicating a '4'.

The time trade-off method

This part of the questionnaire asked participants to state how much time, out of a period of 10 years, they would be willing to sacrifice in order to forgo the effects of an augmentation cystoplasty procedure. The participants were also asked about their familiarity with the TTO approach. 2 out of 4 urologists had no knowledge of the TTO approach, with the other two indicating medium to good knowledge (recording results of '3' and '4' on the 5 point Lycart scale). It was difficult to draw any conclusions regarding correlation of the amount of time willing to trade against the familiarity of the TTO approach and against the familiarity with augmentation cystoplasty as the sample size was so small.

Using equation 1 the time traded was converted into utility scores. The summary statistics of the utility scores elicited from the TTO responses are shown in table 1. The mean utility for the period of maximum symptoms was calculated as 0.96 (95% CI: 0.94, 0.97) from four responses and will be used in the subsequent cost-effectiveness analysis in chapter 4.

Equation 1: QoL = 1 – (TTO ÷ t)

The cost benefit method

In this question participants were asked to state how much they would be willing to pay for a treatment that would avoid the clinical effects of augmentation cystoplasty. They were also asked about there familiarity with the cost-benefit approach. As with the previous section, it was difficult to draw any conclusions regarding correlation of the amount willing to pay against the familiarity of the cost benefit approach as the sample size was so small.

The summary statistics of the amount willingness to pay (WTP) elicited from the questionnaires are shown in table 1. The mean willingness to pay to avoid the period of maximum symptoms was calculated as £8,750 (95% CI: £1,400, £16,000) from four responses. The large confidence intervals are due to a small sample size. By combining the results of the above two questions, the mean WTP per QALY can be calculated as £9, 076 (95% CI: £1,603, £16,548) from four responses.

Table 1: Summary statistics for the clinical effects of ileocystoplasty

Statistic	Utility	WTP	WTP/QALY
N	4	4	4
Mean	0.96 (0.94, 0.97)	£8,750 (£1,400, £16,100)	£9,076 (£1,603, £16,548)
Median	0.95 (0.94, 0.96)	£5,000 (£0, £12,350)	£5,263 (£0, £12,730)
Minimum	0.95	£5,000	£5,263
Maximum	0.98	£20,000	£20,513
Standard Deviation	0.01	£7,500	£7,625

Questionnaire 2: Urethroplasty using Buccal Mucosa

Buccal mucosa is the skin which forms the inside lining of the mouth. It is extremely useful in treating certain diseases. The mucosa is surgically removed from the mouth, after which it can be used in a number of applications. We would appreciate your help in estimating how much people would be willing to sacrifice in life-years or money in over to avoid having to undergo the buccal mucosa donation.

The side effects of the donation are:

A degree of pain, comparable to a large and deep cut of the lip or cheek, but not to the extent that it would stop you sleeping.

Pain upon eating that would be bad enough to prevent consumption of particularly dry or hard food, but would in no way limit you to a liquid diet.

Your mouth would be slightly numb, comparable to the feeling of a weak dose of the local anaesthetic you may have had during dentistry, but without affecting taste or speech.

You would have slight difficulty opening your mouth, but not so much that it would prevent any desired actions.

There would be slight reduction in the ability to move your bottom lip.

These side effects would last continuously and would not diminish with time.

Considering these side effects, please complete the questionnaire which follows.

The Questionnaire

How familiar were you with the buccal mucosa donation previously described, where 1 is “not at all”, and 5 is “extremely well”? Please circle your response.

1 2 3 4 5

Question 1: The Time Trade-Off Method

In the Time Trade-Off (TTO) method, you are asked the maximum amount of life you would be willing to trade, as a patient, out of your remaining lifespan, in return for avoiding the restrictions and effects of a condition. The trade off can be any period of time up to the maximum, e.g. no time, 1 day or any time upwards. For example, your maximum life span might be a further 10 years, but during that time you would be suffering from blindness. You might therefore be willing to trade 9 of those years to live a perfectly healthy life for the time remaining, in this case 1 year.

Were you already familiar with the TTO method? Please circle your response, where 1 is “not at all”, and 5 is “extremely well”.

1 2 3 4 5

Now assume your remaining life span is 10 years. You can either have the condition described on the explanation sheet for all those 10 years, or perfect health for a shorter period of time. How much time would you be willing to trade to have a perfect quality of life, instead of having the condition outlined? Please specify in days, weeks, months, or years. _____

Comments:

Question 2: The Cost-Benefit Method

In this method, you must consider the benefits of using an alternative treatment and decide how much you would pay to receive those benefits. For example, in the case of avoiding blindness for a remaining lifespan of 10 years, you might be willing to pay £25,000.

Were you already familiar with the Cost-Benefit method? Please circle your response, where 1 is "not at all", and 5 is "extremely well".

1 2 3 4 5

Now assume you are suffering from the symptoms described on the explanation sheet. You can either have the condition described on the explanation sheet for six months, or perfect health for six months. How much money would you be willing to pay to have a perfect quality of life, instead of the condition outlined? _____

Please select from below the category into which your personal (not household) yearly income falls. This is to assist us with the analysis of your response.

Under £10 000

£10 000 to £27 000

£ 27 000 to £40 000

£ 40 000 to £100 000

£100 000 or over

Comments:

This is the end of the questionnaire. Thank you very much for your time.

Results: Urethroplasty Using Buccal Mucosa

The questionnaire was completed by individuals located within the public health building at the University of Birmingham, (unknown to those collecting the data) and from Birmingham city centre (outside Birmingham Central Library and New Street Station). In total 112 questionnaires were completed. Figure 1 shows the number of completed questionnaires categorised by place of completion. 80 of 112 (72%) questionnaires were completed from individuals located in Birmingham city centre. It could be hypothesised that these individuals would have less medical knowledge and may have less understanding of how the clinical effects would impact on quality of life. To investigate this hypothesis further I analysed the results of the first part of the questionnaire - familiarity with buccal mucosa donation – also by place. The respondents indicate their familiarity on a 5 point Lycart scale from 1 to 5, where 1 represented no familiarity and 5 represented very good familiarity. Of those interviewed in Birmingham city centre 79 of 81 individuals (97.6%) were not familiar with buccal mucosa donation procedure compared to 28 of 31 (90%) (Figure 2).

Figure 1: Number of completed questionnaires categorised by place of survey

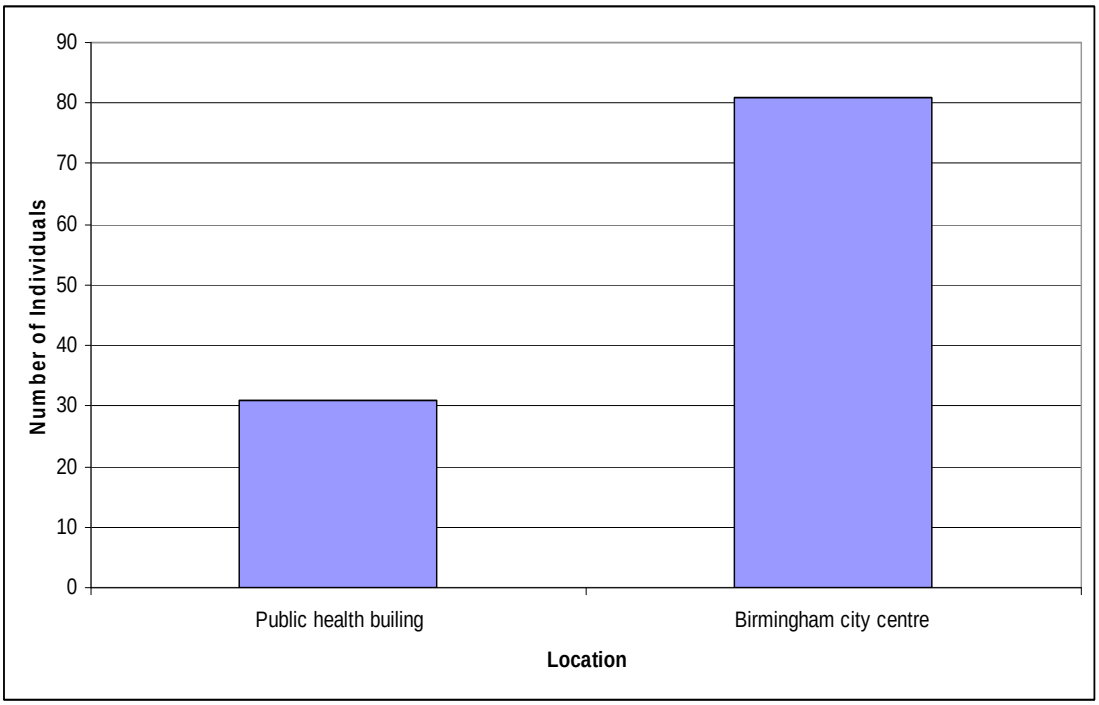
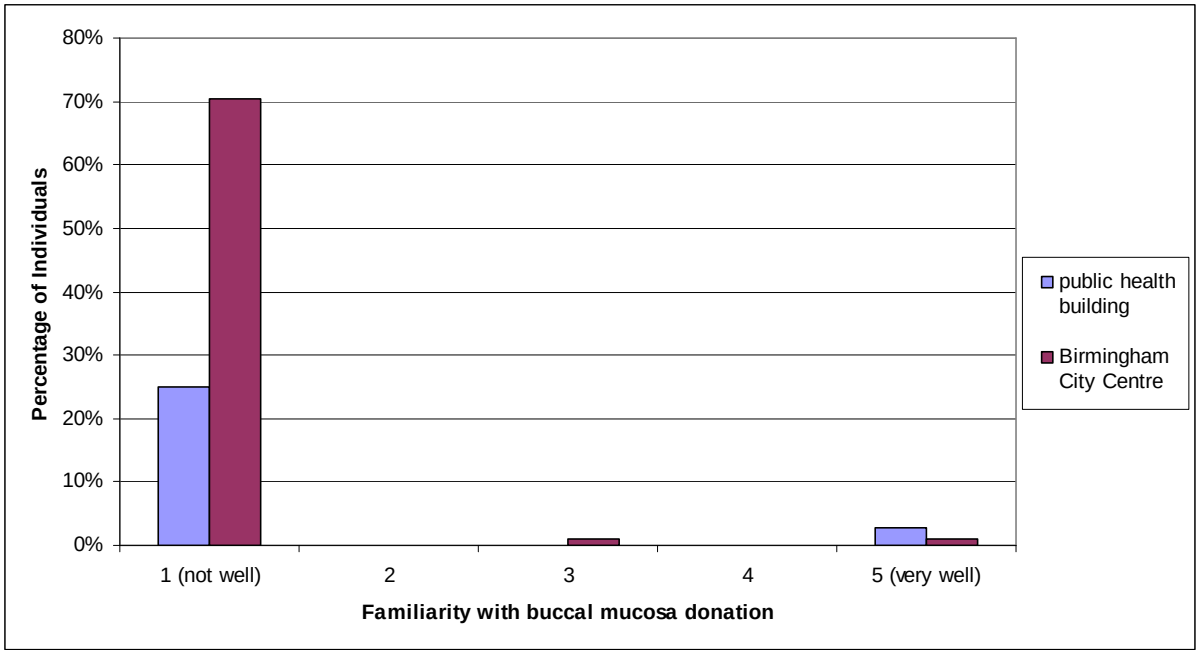


Figure 2: Familiarity with buccal mucosa donation categorised by place of survey



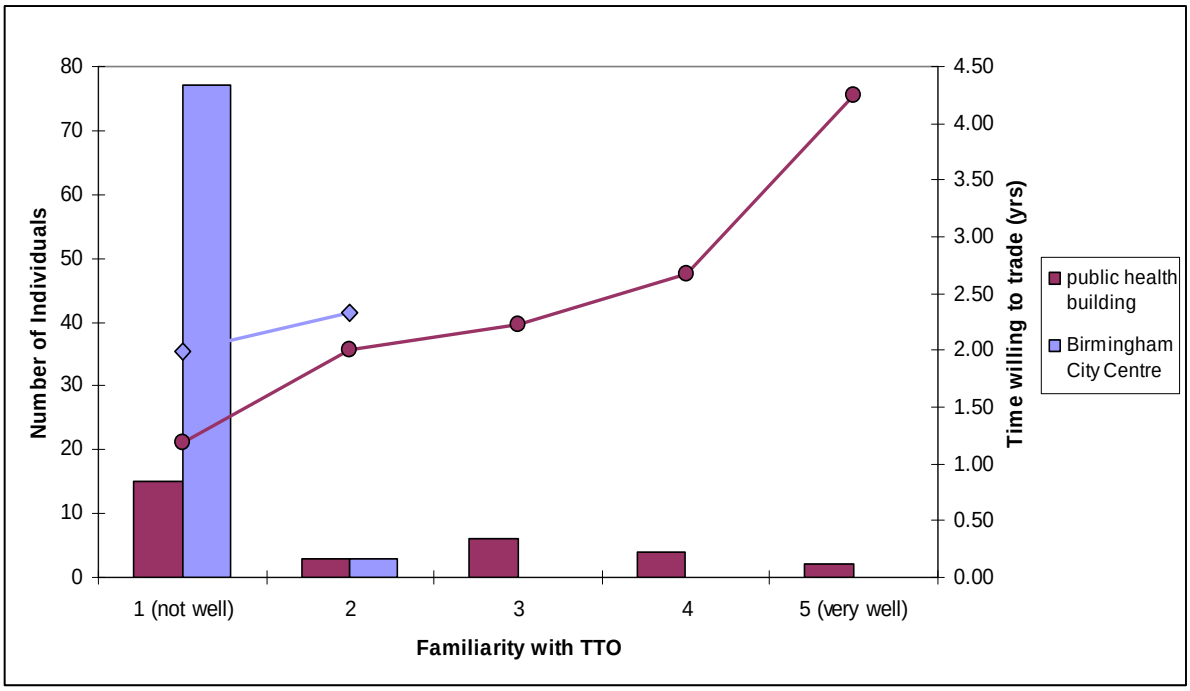
The time trade-off method

Of the 112 completed questionnaires, two (1.8%) did not provide a response to the TTO question. One of the individuals who did not answer this question said they "would not like to answer due to lack of knowledge about disease". The other individual offered no reason for not completing this part of the questionnaire.

This part of the questionnaire asked participants to state how much time, out of a period of 10 years, they would be willing to sacrifice in order to forgo the effects of buccal mucosa donation. The participants were also asked about there familiarity with the TTO approach. Once again I would expect that those interviewed from the public health building would be more familiar with this approach than those interviewed from Birmingham city centre. I found that 77 out of 80 patients (96%) interviewed in Birmingham city centre were not familiar with the TTO approach compared with 15 out of 30 (50%) interviewed from the public health building. I would have speculated that those who were more familiar with the TTO approach would have been willing to trade less time than those less familiar, but this was not the case, as is illustrated in figure 3. However, a comparison of time willing to trade versus

familiarity with buccal mucosa donation does show that those more familiar with buccal mucosa donation are willing to trade less, although, it is difficult to draw conclusions due to the very small numbers of individuals expressing a familiarity with buccal mucosa donation (figure 2).

Figure 3: Individual time willing to trade compared with familiarity of the TTO method categorised by place of survey



Using equation 1 the time traded was converted into utility scores. The distribution of the utility scores ranges from 0 to 1 and has a negative skew (see figure 4.5, chapter 4.7). The summary statistics of the utility scores elicited from the TTO responses are shown in table 2. I calculate the utility with and without the outliers identified in chapter 4.7. However I decide to select the final utility score based on all elicited values. The median utility for the period of maximum symptoms was calculated as 0.94 (95% CI: 0.89, 0.99) from 110 responses. This value will be used in the subsequent cost-effectiveness analysis in chapter 4.

Equation 2: QoL = 1 – (TTO ÷ t)

Table 2: Summary statistics for the clinical effects of urethroplasty using buccal mucosa

Summary Measure	Utility (With Outliers)	Utility (Without Outliers)
Sample Size	112	112
Missing data	2	11
Mean	0.81 (0.76, 0.86)	0.87 (0.84, 0.91)
Median	0.94 (0.89, 0.99)	0.98 (0.94, 1.0)
Minimum	0.0	0.5
Maximum	1.0	1.0
Standard Deviation	0.28	0.18

The cost benefit method

Of the 112 responses, 4 (3.6%) did not answer this question, 30 (26.8%) furnished a WTP value for avoiding the condition but refused to trade any life for the TTO question and 5 (4.5%) were willing to sacrifice some of their life expectancy but not to pay any money for the treatment. No reasons were given for none completion of this part of the questionnaire.

In this question participants were asked to state how much they would be willing to pay for a treatment that would avoid the clinical effects of urethroplasty using buccal mucosa. The participants were also asked about their familiarity with the cost-benefit approach, which they indicated on a 5 point Lycart scale. I found that 68 out of 78 patients (87%) interviewed in Birmingham city centre were not familiar with the cost-benefit approach compared with 9 out of 30 (30%) interviewed from the public health building. As with the TTO question, I expected those with a greater familiarity of this approach to express a lower WTP for an alternative treatment to urethroplasty using buccal mucosa. This is shown in figure 4. In this case I have not separated the results by place of survey due to small numbers in each of categories on the familiarity of cost-benefit approach Lycart scale. A comparison of time willing to trade versus familiarity with buccal mucosa donation does show that those more familiar with buccal mucosa donation are willing to trade less, although, it is difficult to draw conclusions due to the very small numbers of individuals expressing a familiarity with buccal mucosa donation. The effect of individual income on amount willing to pay is illustrated in figure 5. As I would have expected an increase in amount willing to pay as income increased. The summary statistics of the amount WTP

elicited from the questionnaires are shown in table 3. The mean WTP to avoid the period of maximum symptoms was calculated as £500 (95% CI: £0, £1,418) from 108 responses.

Figure 4: Overall individual WTP compared to familiarity of the cost-benefit method

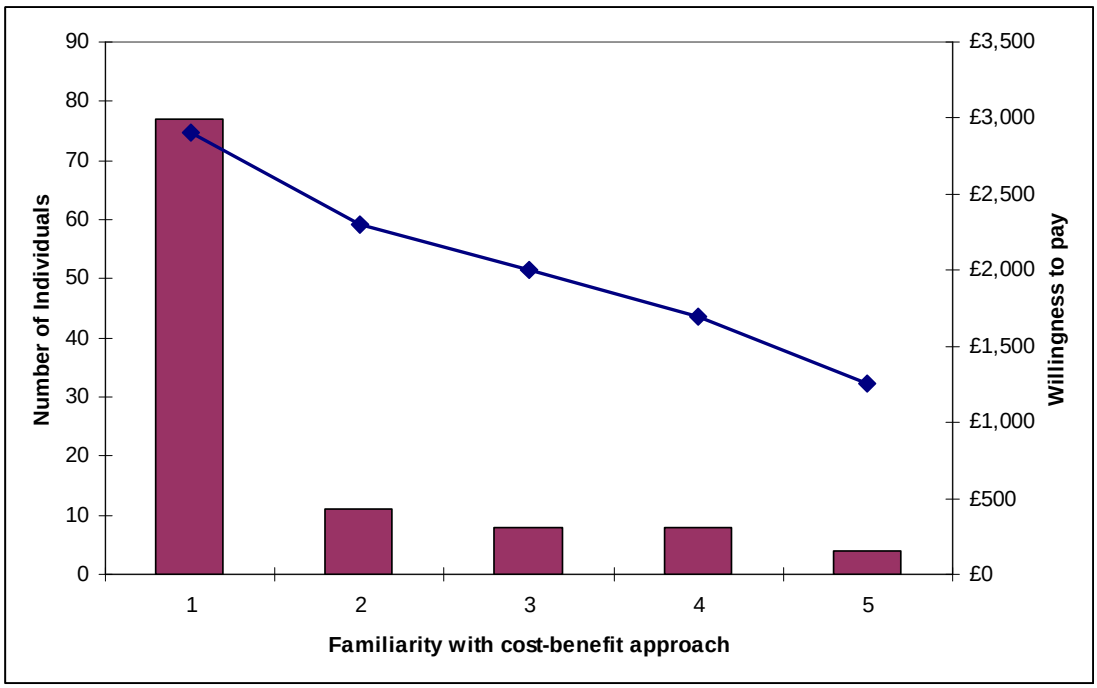
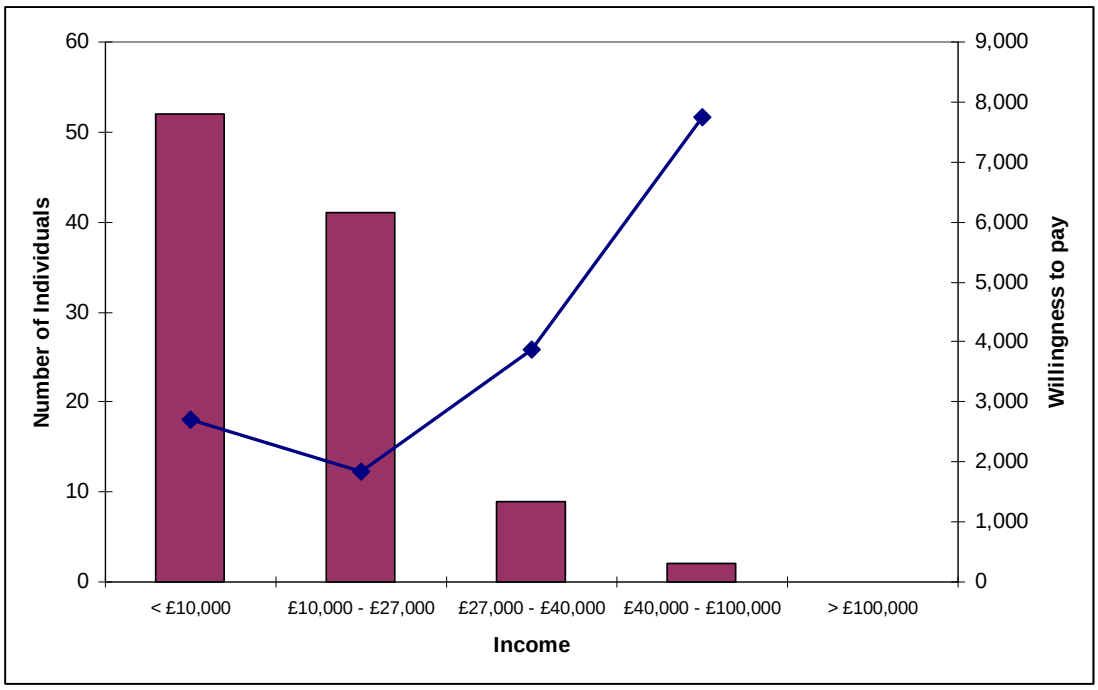


Figure 5: Individual WTP compared to personal income



I combined all the responses from the above two questions to assess whether the distribution of amount of time willing to trade and amount willing to trade compare. This is illustrated in figure 6. It can be seen from the figure that the responses are not perfectly correlated. However those willing to trade the most amount of life do correspond with those willing to pay the most amount of money. Finally, I calculate the mean WTP per QALY as £857 (95% CI: £0, £2,462) from 108 responses (table 3).

Figure 6: distribution of individual amount willing to trade versus amount willing to pay

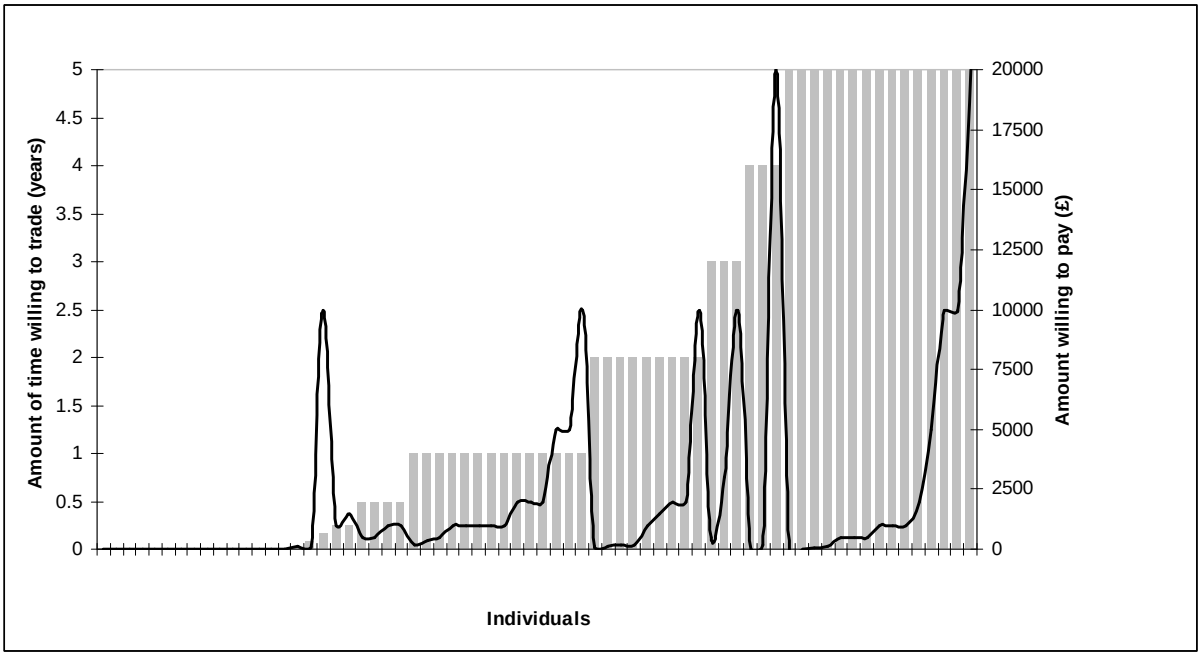


Table 3: Summary statistics for the clinical effects of urethroplasty using buccal mucosa

Measure	WTP	WTP per QALY
Sample Size	108	102
Missing data	4	10
Mean	£2,627 (£1,709, £3,545)	£3,930 (£2,326, £5,535)
Median	£500 (£0, £1,418)	£857 (£0, £2,462)
Minimum	£0	£0
Maximum	£30,000	£40,00
Standard Deviation	£4,867	£8,269

Appendix 4: Search Strings used in Chapter 5

Search	Database	Term	Yield
1.	PubMed	Abdominal wall defects	2054
2.	PubMed	1 AND management	301
3.	PubMed	1 AND Wound Management	260
4.	PubMed	1 AND management of open wound	11
5.	PubMed	Temporary closure of abdominal wall	87
6.	PubMed	3 AND temporary closure	20
7.	PubMed	3 AND 5	6
8.	PubMed	Mesh repair	3704
9.	PubMed	mesh versus non mesh repair	14
10.	PubMed	1 AND 8	236
11.	PubMed	3 AND 8	15
12.	PubMed	Hernia	40086
13.	PubMed	Abdominal wall defects AND Hernia	829
14.	PubMed	Abdominal wall repair AND 5	101
15.	PubMed	Abdominal wall repair AND 5 AND 8	60
16.	PubMed	Inguinal hernia	9978
17.	PubMed	Abdominal wall defects AND inguinal hernia	50
18.	PubMed	17 AND 8	15
19.	PubMed	16 AND cost analysis	226
20.	PubMed	16 AND Economic analysis	180
21.	PubMed	16 AND Quality of life	16
22.	PubMed	laparoscopic versus open hernia repair	121
23.	PubMed	16 AND 22	88
24.	PubMed	incisional hernia	1634
25.	PubMed	24 AND 8	505
26.	PubMed	24 AND biological OR synthetic mesh repair	279
27.	PubMed	24 AND cost analysis	23
28.	PubMed	24 AND economic analysis	18
29.	PubMed	24 AND laparoscopic versus open hernia repair	15
30.	PubMed	parastomal hernia	151
31.	PubMed	parastomal hernia AND mesh repair	65
32.	PubMed	Abdominal wall defect AND tissue necrosis	34
33.	PubMed	Abdominal wall defect AND gangrene	8
34.	PubMed	Fournier's gangrene	316
35.	PubMed	contaminated abdominal wall defects	40
36.	PubMed	omphalocele	3310
37.	PubMed	giant abdominal wall defects	56
38.	PubMed	omphalocele AND 8	74
39.	PubMed	giant abdominal wall defects AND 8	17
40.	PubMed	Cellular grafts	5190
41.	PubMed	Cellular grafts AND Abdominal wall defects	3
42.	PubMed	Acellular grafts	518
43.	PubMed	Acellular grafts AND Abdominal wall defects	5
44.	PubMed	AlloDerm	256
45.	PubMed	AlloDerm AND Abdominal wall defects	13

46.	PubMed	Permacol	46
47.	PubMed	Permacol AND Abdominal wall defects	6
48.	Cochrane	Hernia	1457
49.	Cochrane	Inguinal hernia	882
50.	Cochrane	Incisional hernia	136
51.	Cochrane	incisional hernia OR ventral hernia	167
52.	Cochrane	parastomal hernia	6
53.	Cochrane	laparoscopic versus Open hernia repair	53
54.	Cochrane	mesh versus non mesh repair	8
55.	Cochrane	incisional hernia OR ventral hernia	170
56.	Cochrane	incisional hernia AND ventral hernia	8
57.	Cochrane	incisional hernia OR ventral hernia AND Quality of life	128
58.	Cochrane	incisional hernia OR ventral hernia AND utilit*	128
59.	Cochrane	incisional hernia AND ventral hernia AND Quality of life	1
60.	Cochrane	incisional hernia AND ventral hernia AND utilit*	0

Appendix 5: Health State Questionnaire to Elicit Utility-Based Quality of Life associated with Abdominal Wall Defects

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Quality of life associated with abdominal wall defect repair: A questionnaire for key opinion leaders

We are based in the team of Professor Richard Lilford in public health at the University of Birmingham, UK. We are a partner in the EU STEPS (a systems approach to tissue engineering processes) project and our work is centred on the cost-effectiveness analysis of potential new tissue engineering products. Cost-effectiveness analysis aims to identify where more benefit can be produced at the same cost, or a lower cost can be achieved for the same benefit. Based on a decision-making philosophy, this analysis assumes the decision maker seeks to maximise achievements of a defined objective, by using a given budget.

We have been working in collaboration with a European medical technology company involved in Tissue Engineering to investigate the potential applications of a new generation, tissue engineered mesh. We have reviewed the epidemiology and current treatments of many abdominal wall defects and concluded that there is a potential gap in the market for a mesh that could be used when defects are large and infected. The next stage of the project requires us to estimate the potential benefit that could be gained from a new generation mesh compared to existing treatments. This new technology will be very expensive and it is necessary for the costs to be justified by an increase in benefit. Estimation of the potential benefit can be quantified by directly measuring preferences for a given health state using two approaches called time trade-off and willingness-to-pay.

We would appreciate your help in estimating the quality of life associated with complications arising from current treatment by completing the short questionnaire overleaf and returning it to me in the envelope provided.

We thank you in advance for your cooperation and greatly appreciate the time you have given us. If you have any questions or wish to discuss anything further please do to hesitate to ask one of the team here today or following the conference contact Helen McAteer on the number below. All questionnaires will be anonymous.

Public Health, Epidemiology and Biostatistics, School of Health and Population Sciences,
University of Birmingham, Edgbaston, B15 2TT
Tel: 0121 414 8465 Email: hlm569@bham.ac.uk

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Before completing the time trade-off (page 3) and the willingness-to-pay (page 4) questions please could you answer the five short questions below (please tick where applicable):

1. What is your gender?

Male	☐
Female	☐

2. What is your age group?

<30 years	☐
31 – 40 years	☐
41 – 50 years	☐
51 – 60 years	☐
> 61 years	☐

3. How many years have you been a surgeon?

<10 years	☐
11 – 20 years	☐
21 – 30 years	☐
31 – 40 years	☐
> 41 years	☐

4. Have you used an acellular mesh in the past?

Yes	☐
No	☐

5. If yes, which meshes have you used?

Porcine dermal collagen (e.g. Permacol)	☐
Acellular dermal matrix (e.g. AlloDerm)	☐
Porcine small intestine submucosa (e.g. Surgisis)	☐
Other (please specify)	☐
Don't Know	☐

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In the following questions we ask you to **imagine that you are the patient**.

We would like you to imagine that you (as a patient) have had an incisional hernia repaired using a synthetic mesh. The mesh became infected (for whatever reason, the detail of which is not necessary here), and therefore has been removed. We envisage two possible scenarios for further treatment:

Scenario 1: The open wound infection is treated and the wound is kept open for 3 – 6 months before the patient can undergo second surgery to close the defect. Patient recovery is slow and closure of defect is complex. Ongoing medical attention is required.

Scenario 2: The open wound infection is treated and wound is closed after 3 – 7 days using a new generation cellular mesh. This speeds up patient recovery and reduces treatment management time to around 1 month.

Using your knowledge of the repair of infected abdominal wall defects and the effect this has on the patient we would like you to answer the following two questions.

1. Time Trade-off (TTO)

In the time trade-off (TTO) approach you are being asked the maximum amount of life you would be willing to trade, as a patient, out of your remaining lifespan, in return for avoiding the effects of a condition for the rest of your life. The trade-off can be any period of time up to the maximum stated.

Imagine you have 10 years of remaining life. You could experience an open abdominal wall defect requiring regular medical attention for 10 years followed by death or you could experience perfect health for a period of time less than 10 years followed by death.

How many days, weeks, months or years would you be willing to forgo in order to have a treatment that would avoid an open abdominal wall defect and give you perfect health?
Answer:

Any additional comments:

P.T.O

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2. Willingness-to-pay (WTP)

In the WTP approach you are asked how much money you are willing to pay to avoid the effects of a condition for the rest of your life. One way of measuring value is to ask you what you would be prepared to give up to receive this treatment i.e. how much money you would be willing to pay for it. Of course, if this treatment did come into existence then it would be provided free by the NHS. We also believe that people should not have to pay for health care. This is simply a method of measuring how strongly you feel about having this treatment in place and how much you would value such a treatment.

Imagine you have 10 years of remaining life. You could experience an open abdominal wall defect requiring regular medical attention for 10 years followed by death or you could experience perfect health for a period of time less than 10 years followed by death.

How much money would you be willing to pay for a treatment that would avoid an open abdominal wall defect and give you perfect health?
Answer:

To assist us with the analysis of these results could you please estimate the annual income of your household before deducting tax and national insurance?

<£70,000	
£70,001 - £90,000	
£90,001 – £110,000	
£110,001 - £130,000	
£130,001 - £150,000	
> £150,001	

Any additional comments:

- End of questionnaire -

Thank you

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Quality of life associated with abdominal wall defect repair: Results

Preliminary analysis

Population

The questionnaire was completed by 54 healthcare professionals, comprising of: 37 Consultants, 8 Trainees, 5 Nurses, 3 Registrars and 1 Senior Registrar. It was calculated that of those that had completed the questionnaire; 44 (81%) were male and 10 (19%) were female. The distribution of healthcare professionals whom completed the questionnaire is illustrated in figure 1.

Age

Twenty-one of fifty-three (39%) respondents were aged between 31 and 40 years, 28% were aged between 41 and 50 years, with 17% being aged between 51 and 60 years. Only 11% were aged below 30 years; and those that were aged over 61 years made up the smallest proportion consisting of just 4%. This information is illustrated in figure 2.

Number of years experience as a surgeon

The majority of the healthcare professionals (39%) had between 11 and 20 years experience as a surgeon, 35% had had less than 10 years experience and 22% had between 21 and 30 years of experience. Both the 31 to 40 years and above 41 years of experience categories had the same number of clinicians (2%). This is illustrated in figure 3.

Meshes

Forty-three of fifty-four (80%) respondents stated that they had used an acellular mesh in the past. Of those that had used an acellular mesh some had used more than one type. A result of 38 of 56 (68%) had used Permacol, 23% had used Surgisis, 4% had used AlloDerm, 4% had used another mesh and 2% did not know exactly which mesh they had used. These results are illustrated in figure 4.

Figure 1: Distribution of healthcare professionals whom completed questionnaire

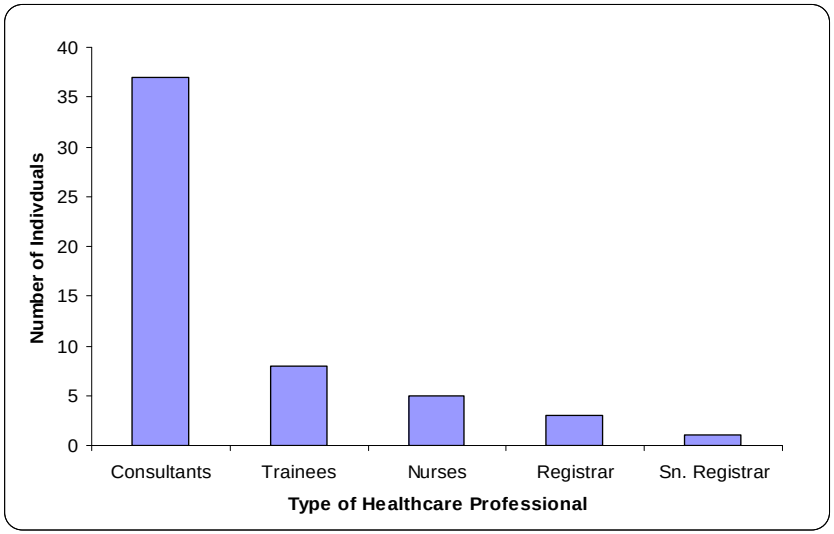


Figure 2: Age distribution of healthcare professionals

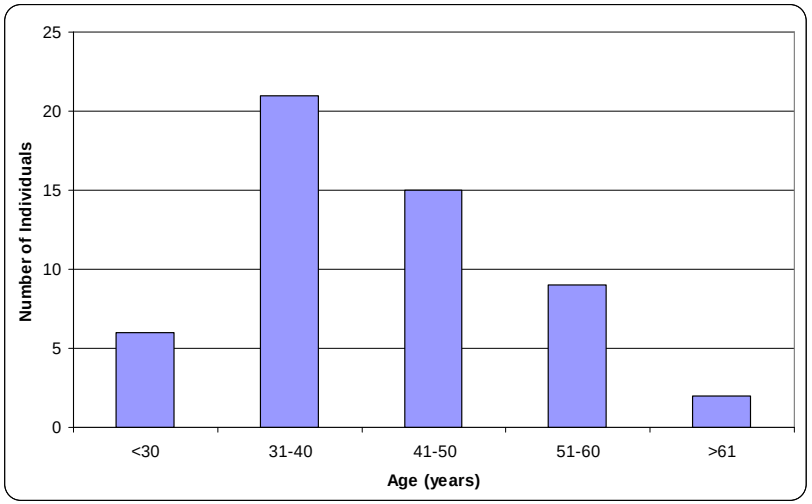


Figure 3: distribution of years of experience of healthcare professionals

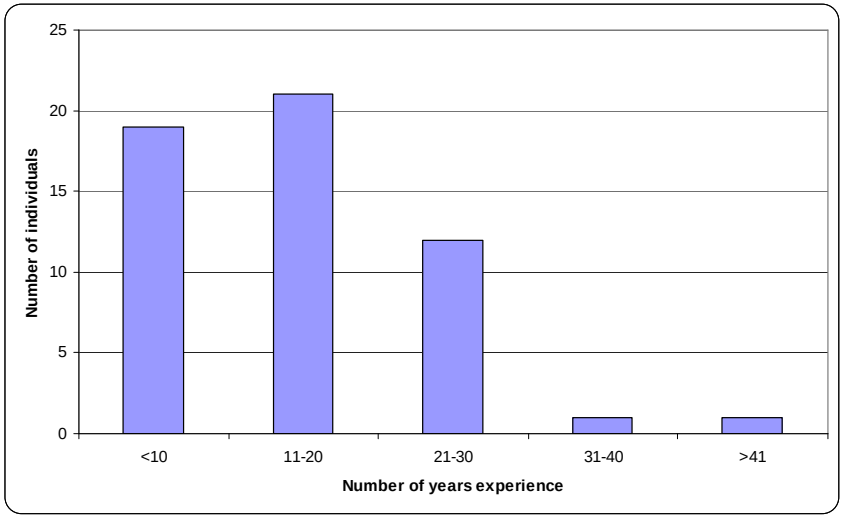
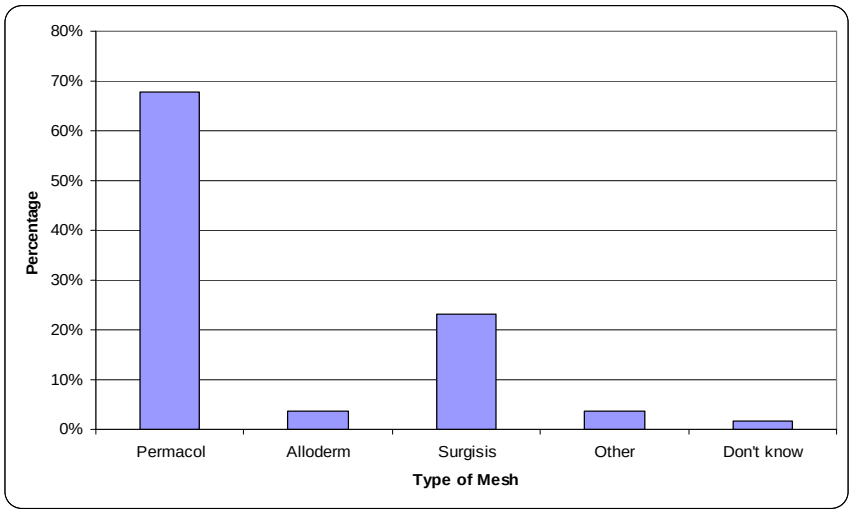


Figure 4: distribution of the different types of meshes used by the clinicians



Analysis of time trade-off question

Of the 54 completed questionnaires, 50 (93%) had satisfactorily answered this question. The general feedback received from the healthcare professions upon answering this question was that there are a variety of factors (including social/family circumstances, level of symptoms, site and size of defect, co-morbidity of problem and degree of problem with infection) that need to be considered before any reasonable judgment can be established; hence it was a difficult question to answer.

Of those that had adequately completed this question it was found that consultants would be prepared to trade the most amount of time, equating to an average of 1.7 years. Nurses were willing to forgo 1.4 years, and trainees 1.1 years on average. Senior Registrars and Registrars were prepared to forgo the least amount of time, 0.13 and 0.09 years respectively. The overall average time trade-off across all 50 healthcare professionals was calculated as 1.47 years.

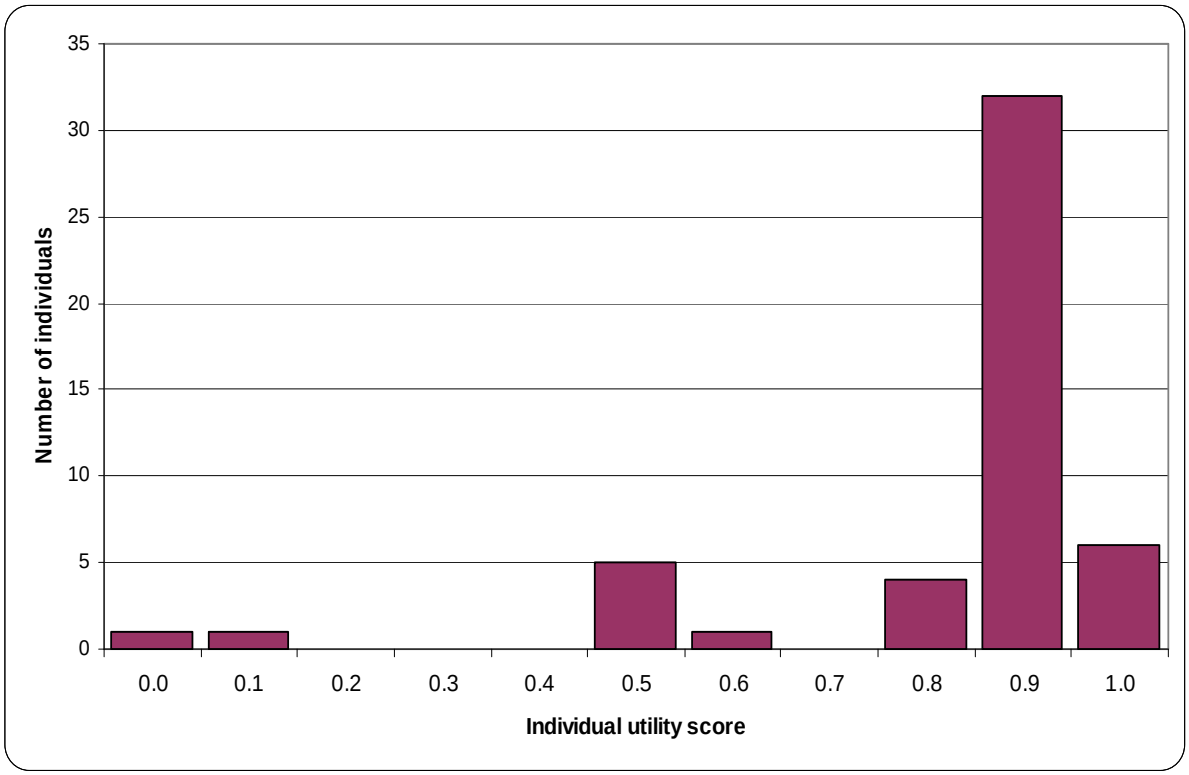
Using equation 1 the time traded was converted into utility scores. The distribution of the utility scores ranges from 0 to 1, has a negative skew and a modal utility score of 0.9 (figure 5). The summary statistics of the utility scores elicited from the TTO responses are shown in table 1. The mean utility for the period of maximum symptoms was calculated as 0.85 (95% CI: 0.79, 0.91) from four responses and will be used in the subsequent cost-effectiveness analysis in chapter 4.

Equation 1: $QoL = 1 - (TTO \div t)$

Table 1: Summary statistics for the clinical effects of incisional hernia repair

Statistic	Utility
Sample Size	50
Missing Data	4
Mean	0.85 (0.79,0.91)
Median	0.94 (0.88, 1.0)
Minimum	0
Maximum	1.0
Standard Deviation	0.22

Figure 5: Distribution of utility scores



Analysis of willingness to pay question

Of the 54 completed questionnaires, 44 (81%) had satisfactorily answered this question. Again the general feedback received from the healthcare professions upon answering this question was that it was a difficult question to answer. As a result 13% completely failed to answer this question and 6% gave an answer which was too vague to convert into a certain sum of money for example; “a few months”, “all my money” and “as much as it takes”.

Of those whom answered this question, 64% (28 of 44) of healthcare professionals stated that they would be prepared to pay between £1,001 and £10,000 for the new treatment. Fourteen percent would be willing to pay in excess of £20,001, 11% would pay between £10,001 and £15,000; and just 7% stated they would pay between £15,001 and £20,000. Only 5% were willing to pay between £500 and £1000. These findings are shown in figure 6.

Figure 6: Distribution of amount healthcare professionals are willing to pay for new treatment

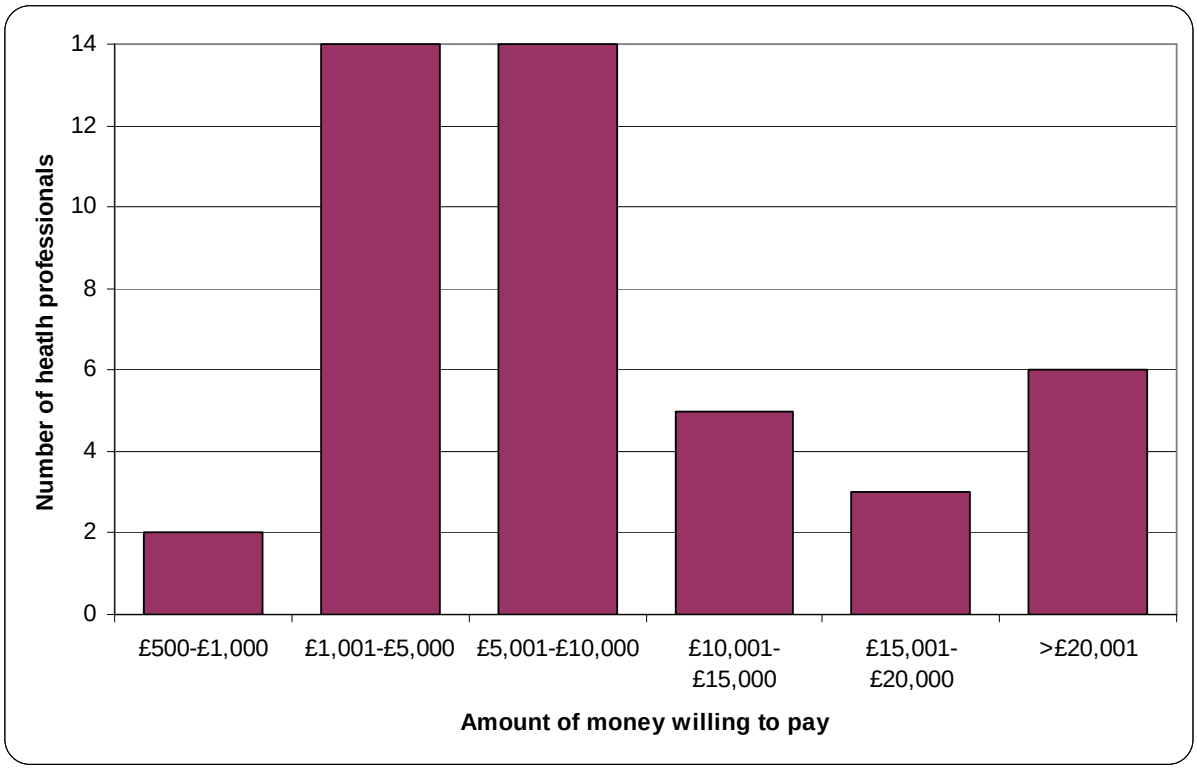
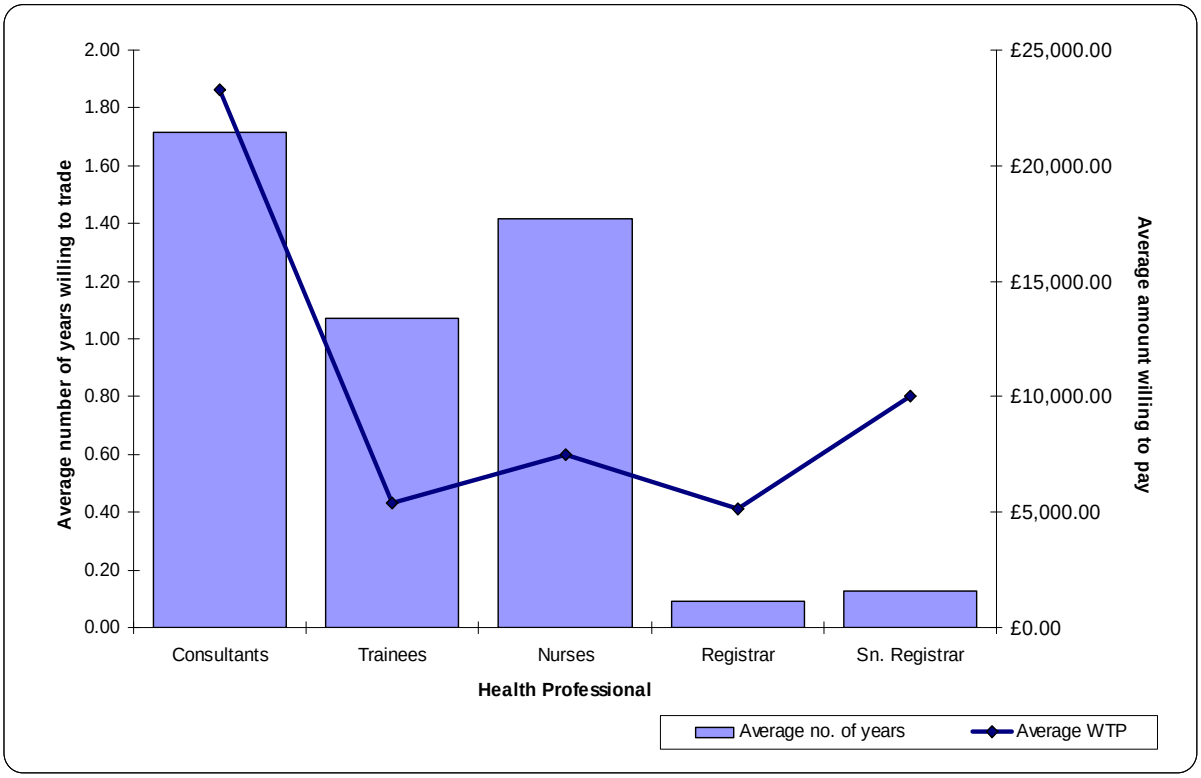


Figure 7: Distribution of amount healthcare professionals are willing to pay for a new treatment



A comparison of willingness to pay between the five categories was also made. On average the consultants were willing to pay the most amount of money for a new treatment (£23,317) and nurses willing to pay the second highest amount (£7,500). On average, Senior Registrars were willing on to pay £10,000 and Trainees £5,375. Registrars were willing to pay the least amount for the new treatment (£5,167). Figure 7 illustrates the average amount willing to pay and the average amount of life years willing to trade for each of the five categories.

Upon analysis of the answer to this question we encountered one potential anomalous result, with one professional stating a WTP figure of £250,000. The discussion of this anomalous result as well as its impact upon the overall findings can be found within *the willingness-to-pay for consultants only* section below. The overall average amount one would be willing to pay across all professions was calculated to be £18,611.29 (inclusive of the anomalous result) and £13,230.15 (omission of the anomalous result). The full summary statistics regarding the amount the respondents were WTP (with and without the outlier) is shown in table 2.

Table 2: Summary statistics for the clinical effects of incisional hernia repair

Statistic	WTP (with outlier)	WTP (without outlier)	WTP/QALY (with outlier)	WTP/QALY (without outlier)
Sample Size	44	43	42	42
Missing Data	10	11	12	12
Mean	£18,611 (£7,374, £29,848)	£13,230 (£9,262, £17,198)	£32,475 (£7,853, £57,096)	£21,072 (£10,485, £31,658)
Median	£10,000 (£1,237, £21,237)	£10,000 (£6,032, £13,968)	£10,256 (£0, £34,878)	£10,256 (£0, £20,843)
Minimum	£500	£500	£501	£501
Maximum	£250,000	£50,000	£500,000	£200,000
Standard Deviation	£38,029	£13,275	£81,414	£34,585

Analysis of the outlier

Upon taking into account the consultants income, and then calculating the average a consultant would be willing to pay for each income band; the subsequent result was that those who were in the lowest

income band (£<70,000) were willing, on average, to pay the most amount of money (£59,063). The £110,001-£130,000 band was willing to pay the second highest amount, an average of £26,667, followed by the £130,001-£150,000 band, willing to pay £16,667. In the highest income band (>£150,000), the average amount a consultant was willing to pay equated to just £14,571; whereas in the second to lowest band (£70,001-£90,000) the average amount was calculated to be £14,354. Finally in the £90,001-£110,000 band, the average amount a consultant would pay for this new treatment was £10,800. This resulted in a surprising downward trend (figure 8) illustrating the fact that, the greater the annual income, the lower the amount of money a consultant would be willing to pay for this new treatment. The overall average amount a consultant would be willing to pay for the new treatment was calculated to be £23,317.

However, a point to note is that in the lowest band category (<£70,000) there was one consultant who had stated that they would pay £250,000 for a new treatment; which was a relatively extortionate amount of money considering all other consultants stated a figure of less than £51,000. This affected the results drastically and had upset the overall trend. A new chart was implemented in order to show what the results and trends would have been like, if this excessive amount of money had been omitted (figure 9). The result of this omission was that the trend had changed from being a downward trend i.e. the greater the annual income, the lower the amount of money a consultant would be willing to pay for this treatment; to an upward trend i.e. the greater the annual income, the greater the amount of money a consultant would be willing to pay for this treatment. The overall average amount a consultant would be willing to pay for the new treatment, excluding this anomaly, was calculated to be £16,005, which is £7,312 less than the average calculated in the previous section.

This pattern can also be seen when all the WTP data form the healthcare professionals are plotted against income band. Figure 10 shows the amount all the healthcare professionals were willing to pay to based on income, including the outlier. From this graph it appears that those in the lower income band appear are willing to pay more for the new treatment. However figure 11 shows the same distribution excluding the outlier and here the line of best fit indicates that the amount willing to pay for the new treatment increases as income increases, as would be expected.

Figure 8: Average amount a consultant would pay for a new treatment dependent on their annual income

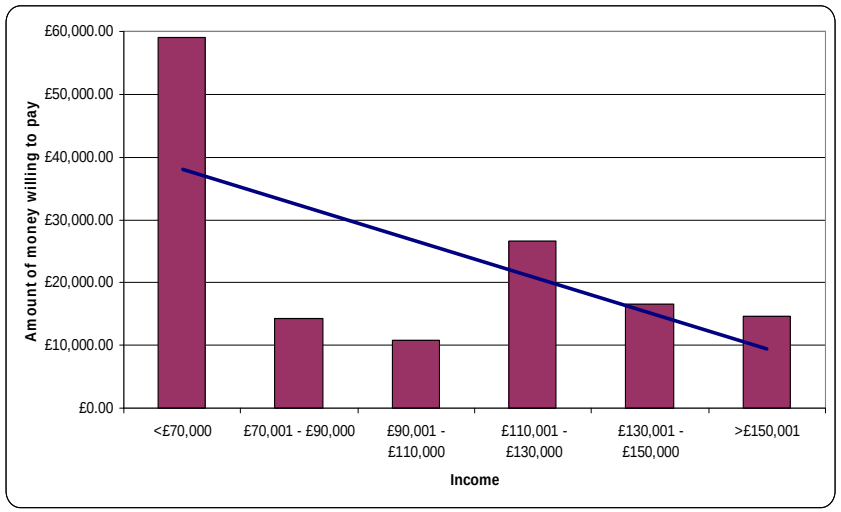


Figure 9: average amount a consultant would pay for a new treatment dependent on their annual income, excluding outlier

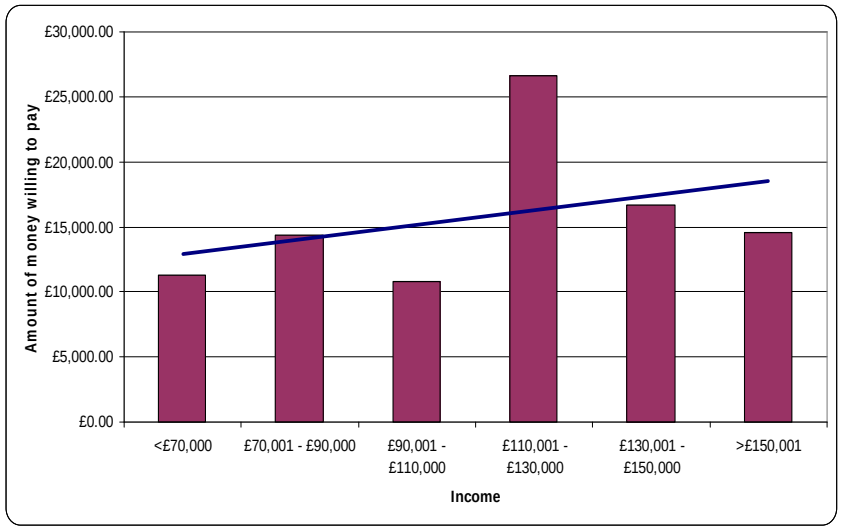


Figure 10: Amount willing to pay categorised by income (including outlier)

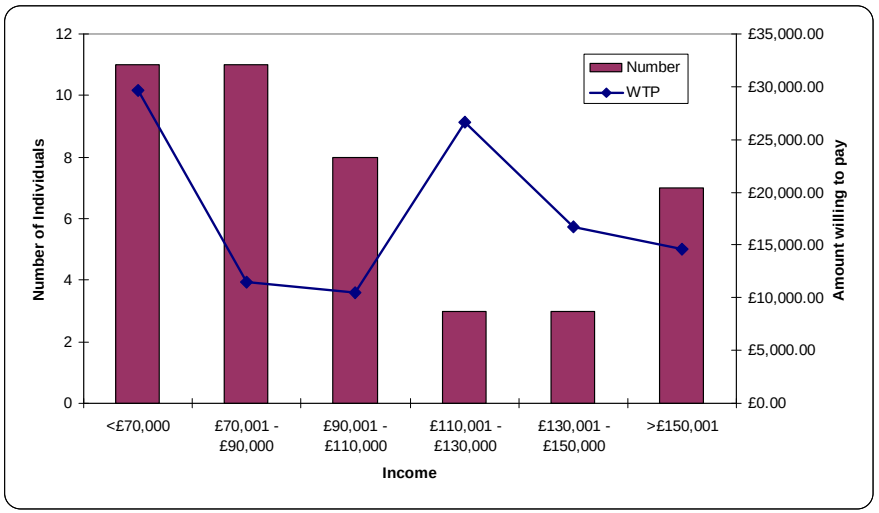
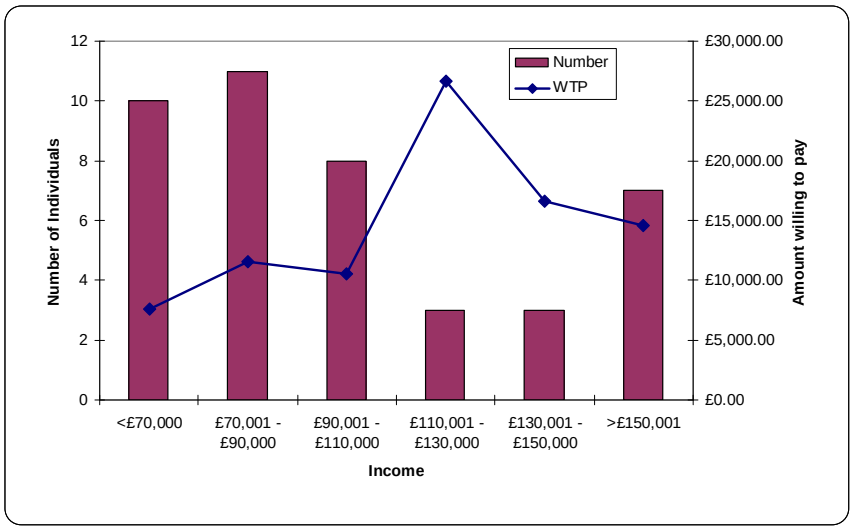


Figure 11: Amount willing to pay categorised by income (excluding outlier)



Appendix 6: Review of Effectiveness of Mesh Versus Non-Mesh for Inguinal Hernia Repair

There are four systematic reviews of RCTs comparing mesh with non-mesh approaches to inguinal hernia repair. Three of the four reviews were published by the EU hernia trials collaboration and they evaluated 15 trials (EUHTC, 2000), 20 trials (Grant et al., 2002) and 58 trials (EUHTC et al., 2002) respectively, the fourth review, published by Scott and colleagues, appraised 20 trials (Scott et al., 2001a). I have also identified an RCT (Vrijland et al., 2002) assessing quality of life and cost, and a recent RCT (van Veen et al., 2007) assessing long term follow-up. In addition I have identified two systematic reviews of RCTs investigating wound infection following inguinal hernia repair (Aufenacker et al., 2006;Sanchez-Manuel et al., 2007). The findings are summarised below and in table 1.

Overall the reviews conclude that mesh repair is associated with a number of improved outcomes compared to simple suture. The rates of haematomas, seromas and infections were similar for mesh and non-mesh groups (EUHTC, 2000;Grant et al, 2002;Scott et al., 2001b) and significantly fewer hernia recurrences were reported in the mesh group in all of the reviews (OR=0.39, P<0.001 (EUHTC, 2000)), (OR=0.43, P<0.001 (EUHTC et al, 2002)), (OR=0.37, (Scott et al, 2001b)). Operative time was reported to be 1-4 minutes longer for mesh repair than for non-mesh repair (Scott et al, 2001b). However, in one of the earliest reviews (EUHTC, 2000) mean operative time was lower in the mesh group in 6 out of 15 trials, lower in the non-mesh group in 3 out of 15 trials and unclear in 6 out of 15 trials (P=0.51). Length of hospital stay was reported as shorter for the mesh group in 5 of 6 trials (p=0.22) (EUHTC, 2000) and reported to be shorter by between 0.22 and 0.35 days (Scott et al, 2001b). A more rapid return to usual activities was indicated for mesh repair in seven out of 10 trials, more slowly in 2 out of 10 trials and similar in one trial, P=0.34 (EUHTC, 2000). In two of the reviews (EUHTC, 2000;Scott et al, 2001b) it was concluded that there was insufficient evidence to determine whether the use of mesh reduces levels of pain. However, in the 2002 reviews (EUHTC et al, 2002;Grant et al, 2002) the meta-analysis showed that the levels of persisting pain were reduced after

mesh repair (OR=0.36, P<0.001(EUHTC et al, 2002)), (OR=0.68, P=0.04 (Grant et al, 2002)) although they did also state that the definition and results were highly variable among trials.

Vrijland and colleagues (n=300) assessed quality of life (measured using EQ-5D and VAS) and cost (based on Dutch hospital costs) in addition to clinical outcomes. Just one outcome (recurrence rate) that was significantly different between the two groups. Recurrence rates were reported as 7% and 1% for non-mesh and mesh repair, respectively (P=0.009). There was no difference between the two groups with regard to operation-related factors (median surgery time was 45 min for both groups and median hospital stay was 2 days for both groups) and quality of life score at any time point (85 for EQ-5D and 81 for VAS), therefore cost-effectiveness was determined by the cost of mesh and the number of recurrences. It was concluded that €6821 ($10,000, £6,100) could have been saved if mesh repair was standard treatment and thus mesh repair is a cost-effective treatment for inguinal hernia repair.

The RCT by Van Veen and colleagues (n=300) found that the ten year cumulative hernia recurrence rates were 17% and 1% for non-mesh and mesh repair, respectively (P=0.005) (of which half occurred in the first three years) suggesting that recurrence rates may be generally underestimated. There was no significant correlation between recurrence and age, obesity, history of pulmonary disease, constipation, or prostate cancer. The authors of both RCTs reported here recommend mesh repair as primary treatment for inguinal hernia repair.

Inguinal hernia repair is a clean wound and thus postoperative infection rates are expected to be low and not exceed 2% (Sanchez-Manuel et al, 2007). However, incidence of infection has been reported to vary between 0 to 9% (Aufenacker et al, 2006). A number of trials have been conducted to assess the effect of antibiotic prophylaxis in prevention of wound infection after mesh repair here we summarise the results of two systematic reviews on the topic. In 2006 a systematic review of eight trials (Aufenacker et al, 2006) found an incidence of infection of 3% in the control group and 1.5% in the antibiotic group but this was not significant (OR=0.54, P=0.18). The incidence of deep infections was reported as 0.6% in the control group and 0.3% in the antibiotic group (OR=0.50). A more recent systematic review of twelve randomised controlled trials (Sanchez-Manuel et al, 2007) (six

hernioplasty and six herniorrhaphy) found overall infection rates of 3.9% in the control group and 2.9% in the antibiotic group (OR=0.64). For herniorrhaphy (non-mesh repair) the infection rates were 4.9% in the control group and 3.5% in the antibiotic group (OR=0.71), whereas hernioplasty (mesh repair) showed infection rates of 2.9% in the control group and 1.4% in the antibiotic group (OR=0.48). This review shows that mesh repair is associated with lower rates of infection. Both the reviews suggest that antibiotic prophylaxis may be useful in preventing wound infection.

Table 1: Summary of the effectiveness of synthetic mesh versus non-mesh repair of inguinal hernias

Study	EUHTC 2000	Scott et al. 2001	Grant 2002	EUHTC 2002	Vrijland et al. 2002	Van Veen et al. 2007	Aufenacker et al. 2006	Sanchez-Manuel et al. 2007
Type	Systematic review	Systematic review	Systematic review	Systematic review	RCT	RCT	systematic review	systematic review
No of trials	15	20	20	58			8	12
No of Patients	4005		5016	11,174	300	300		
Hernia recurrence rates	Mesh = 1.4%, Non-mesh = 4.4%, OR=0.39, P<0.001	Mesh = 50% to75% reduction, OR=0.37, P<0.001	Mesh = 50% to 75% reduction, OR=0.37, P<0.001	Mesh = 2%, Non-mesh = 5%, OR = 0.43, P<0.001	Mesh = 1%, Non-mesh = 7%, P=0.009	mesh = 1%, Non-mesh = 17%, P = 0.005		
Hematomas		OR=0.93	OR=0.93, P=0.6					
Seromas		OR=1.52	OR=1.52, P=0.1					
Wound infection		OR=1.24	OR=1.24, P=0.3				3% (deep infection = 0.6%)	mesh = 2.9%, non-mesh = 4.9%
Operative time		open mesh 7 to 10 minutes less than Shouldice repair but 1 to 4 minutes longer than other non-mesh methods			Both groups = 45 mins			
Hospital stay	Mesh = 1.1 to 6.7 days, Non-mesh = 1.3 to 7.2 days, P=0.22	Mesh repair shorter by between 0.22 and 0.35 days			Both groups = 2 days			
Return to usual activities	mesh quicker in 7 out of 10 trials, slower in 2 out of 10 trials and similar in 1, P=0.34	HR=0.81	HR=0.81, P<0.001					
Persisting pain		OR=0.68	OR=0.68, P=0.04	Mesh = 5%, Non-mesh = 10.1%, OR = 0.36, P<0.001				
Persisting Numbness		OR=0.70	OR=0.70, P=0.4					
Quality of life score					EQ-5D = 81, VAS = 85			

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Appendix 7: A Review of Laparoscopic Versus Open Mesh Repair

Laparoscopic repair is considered a safe alternative to open repair but is technically more demanding (Reuben et al., 2006). The two most common laparoscopic techniques used for hernia repair are transabdominal preperitoneal (TAPP) repair and totally extraperitoneal (TEP) repair. The approaches differ in terms of whether the peritoneal cavity is entered; TAPP repair requires access to the peritoneal cavity to place the mesh through a peritoneal incision, whereas for TEP repair the peritoneal cavity is not entered and the mesh seals the hernia from the outside of the peritoneum; and the later is generally considered more demanding (Wake et al., 2005).

A systematic review (Wake et al, 2005) identified 1 RCT, 5 studies with concurrent comparators, 1 study with a non-concurrent comparator and 3 case series comparing TAPP (n=28) repair with TEP (n=24) repair and found no significant difference between the two groups in a number of outcomes, including operation time (52.3 minutes for TEP compared with 46 minutes for TAPP, P=0.06), number of hematomas (1 in 28 vs. 0 in 24, P=0.6), time to return to usual activities (no overall figure, but several separate activities listed in the paper) and hernia recurrence (1 in 28 Vs. 0 in 24, P=0.6). There was a significant difference found between the two groups with regard to length of stay which was shorter for the TAPP group (mean of 3.7 days for TAPP vs. 4.4 days for TEP). It was concluded that there was insufficient evidence to determine which approach was most effective (Wake et al, 2005).

i. Inguinal Hernia

Writing in the annals of the royal college of surgeons of England Michael Bailey {Bailey, 2005 321 /id} and Andrew Kingsnorth {Kingsnorth, 2005 320 /id} respectively argue the cases for and against laparoscopic repair. Both acknowledge laparoscopic repair is more challenging and is associated with a learning curve. However, Bailey claims training is straightforward, with surgical competency of TEP

achieved after 30-40 procedures and trainee surgeons having no increase in morbidity compared to open repair, followed by a reduction in complications to below that reported for open repair with increasing experience. Conversely, Kingsnorth claims that training takes much longer, around 100 procedures, and therefore puts patients at unnecessary risk of complications. Bailey and Kingsnorth state that direct hospital costs are probably greater for laparoscopic repair, but do not agree on by how much. Laparoscopic repair requires a general anaesthetic (GA) unlike open repair which can be performed under local anaesthetic (LA), but how often LA is used compared to GA for open repair remains contentious, as does the additional direct cost associated with laparoscopic repair. However if societal costs relating to quicker recovery and return to employment are taken into account laparoscopic repair may not be the most expensive. In conclusion this debate continues and it may be sometime before a consensus is reached. However there are four systematic reviews comparing laparoscopic to open repair methods (EUHTC, 2000;EUHTC et al., 2002;McCormack et al., 2003;McCormack et al., 2005) and the results are summarised below (in chronological order).

The first review (EUHTC, 2000) published by the hernia trialists collaboration identified 34 trials and found that laparoscopic repair had significantly improved outcome ($P<0.05$) with regard to operative time (no data) and return to work (24 out of 34 trials). Also, laparoscopic repair is associated (but not significantly) with less haematomas, less reoperations (8 for laparoscopic repair compared to 12 for open repair), reduced pain (reported in 12 out of 16 trials, $P=0.08$) and reduced length of hospital stay (hospital stay ranged from 225 min to 4.9 days for laparoscopic repair and 134 min to 7.3 days for open mesh repair, 12 out of 20 trials reported a reduction associated with laparoscopic repair, $P=0.50$). Furthermore, laparoscopic repair showed a reduction in recurrence rate (2.3% and 2.9% for laparoscopic versus open repair, respectively, OR=0.76) but no significance value was stated. In 2002 (EUHTC et al, 2002) the hernia trialists collaboration conducted a meta-analysis of 58 trials on groin hernia repair compared the use of synthetic mesh to no mesh (described in appendix 7) and laparoscopic technique to open technique. The only outcomes measured were hernia recurrence rate and persisting pain. The use of laparoscopic repair compared to open surgery showed no difference in recurrence rate (OR 1.26, 95%CI: 0.76-2.08, $P=0.36$), but there was a reduction in persisting pain (OR 0.64, 95%CI: 0.52-0.78, $P<0.001$) (EUHTC et al, 2002).

McCormack and colleagues identified 41 RCTs (McCormack et al, 2003). The evidence suggested that laparoscopic repair had a number of benefits over open repair, including decreased post-operative pain (overall, 13.1% and 19.1% for laparoscopic and open repair, respectively; OR=0.54, P<0.0001), persisting numbness (overall, 7.2% and 13.4% for laparoscopic and mesh repair, respectively, OR=0.38, P<0.0001), fewer haematomas (8.7% and 10.5% for laparoscopic and open repair, respectively, P<0.01), less frequent wound infection (OR=0.45, P<0.0001) and early return to normal activity (HR=0.56, P<0.001). However, the laparoscopic technique also had drawbacks including increased operation time (mean difference=14.81 minutes, P<0.0001) and a higher rate of seromas (5.8% and 3.8% for laparoscopic and open repair, respectively, P=0.001). There was no significant difference between laparoscopic and open mesh repair with regard to hernia recurrence (2.7% and 3.1% for laparoscopic and open repair, respectively, OR=0.81, P=0.16) and there was insufficient evidence to make any conclusions regarding hospital stay. It was concluded that it is the use of mesh rather than the surgical approach which is associated with the greatest improvement in outcomes.

A HTA review (McCormack et al, 2005) of laparoscopic surgery for inguinal hernia repair identified 37 RCTs and 14 cost-effectiveness studies. The benefits associated with laparoscopic repair are similar to those mentioned in the previous McCormack trial. Faster return to usual activities (P<0.0001), less persisting pain (RR0.77, P=0.004 for TEP vs. open repair and RR0.72, P=0.001 for TAPP vs. open repair) and numbness (RR0.67, P=0.002, for TEP vs. open repair and RR0.26, P<0.0001 for TAPP vs. open repair). There were fewer cases of wound infection (RR0.62, P=0.41 for TEP vs. open repair and RR0.41, P=0.0001 for TAPP vs. open repair) and haematomas (RR0.44, P<0.0001 for TEP vs. open repair and RR0.76, P=0.009 for TAPP vs. open repair). However laparoscopic repair was also associated with longer operative time (mean difference = 13.33, P<0.0001) and increased number of seromas (RR0.73, P=0.17 for TEP vs. open repair and RR1.97, P=0.003 for TAPP vs. open repair). There was no significant difference between laparoscopic and open repair with regard to recurrence rates (2.5% and 2.07% for laparoscopic and open repair, respectively, P=0.5). The economic evaluation of laparoscopic versus open repair found that laparoscopic repair is more costly to the health service than open repair for the treatment of inguinal hernias. This has been shown by UK

based studies, which estimate an extra cost of about £300-350 (€450-520, $600-700) per patient, and point estimates of cost provided by an economic model, which amount to an additional cost of £100-200 per patient after 5 years (McCormack et al, 2005).

Overall, laparoscopic surgery compared to open surgery has led to improvements in clinical outcomes although no difference has been found in recurrence rate, the most frequent complication. Operative time can be longer with laparoscopic repair but it appears as though these additional hospital costs may be balanced out when social costs of more rapid return to work are taken into account.

ii. Incisional Hernia Repair

One retrospective of 91 patients (Bencini et al., 2003) compared laparoscopic (n=42) and open (n=49) techniques for incisional hernia repair along with one prospective study of 31 patients (Engledow et al., 2007) investigating whether day case laparoscopic repair for incisional hernias is feasible, acceptable and cost-effective.

Bencini and colleagues found that there was no significant difference between laparoscopic and open repair in terms of operative time (108 min and 112 min for laparoscopic and open repair, respectively, P=0.73), overall rate of complications (26% and 44% for laparoscopic and open repair, respectively, P=0.10), incidence of seroma (14% and 10% for laparoscopic and open repair, respectively, P=0.93) and recurrence rate (0% and 6% for laparoscopic and open repair, respectively, P=0.30). There was a significant difference between the two groups in terms of hospital stay (5days vs. 8 days for laparoscopic vs. open repair, respectively, P<0.0001) and this lead to a difference, in favour of laparoscopic repair, in mean hospital cost (€2357 for laparoscopic repair vs. €3890 for open repair, P=0.0011) and overall cost (mesh + hospital stay) (€3091 for laparoscopic repair vs. €3936 for open repair, P=0.017). However it should be noted that the hernia defect was significantly larger in the open repair group (122cm^2) compared to the laparoscopic repair group (83cm^2, P=0.0006).

Engledow and colleagues concluded that laparoscopic day case repair is possible as the previously documented advantages of laparoscopic methods over open methods lend themselves to day case

surgery, including the use of local over general anaesthetic. They do state that community support would need to be available to all but do not include these costs in their cost analysis. They find that an analysis of direct hospital costs for day case laparoscopic repair leads to an overall saving of £616 per procedure, due to shorter operative time and lack of inpatient stay. Overall, currently there is insufficient evidence to determine whether laparoscopic or open repair is better.

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Appendix 8: Clinical Market Analysis of Meshes

Here I summarise the key findings of a market evaluation, conducted in the US by Medpanel, Inc. (MedPanel 2007), of synthetic versus biologic meshes used to repair complex defects. The aim is to gain an understanding of market potential for biologics from a clinical perspective. The evaluation questioned 40 surgeons with the following criteria: board certified as a general surgeon, greater than 2 years surgical experience, spent a minimum of 75% of time on clinical practice and perform a minimum of 20 hernia repairs a month if positioned in an academic setting and 10 per month if in a non-academic setting. They were asked to complete a 20-minute questionnaire comprised of 5 sections: surgery classification; product comparison; cost considerations; comparisons of sales representatives; and alternative product applications.

The key factors contributing to a complex ventral hernia classification were significant loss of abdominal fascia, presence of mesh from a previous repair followed by infection and bowel contamination. Currently about one third of ventral hernias are classified as complex however, 48% felt this was likely to increase (although no reason given). As expected synthetic mesh is the current treatment choice for ventral hernia repair although 70% had used a biological implant at some stage.

It is widely believed that biologics will and do perform better than synthetics when used in complex defects; 85% said they would prefer to use biologics for a complex or infected hernia repair, for a clean-contaminated field after first recurrence and in cases where more than one recurrence has occurred. However, 85% believe that synthetic mesh is the most cost-effective treatment due to the high cost of biological meshes. Overall, the surgeons thought the use of AlloDerm and other biologics was likely to increase over the coming years (no further explanation) but 70% said that would remain most important in terms of their product selection.

References

MedPanel, I. 2007. Market Evaluation of Synthetic Meshes and Biologic Implants Used for Ventral Hernia Repair. PowerPoint Slides

Appendix 9: Search Strings for Chapter 6

Search	Date	Database	Term	Yield
1	Mar-07	Medline	bone repair AND current treatment	715
2	Mar-07	Medline	bone repair AND current treatment AND autograft AND autogenous bone graft	2849
3	Mar-07	Medline	bone AND tissue engineering	4056
4	Mar-07	Medline	bone AND tissue engineering AND growth factors	859
5	Mar-07	Medline	bone AND tissue engineering AND growth factors AND BMP OR bone morphogenic proteins	859
6	Mar-07	Medline	bone AND tissue engineering AND cells	2662
7	Mar-07	Medline	bone AND tissue engineering AND stem cells	1172
8	Mar-07	Medline	bone AND tissue engineering AND cells AND MSCs	287
9	Apr-07	Medline	spinal fusion	13551
10	Apr-07	Medline	spinal fusion AND epidemiology	678
11	Apr-07	Cochrane	spinal fusion AND epidemiology	33
12	Apr-07	Medline	degenerative disc disease	847
13	Apr-07	Cochrane	degenerative disc disease	82
14	Apr-07	Medline	degenerative disc disease AND epidemiology	64
15	Apr-07	Medline	spinal fusion AND degenerative disc disease	297
16	Apr-07	Medline	spinal fusion AND degenerative disc disease AND epidemiology	21
17	Apr-07	Medline	spinal fusion AND tissue engineering	48
18	Apr-07	Medline	degenerative disc disease AND non-surgical OR disc replacement	937
19	Apr-07	Medline	degenerative disc disease AND total disc replacement	42
20	Apr-07	Cochrane	degenerative disc disease AND total disc replacement	8
21	Apr-07	Medline	degenerative disc disease AND nucleus pulposus replacement	13
22	Apr-07	Medline	Fracture nonunion AND nonunion of fractures	8925
24	Apr-07	Cochrane	Fracture nonunion AND nonunion of fractures	52
25	Apr-07	Medline	Fracture nonunion AND nonunion of fractures AND epidemiology	119
26	Apr-07	Medline	fracture nonunion AND segmental defects	72
27	Apr-07	Medline	segmental defects AND epidemiology	192
28	May-07	Medline	osteoporotic fractures	3975
29	May-07	Cochrane	osteoporotic fractures	418
30	May-07	Medline	osteoporosis AND spinal fractures	2780
31	May-07	Cochrane	osteoporosis AND spinal fractures	360
32	May-07	Medline	osteoporotic fractures AND epidemiology	966
33	May-07	Medline	osteoporotic fractures AND osteoporosis AND spinal fractures AND epidemiology	218
34	May-07	Medline	osteoporotic fractures AND current treatment	279
35	May-07	Medline	osteoporotic fractures AND kyphoplasty AND vertebroplasty	325

36	May-07	Cochrane	osteoporotic fractures AND kyphoplasty AND vertebroplasty	4
37	May-07	Medline	osteoporotic fractures AND kyphoplasty AND vertebroplasty AND filler materials	2
38	Jun-07	Medline	bone cysts	973
39	Jun-07	Cochrane	bone cysts	44
40	Jun-07	Medline	bone cysts AND epidemiology	374
41	Jun-07	Medline	simple bone cysts	325
42	Jun-07	Medline	aneurysmal bone cysts	1271
43	Jun-07	Medline	bone cysts AND current treatment	66
44	Jun-07	Medline	bone cysts AND tissue engineering	6
45	Nov-07	Medline	autograft AND cost AND effectiveness	93
46	Nov-07	Medline	autograft AND BMP AND cost AND effectiveness	3
47	Nov-07	Medline	autograft AND spinal fusion AND cost-effectiveness analysis	6
48	Nov-07	Medline	autograft AND fractures AND cost-effectiveness analysis	2
49	Nov-07	Medline	harvesting iliac crest bone	
50	Nov-07	Medline	Harvesting iliac crest bone and duration	10
51	Nov-07	Medline	QoL OR “Quality of Life” OR Utilit* OR disutilit* OR cost effective* OR cost-effective* OR contingent valuation OR willingness to pay OR willingness to accept OR WTP AND autogenous OR autologous AND “iliac crest bone graft” OR “bone graft” OR ICBG	6076
52	Nov-07	Medline	QoL OR “Quality of Life” OR Utilit* OR disutilit* OR cost effective* OR cost-effective* AND autogenous OR autologous AND “iliac crest bone graft” OR “bone graft” OR ICBG	6076
53	Nov-07	Medline	QoL OR “Quality of Life” OR Utilit* OR disutilit* OR “cost effective*” OR “cost-effective*” AND autogenous OR autologous AND “iliac crest bone graft” OR ICBG	123
54	Nov-07	Medline	VAS AND health related QOL OR EuroQOL OR health valuations	968
55	Nov-07	Medline	VAS score AND QoL score OR "quality of life" score AND back pain	120
56	Nov-07	Medline	VAS OR Visual Analogue Scale AND QoL OR "quality of life" AND utilit* AND Back Pain	16

Appendix 10: A Review of the Alternative to Spinal Fusion for the Treatment of Degenerative Disc Disease

There is continued debate regarding the appropriateness and effectiveness of spinal fusion in the treatment of back pain and disc degeneration. A vast number of alternatives, both surgical and non-surgical, are being developed at a rapid pace. Here I discuss evidence on the proposed alternatives to spinal fusion.

Non-surgical Approaches

Although spinal fusion has been the primary surgical treatment for DDD it does possess several limitations that would not be avoided by a RM method e.g. infection and pseudoarthrosis (Sakalkale et al., 2003). These would be a price worth paying if the surgery was effective, but the evidence from three published RCTs {Brox, 2003 164 /id;Fairbank, 2005 139 /id;Fritzell, 2001 166 /id} comparing spinal fusion to non-surgical interventions remains unclear.

Of the three RCTs conducted to compare spinal fusion to non-surgical interventions, one trial (N=294) found fusion to be more effective than non-surgical treatments at reducing back and leg pain ($p = 0.0002$ and $p = 0.005$, respectively) and disability (assessed using the Oswestry Disability Index (ODI), $p = 0.015$) {Fritzell, 2001 166 /id}, one trial (N=64) found that there was no significant ($P = 0.33$) difference between lumbar fusion and cognitive intervention plus exercise at the 1-year follow-up (assessed using the ODI) (Brox et al, 2003), and one trial (N=349) found that there was “no clear evidence” as the difference between lumbar fusion and intensive rehabilitation was marginal (measured using the ODI, $p = 0.045$), only just reaching the predefined clinical difference (Fairbank et al, 2005). For this reason, and because even large RCTs cannot exclude small benefits, it remains possible that the operation has some benefit, although any such benefit must be smaller than many previously thought and the results are also compatible with a small disbenefit.

A cost utility analysis was conducted by Rivero-Arias et al. (2005) based on a RCT comparing spinal fusion to intensive rehabilitation for the management of patients with chronic low back pain (Rivero-Arias et al., 2005). At the two-year follow-up 38 patients (22%) randomised to the rehabilitation group underwent surgical fusion in addition to rehabilitation, 11 patients (6%) in the surgical group underwent re-operations and 7 patients (4%) in the surgical group received rehabilitation in addition to surgery. When the additional costs of unplanned surgery and patient care are taken into account the overall costs (after two years) associated with spinal fusion surgery and intensive rehabilitation were £7,830 and £4,526, respectively, resulting in a cost difference of £3,304 (£2317 to £4291, $P<0.001$) in favour of intensive rehabilitation.

No significant difference in utility was found between any of the follow-up points, except that for baseline. The mean QALY difference in favour of surgery was 0.068. The cost-effectiveness of surgery, expressed as an incremental cost per QALY, was estimated to be £48,588 (patient utility was estimated using the EuroQol questionnaire), and therefore at two years the chance that surgery will be cost-effective is less than 20%. However, the cost-effectiveness of surgery cannot be determined with certainty. Since it is possible that the number of patients receiving both interventions could increase beyond the two-year follow-up, and that this increase may disproportionately affect one arm of the trial more than the other, the cost-effectiveness of the surgery could be severely affected (this has been shown by sensitivity analysis) (Rivero-Arias et al, 2005). Therefore further follow-up of patients is required to determine the long-term effectiveness.

Posterior Dynamic Stabilisation

Posterior dynamic stabilisation is a surgical alternative, which like spinal fusion, is targeted at stabilisation of the spine, however it is designed to control rather than eliminate motion between vertebrae. This system uses autograft along with pedicle screws (e.g. Dynesys System) or an interspinous device to restabilise spinal segments and reduce intradiscal pressure (Schnake et al., 2006). Adjacent vertebrae are connected with flexible rods allowing some restriction in motion and the disc between the two vertebral bodies is partially loaded. There evidence on the effectiveness of dynamic stabilisation remains unclear due to a lack of RCTs.

Intradiscal Electrothermal Therapy (IDET)

IDET is a minimally invasive technique, which places a temperature controlled thermal resistive heating coil into the outer region of the disc (Freeman, 2006). A systematic review (Andersson et al., 2006) of studies comparing IDET with spinal fusion yielded similar results in improvement for two out of three outcomes evaluated: pain severity was reported as 51% and 50%, respectively and quality of life was determined as 43% and 46%, respectively. There was a difference observed for the back function outcome. The percentage improvement reported was 42% and 14% in favour of spinal fusion (p-value not given). However, the review identified just two RCTs for IDET treatment. IDET appears less expensive; Andersson and colleagues (Andersson et al, 2006) report that mean costs for fusion operations are $50,000, whereas IDET has been estimated to cost only $7,000 (these costs do not include management of any postoperative complications which may arise).

Total Disc Replacement

Total disc replacement involves the surgical insertion of a disc prosthesis anteriorly through an abdominal incision. There are numerous types currently being developed and under investigation (Table 1: Summary of artificial disc prosthesesTable 1) (Freeman et al., 2006). Two RCTs comparing total disc replacement with spinal fusion are reported in literature; the first involving the Charité artificial disc and the second involving the Pro-Disc II total disc replacement (Freeman et al, 2006).

The first RCT (n=304) compared spinal fusion (n=99) to total disc replacement using the Charité artificial disc (n=205). The findings reported an ODI and visual analogue score (VAS) for back pain improvement in favour of the Charité artificial disc at 24 months (ODI improvement of 24.8 points (from 50.6 to 25.8) for Charité artificial disc and 22 points (from 52.1 to 30.1) for spinal fusion (no p-value given), and a Visual Analogue Score (VAS) for back pain improvement of 41.4 points (from 72 to 30.6) for Charité artificial disc and 35.5 points (71.8 to 36.3) for spinal fusion (no p-value given)) (Freeman et al, 2006). Furthermore, only 57% of patients with disc replacement and 46% of those with fusion met all four criteria for success (greater than 25% improvement in ODI at 24 months, no device failure, no major complications, and no neurological deterioration) (Freeman et al, 2006).

The Pro-Disc II clinical trial compared disc replacement to spinal fusion in both single and double DDD. The trial reported that there was no significant difference in the preoperative values of ODI or VAS scores between the two groups. At 6 weeks and 3 months the disc replacement patients showed significantly more improvement (in VAS score) compared to the fusion group (no p-value given). By 6 months both groups showed significant improvement in ODI and VAS compared to preoperative values (no p-value given) however, the difference between the two groups was not significant (no p-value given) (Delamarter et al., 2005). However, it has been suggested total disc replacement using Pro-Disc II may only be beneficial for a highly selective group of patients (Siepe et al., 2006).

Disc replacement is technically demanding as it is conducted in close proximity to the spinal cord, nerve roots and a complex network of large blood vessels. As yet no study has shown total disc replacement to be significantly superior to spinal fusion in terms of clinical outcome. Furthermore, the potential long-term benefits of total disc replacement in preventing adjacent level disc degeneration and any long-term complications also remain unknown (Freeman et al, 2006). However, postoperative recovery following disc replacement is reported to be more rapid than that following spinal fusion with commensurate reductions in hospital stay (Wilson-MacDonald et al., 2007). In my opinion it is too early to say whether, or in what circumstance disc replacement yields better outcomes than spinal fusion, and as discussed above, many think the jury is still out on the subject of spinal fusion itself.

Table 1: Summary of artificial disc prostheses

Device	Characteristics	Studies	Results	References
Charite	Bi-convex ultra high molecular weight polyethylene spacer, which acts as a mobile core.	Many single studies. Undergoing an FDA approved RCT	Early clinical results equivalent to spinal fusion	(Errico, 2004;Freeman et al, 2006)
ProDisc	A metal on plastic device. The end plates are secured to vertebral end plates by a central keel, spikes and a porous coated surface	Undergoing an FDA approved RCT	Preliminary results promising. Some indications for patients	(Errico, 2004;Freeman et al, 2006;Siepe et al, 2006)
Acroflex	Elastomeric core sandwiched between two titanium endplates to optimize shock absorption qualities.	One single study. RCT cancelled due to mechanical failure	Disappointing. Implant failure lead to withdrawal from market	(Freeman et al, 2006)
MAVERICK	3rd generation disc technology. A highly polished cobalt chrome ball and socket in a metal on metal design. Device provides a fixed posterior centre of rotation and resists both anterior and posterior shear forces.	Approved for a clinical trial		Errico, 2004;Freeman et al, 2006)
Flexicore	A cobalt chrome molybdenum highly polished ball and socket, metal on metal prosthesis.	Approved for clinical trials		(Errico, 2004)

Whole Disc Transplantation

Whole disc transplantation has been investigated following the success of organ transplantation. Disc transplantation has the theoretical advantage over artificial disc replacement and disc regeneration, of providing young, non-degenerated scaffold that could offer the best environment for the endogenous NP cells to survive or regenerate (Ruan et al., 2007). Animal models have shown that to preserve stability and mobility after discectomy is both technically and biologically feasible, and the restoration of mechanical function has been satisfactory (Ruan et al, 2007). Following the success of this method in primates, Ruan and colleagues proceeded with a preliminary study to examine the feasibility, safety, and long-term clinical results of disc transplantation in humans.

Five patients received disc transplantation of fresh-frozen allografts. At 3 months good union of graft endplates was observed and no immunoreaction, migration or complications relating to surgical

procedure or wound healing were reported in any of the patients. At the five-year follow-up, neurological symptoms of all patients had improved compared to before surgery and mobility and stability of the disc was compatible with a satisfactory clinical outcome. Immediately following surgery mean disc height increased (5.32mm to 5.88mm) although was not maintained and soon after transplantation disc height was lost (4.33mm), but remained stabilised. In comparison artificial discs have shown to restore full disc height for the longer term. Three out of five patients had some evidence of pain at the five-year follow-up (although the level of discomfort was lower than that reported before surgery), whether this pain was a result of surgery or due to the natural history of degenerative disc disease at other levels in the spine is unclear (Ruan et al, 2007).

Nucleus Pulposus Replacement

Nucleus pulposus (NP) replacement is a recent alternative to total disc replacement. The NP lies at the centre of the disc (see figure 1), contains large amounts of water, and functions as a shock absorber. Degeneration of the disc results in the gradual loss of water from the NP (Di Martino et al., 2005), therefore reducing the functional capacity of the disc. NP replacement exchanges just the inner part of the disc for prosthesis, leaving the remainder intact. It is a less invasive procedure, achieved via a posterior (e.g. PDN), lateral (e.g. Aquarelle), or anterior (e.g. Regain) approach, involving the splitting of the psoas muscle, removal of the existing nucleus and insertion of the prosthesis in the middle third of the disc. The prosthesis is inserted in its dehydrated state (its smallest size), which absorbs water once inserted, or in a liquid state, if curing polymers (table 6) were used to form the prosthesis, which harden after implantation (Di Martino et al, 2005).

At present NP replacement is intended for use in lumbar disc degeneration (Di Martino et al, 2005), if the disc degeneration shows 10-50% loss of disc space height (Goins et al, 2005). It is thought this treatment could offer several advantages to other surgical treatments such as prevention of more serious injuries; avoidance of major blood vessels, thereby reducing risk to the patient; reduced scaring; avoidance of morbidities associated with fusion and total disc replacement; and be a minimally invasive procedure.

There are a number of NP prostheses currently under investigation and these are summarised in Table 2. To date the most widely studied nucleus replacement device has been the prosthetic disc nucleus (PDN) (Raymedica, Inc., Bloomington, MN), implanted in over 550 patients, a hydrogel pellet designed to absorb 80% of its weight in water allowing response to compressive forces and maintenance of disc height (Goins et al, 2005). Clinical results on 10 patients who received the PDN device for symptomatic lumbar DDD with a minimum 2-year follow up demonstrated “excellent results” with marked decreases in ODI scores (values not stated) in 8 patients, as well as restoration of disc space height and normal motion (Goins et al, 2005).

Table 2 Summary of Nucleus Pulposus Prosthesis

(Adapted from (Di Martino et al, 2005))

Device	Technology	Biomaterial	Studies	FDA approved
Prosthetic Disc Nucleus	intradiscal implant	Hydrogel pellet encased in a polyethylene jacket	Implanted in more than 400 patients	investigational use only
Aquarelle	intradiscal implant	Semihydrated polyvinyl alcohol (PVA) hydrogel	Animal experiments (baboon) plus cadaveric spine New Zealand rabbits	
Neudisc	intradiscal implant	Modified hydrolyzed polymer (Aquacryl) reinforced by a mesh	New Zealand rabbits	
Newcleus	intradiscal implant	Polycarbonate urethane (PCU) elastomer curled into a preformed spiral	Implanted in 5 patients	
Regain	intradiscal implant		implanted in few patients	investigational device exemption to start
IPD	intradiscal implant	Modular intervertebral prosthetic disc	Tested in an animal experimental model in cow	
DASCOR Disc Arthroplasty device	*In Situ* Curing polymer	injectable polyurethane	implanted in 16 patients	
BioDisc	*In Situ* Curing polymer	protein hydrogel	tested on animal models	

Despite some early success with NP implants they are still considered experimental and require further research to answer questions surrounding reliability and maintenance of the viscoelastic properties of the native disc when subjected to multidirectional loads at differing rates (Goins et al, 2005). As yet there have been no clinical trials comparing nucleus replacement to lumbar fusion (Sakalkale et al, 2003).

Nucleus Pulposus Regeneration

Biological disc replacement involves using growth factors or pluripotent cells to re-populate the NP with cells (Ruan et al, 2007). This form of disc regeneration uses gene therapy (GT) to repair damaged tissue and could be the ultimate cure for spinal cord injury (Zigler et al., 2003). Although the precise pathophysiology of IVD degeneration has yet to be clearly defined, the progressive decline in aggrecan, the primary proteoglycan of the NP, appears to be a final common pathway (Sobajima et al., 2004), resulting in gradual dehydration of the ECM within the NP. It has been hypothesised that an imbalance in the synthesis and catabolism of certain critical ECM components can be alleviated by the transfer of genes to IVD cells encoding factors that modulate synthesis and catabolism of these components (Sobajima et al, 2004).

The importance of growth factors in development and healing is already well established and several growth factors (TGF-1b, BMP-2, BMP-7 (described earlier)) have been shown to up-regulate ECM synthesis *in vitro* (Shimer et al., 2004). The effect of growth factors on IVD have shown positive results; demonstrating increased proteoglycan synthesis (Shimer et al, 2004); promotion of mRNA expression, ECM synthesis, and type II collagen; increased proliferation rate of the NP cells (Chen et al., 2006), and the ability to rescue IVD cells following inflammatory stress (Shimer et al, 2004). However, growth factors have a short biological half-life. Currently, GT is being investigated to overcome this through sustaining growth factor concentrations in animal models of degeneration (Shimer et al, 2004).

Disc degeneration is accompanied by a decline in cellularity and successful GT requires the presence of an adequate number of responding cells. Cell numbers can be restored either by both stimulating

the division and inhibiting the death of endogenous cells or by introducing new cells into the disc. The latter strategy may be more successful, as the endogenous cells of a degenerating disc may be unresponsive or abnormal (Evans, 2006). MSC cells, isolated from bone marrow and other sources, have demonstrated an ability to restore pathologically altered disc tissue in animal models under the right environment (hypoxia, growth factor, three dimensional culture), and are seen as good candidates for transplantation and use in the repopulation of the NP (Risbud et al., 2004). Although this work is in its infancy there is significant optimism in this technology.

A recently published paper from the UK centre for Tissue Engineering has shown that the co- culture of human NP cells and MSCs, in the presence of cell-cell contact, causes MSC differentiation to a NP-like phenotype. This could be a viable method for generating a large population of differentiated cells for use in cell-based TE therapies for regeneration of the degenerative IVD (Richardson et al., 2006).

The major disadvantage to the treatments that target the NP is the degeneration of the physical structure of the annulus fibrosus, which could be too advanced for the disc to function normally, or it could continue to degrade and result in worsening of the condition (Ruan et al, 2007).

Conclusion

It is unlikely that spinal fusion will be superseded in the near future as many critics of alternatives point out; there is a real lack of evidence and controlled trials on some of these newer treatments. Furthermore, in the context of these studies which compare surgery and non-surgery interventions one must consider the patient population selected. Patient selection is fundamental to a successful outcome. However the ability to select appropriate patients for surgery can sometimes be a challenging one. Therefore, inconsistencies in the results which suggest excellent results for one patient and a lack of improvement for another are likely to be due to failures in patient selection rather than failures in the intervention. Better identification of the indications which determine a patient's suitability for surgery is needed in order to achieve consistent symptomatic relief (Wilson-MacDonald et al, 2007). Advocates of fusion surgery believe that the spate of recent studies which brings into

question the effectiveness of spinal fusion may be underestimating the benefit due to poor patient selection and poor surgical technique.

Further research in this area should aim to clarify the most effective technique for spinal fusion and determine the effectiveness of alternative treatment options via RCTs. Clear indications should be available stating when surgery is and is not appropriate. The frequency of each treatment option used would also be useful in determining the opinion of the field. There is currently no database of spinal surgery in the UK with adequate coverage and collation of long-term outcomes. There is an international database of back surgery to which some surgeons contribute but the difficulty has been in achieving high rates of follow-up. Likewise some members of the UK society for back pain research are collecting long-term outcomes and it may be that useful to establish a broad based database for spinal surgery in the UK and use tracker trials (Lilford et al., 2000) to determine the effectiveness of the new technologies. Sweden has already established a national register of lumbar spinal surgery and this is reviewed below.

The Swedish National Spinal Register for Lumbar Surgery

The Swedish national register for lumbar surgery aims to prospectively describe the outcome (focusing on pain relief and function) of disc surgery, decompressive surgery and fusion surgery of the lumbar spine, and to report the results annually (Fritzell et al., 2006). The National Board of Health and Welfare funds the register, at a cost of only £30,000 annually (which cover staff costs only with no payment to participating departments). The register is overseen by a management group lead by Bjorn Stromqvist and made up of orthopaedic surgeons (Jönsson, B; Fritzell, P; Hägg, O; Larsson, B-E; Lind, B.) from four hospitals around Sweden.

Degenerative lumbar spine disorders are less well defined compared to hip and knee arthrosis and hip fracture, all of which have prospective registers (Johnsson et al., 2002). The Swedish register therefore records information that allows patients to be characterised in detail, and includes the results of imaging that are increasingly used in diagnosis and planning. Registers have the potential to provide information about the number and type of surgical interventions, by indication, and record

adverse events and outcomes such as patient satisfaction, quality of life and cost-effectiveness (Fritzell et al, 2006) for the different procedures according to indications.

The Swedish national register was the first of its kind to evolve documenting multiple pre- as well as postoperative variables. The latter includes the visual analogue scale (VAS) for back and leg pain, and the SF-36 questionnaire. Although established in 1993 it was not widely disseminated until 1998 due in part to an economic recession and some initial problems centred on the surgeon-based protocol, insufficient IT knowledge, and registration fatigue. In 1999 improvements were made to the protocol; it became patient-based, a support function was created, and improved feedback was established. The register now includes more than 80% of (the estimated 5,000+) spinal operations for degenerative disorders, and the recent addition of a web-based version of the register is estimated to further increase registration (Johnsson et al, 2002).

It is believed that there are four key factors which have contributed to the success of the Swedish endeavour: A national health service and existing unique patient identifiers make possible the identification and follow-up of 'migrating' patients who change the centre of treatment; an established culture for reporting procedures and outcomes; the data collection technology employed is easy to use and provides performance feedback to the surgeons; and the overall simplicity of the register (Roder et al., 2006). The register is being used more frequently with coverage expected to reach 85% in the coming year, and a protocol for the inclusion of Oswestry disability index (ODI) is being considered.

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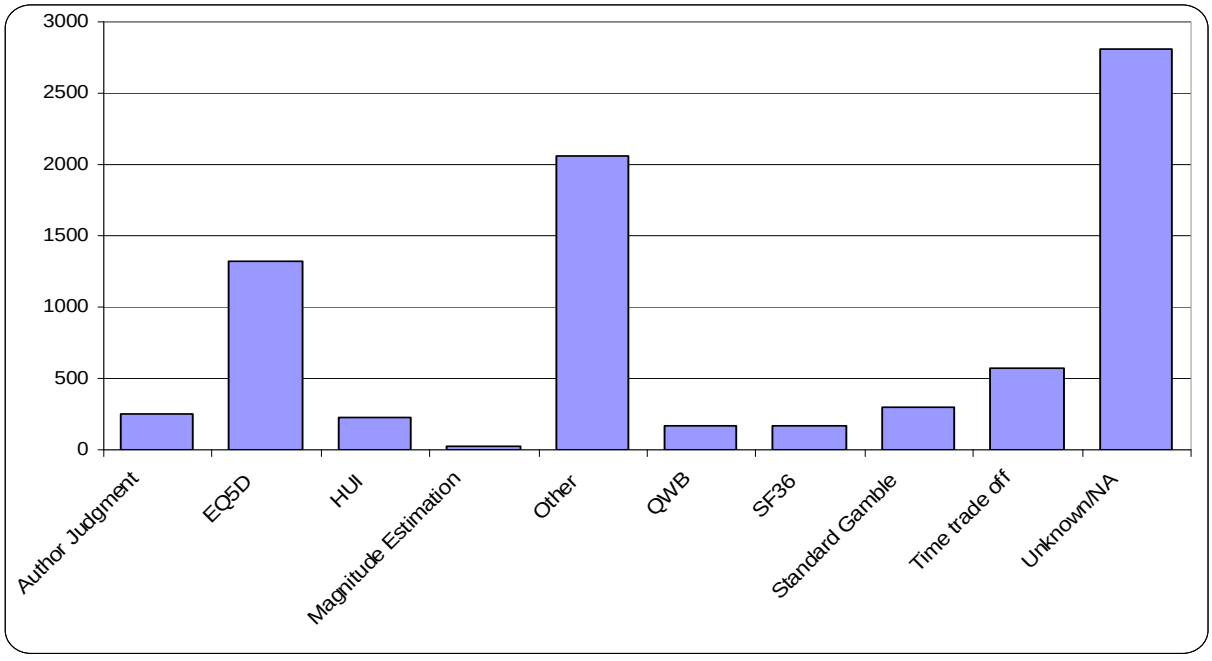
Appendix 11: Search Strings for Chapter 7

Search	Date	Database	Term	Results
1	Jan-08	PubMed	cartilage defect AND knee	527
2	Jan-08	PubMed	cartilage AND defect OR lesion AND knee	2327
3	Jan-08	PubMed	ACI	2788
4	Jan-08	PubMed	ACI AND cartilage AND Knee	62
5	Jan-08	PubMed	ACI AND cartilage AND Knee AND randomised	6
6	Jan-08	PubMed	microfracture	228
7	Jan-08	PubMed	microfracture AND cartilage AND Knee	87
8	Jan-08	PubMed	microfracture AND cartilage AND Knee AND randomised	2
9	Jan-08	PubMed	mosaicplasty	90
10	Jan-08	PubMed	mosaicplasty AND cartilage AND Knee	60
11	Jan-08	PubMed	mosaicplasty AND cartilage AND Knee AND randomised	4
12	Jan-08	PubMed	MACI	101
13	Jan-08	PubMed	MACI AND cartilage	16
14	Jan-08	PubMed	MACI AND cartilage AND Knee	13
15	Jan-08	PubMed	MACI AND cartilage AND Knee AND randomised	2
16	Jan-08	PubMed	osteoarthritis AND epidemiology	2706
17	Jan-08	PubMed	osteoarthritis AND Knee AND epidemiology	999
18	Jan-08	PubMed	osteoarthritis AND Knee AND epidemiology AND systematic Review	119
19	Jul-08	PubMed	quality of life OR QoL OR utilit* AND osteoarthritis of knee	474
20	Jul-08	Cochrane	quality of life OR QoL OR utilit* AND osteoarthritis of knee	16250
21	Jul-08	PubMed	quality of life OR QoL OR utilit* AND mild osteoarthritis of knee	23
22	Jul-08	PubMed	quality of life OR QoL OR utilit* AND severe osteoarthritis of knee	44
23	Jul-08	PubMed	quality of life OR QoL OR utilit* AND replacement of knee OR knee replacement OR total knee replacement	9747
24	Jul-08	PubMed	quality of life OR QoL OR utilit* AND first replacement of knee OR first knee replacement OR first total knee replacement	969
25	Jul-08	PubMed	quality of life OR QoL OR utilit* AND second replacement of knee OR second knee replacement OR second total knee replacement	358
26	Jul-08	PubMed	osteoarthritis AND knee AND knee replacement OR total knee replacement AND quality of life OR utilit*	68624
27	Jul-08	Cochrane	osteoarthritis AND knee AND knee replacement OR total knee replacement AND quality of life OR utilit*	3530
28	Jul-08	PubMed	osteoarthritis AND knee AND knee replacement OR total knee replacement AND quality of life	272
29	Jul-08	Cochrane	osteoarthritis AND knee AND knee replacement OR total knee replacement AND quality of life	218
30	Jul-08	PubMed	osteoarthritis AND knee AND knee replacement OR total knee replacement AND utilit*	51

Appendix 12: Analysis of the TUFTS database

As described in chapter 8, when I needed to find a source of utility values I thought the obvious place to start was the TUFTs database of utilities (Tufts Medical Centre, 2009). For my first task, I entered the information from the TUFTS dataset into an Excel spreadsheet so the data could be analysed. The TUFTS database consists of a large matrix containing 7874 utility values spanning across 1653 studies and 68 disease classifications. The advantage of this database is that it enables the reader not only to find out what utility values have been described to various health states of different disease classifications but also in many instances to provide these results under different methods of elicitation. The measurement of the utility value could fall into one of 10 categories. This is illustrated in figure 1 below. It is, however, obvious from the graph that the categories with the largest number of utilities are in fact 'unknown/NA' and 'other' (I could not find an explanation of the term 'other'). It is also clear though, that of the other defined measurement types, EQ-5D is dominant.

Figure 1. Frequency of different measurements used to elicit utilities



Next, I examined the distribution of the utility values irrespective of measurement and then based on the method of elicitation. The results are illustrated below in figures 2 to 9 below. These graphs show the levelling effect of the utility values around the 1 decimal point values i.e. 05, 0.6, 0.7 etc.

Figure 2: Distribution of all utility values reported on TUFTS database

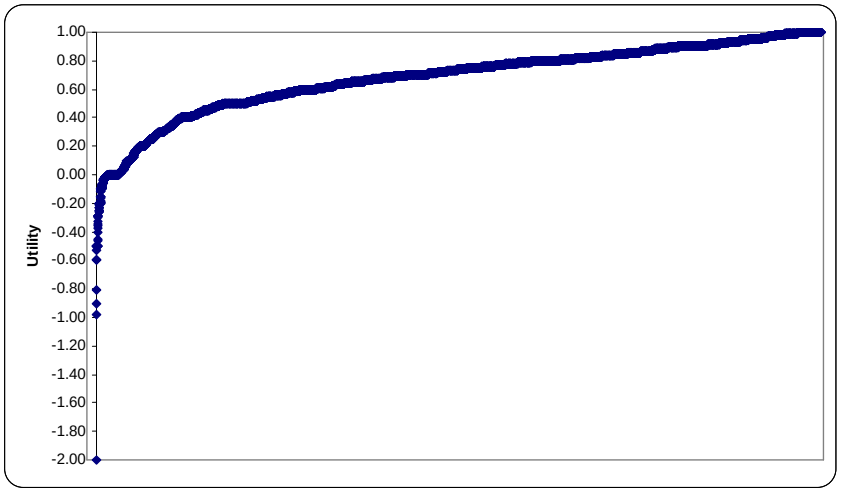


Figure 3: Distribution of all utility values between 0 to 1.0

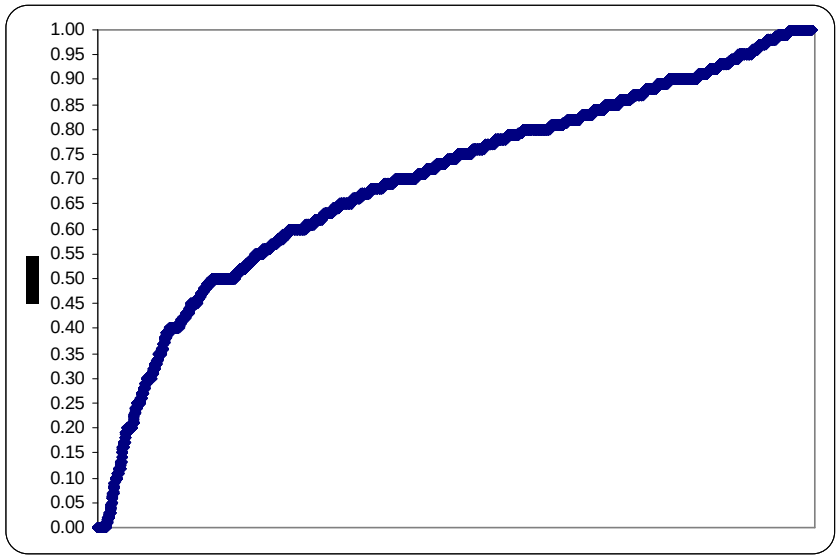


Figure 4: distribution of all utility values between 0.5 to 1.0

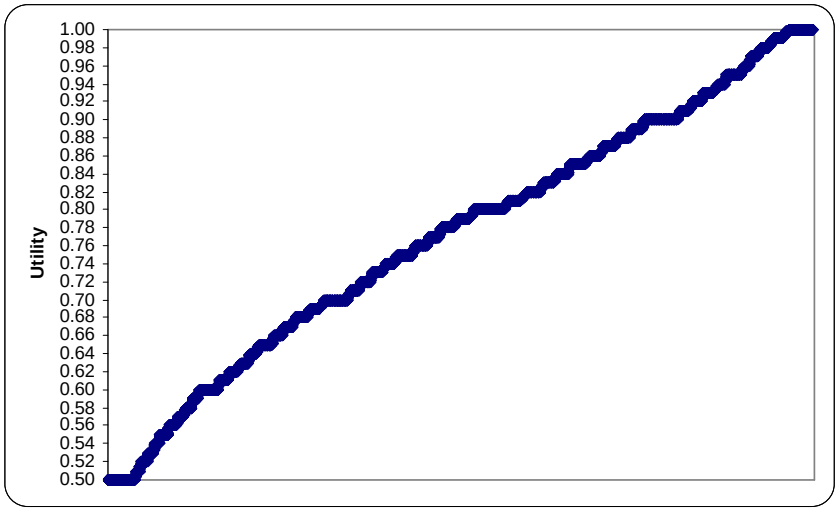


Figure 5: Distribution of all utility values between 0.9 and 1.0

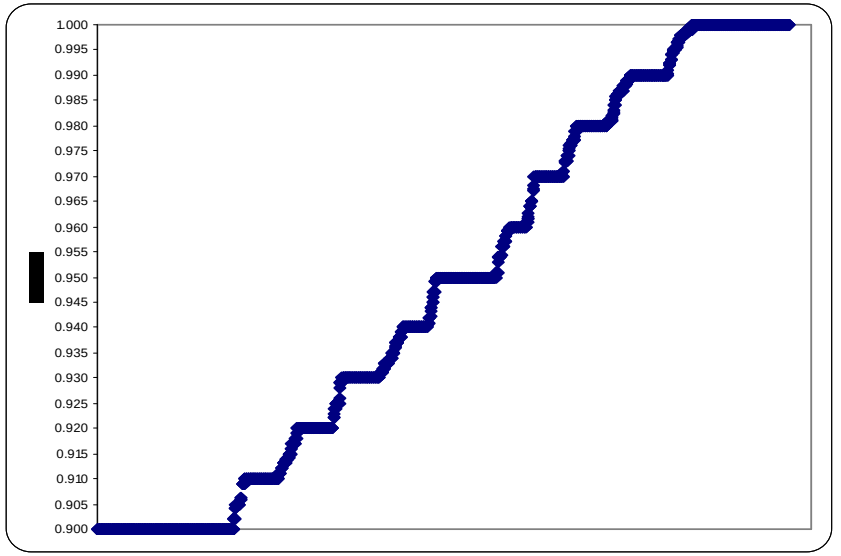


Figure 6: Distribution of utility values based on measurement type between 0.5 and 1.0

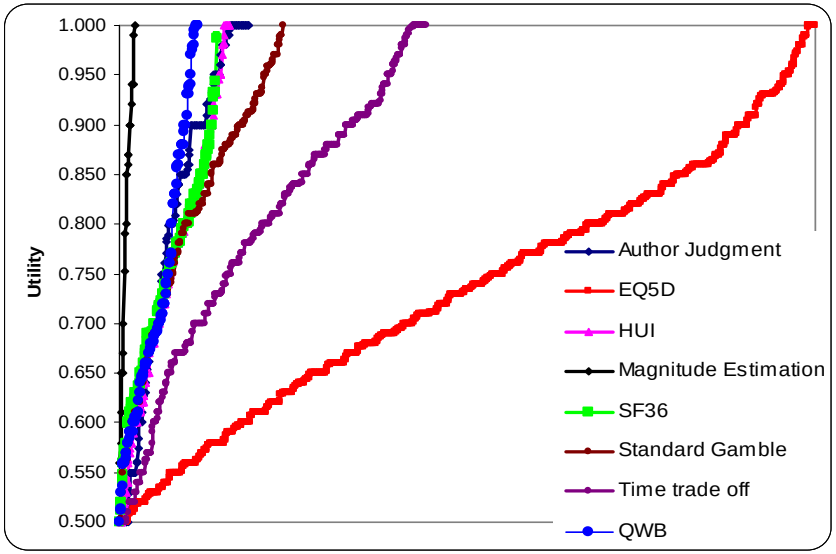


Figure 7: Distribution of utility values between 0.5 and 1.0 for selected measures

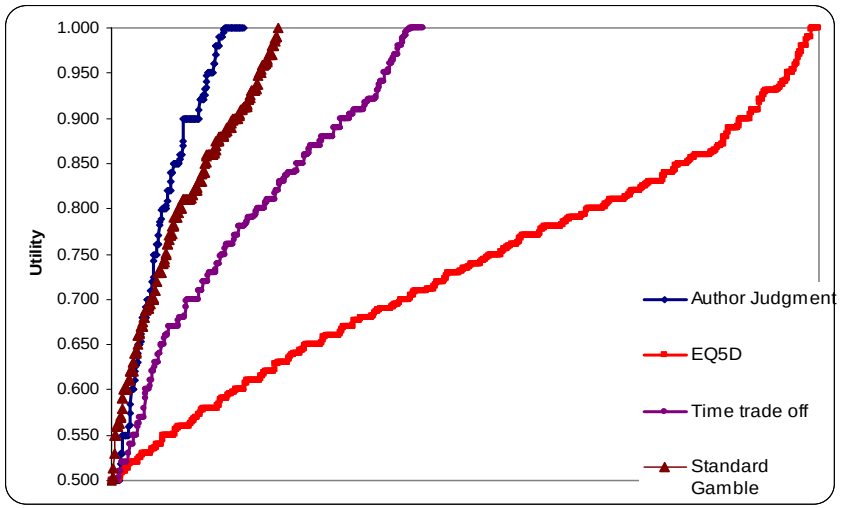


Figure 8: Distribution of utility values based on measurement type between 0.9 and 1.0

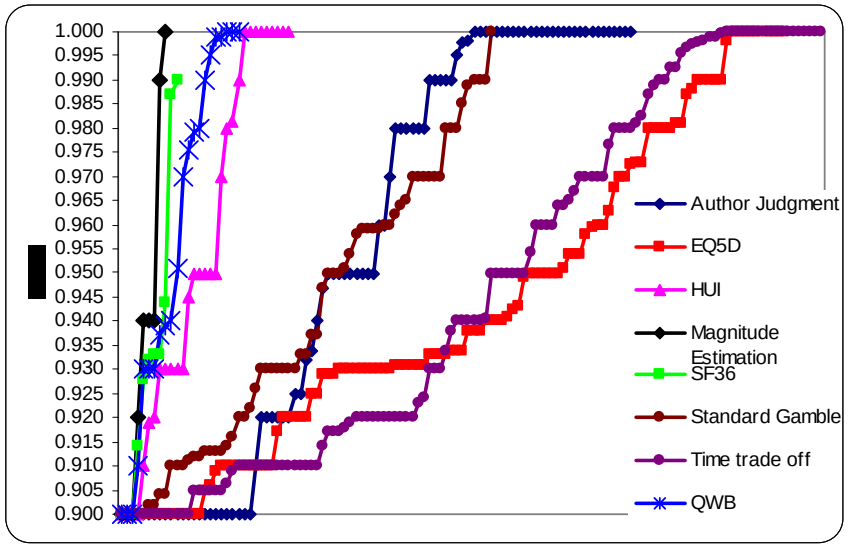
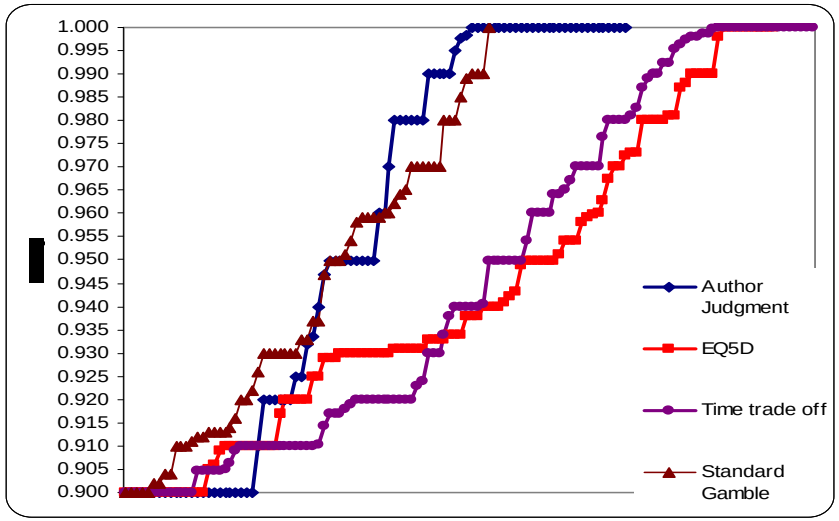


Figure 9: Distribution of utility values between 0.5 and 1.0 for selected measures



There are also disadvantages to this database. The TUFTS database is a large matrix, which makes it difficult to select a limited number of values from a somewhat bewildering array of different values obtained from similar but not necessarily identical health states, elicited by one of 8 different utility measurements. I tried to address this issue by grouping the utilities by method of elicitation, however, a vast number of utilities remained, and this did not help with the issue that the descriptions of the health states were vague and often overlapping. My next approach was to try to tease out the health states, which had a utility value elicited by more than one measurement. I used two approaches to this problem, firstly by examining the studies, which had used several different utility measurements, and secondly by examining across studies within the same disease classification.

For the first approach, I started with 1653 studies (which gave an average of 4.75 utilities per study). I selected only those studies, which reported using more than one type of utility measurement. This resulted in 161 studies (an average of 6.87 utilities per study). I then removed the measurement categories 'other' and 'unknown/NA' as these would not be helpful in any further analysis. This left 48 studies (an average of 5.69 utilities per study). Selecting those utilities, which had a utility elicited using author judgement and at least one other form of utility measurement, I was left with 22 studies (an average of 6.0 utilities per study). I examined these 22 studies in more detail to ascertain whether any of the studies had reported the same health state measured using author judgement and any other measure (see table 1). I was unsuccessful in this endeavour.

For the second approach I started with 68 disease classifications, as defined by the TUFTS database (see figure 10). I selected the most common disease classifications (breast cancer, infectious disease, cardiovascular diseases and musculoskeletal and rheumatologic diseases). I tried to ascertain whether across all studies within a given disease classification the same health state had been reported using different methods of elicitation. This was not possible. It proved very difficult to define the health states so that 'like' could be compared with 'like'.

Table 1. Studies with more than one utility value measured using author judgment and at least one other measurement

Study	Article ID	Classification	Health State	Weight	Measurement
1	2002-01-01169	Hypertension	Swedish general population age >80	0.60	Time trade off
			Swedish general population age 75-84	0.65	Time trade off
			Swedish general population age 65-74	0.81	Time trade off
			Patient at high risk of cardiovascular event (a baseline of 1)	0.90	Author Judgment
2	2003-01-00484	Kidney Disease	Glomerular filtration rate <15 (with or without proteinuria)	0.70	Time trade off
			Glomerular filtration rate =15-89 (with or without proteinuria)	0.95	Time trade off
			Glomerular filtration rate >=90 (proteinuria)	0.98	Author Judgment
			Glomerular filtration rate >=90 (without proteinuria)	0.99	Author Judgment
3	2003-01-00683	Musculoskeletal and Rheumatologic Diseases	Complicated UGI event, surgical management	0.00	Author Judgment
			Non-fatal myocardial infarction	0.00	Author Judgment
			Complicated UGI event, medical management	0.31	Standard Gamble
			Symptomatic ulcer	0.38	Standard Gamble
			Dyspepsia	0.50	Standard Gamble
			Arthritis, no UGI	0.69	Standard Gamble
			Life after myocardial infarction	0.97	Standard Gamble
4	2003-01-00839	Kidney Disease	Patient receiving hemodialysis	0.43	Time trade off
			Patient receiving continuous ambulatory peritoneal dialysis	0.56	Time trade off
			Renal transplant recipient	0.84	Time trade off
			Donor	1.00	Author Judgment
5	2003-01-00843	Kidney Disease	Hospitalization associated with rejection episodes, complications, or the initial surgery.	0.00	Author Judgment
			Dialysis treatment	0.49	Time trade off
			Transplantation	0.78	Time trade off
6	2004-01-00276	Other Non-Infectious GI Diseases	Short term disability from surgery for gastroesophageal reflux disease	0.50	Author Judgment
			Medical therapy for gastroesophageal reflux disease	0.62	SF36
			Surgical therapy with recurrent symptoms for gastroesophageal reflux disease	0.62	SF36
			Surgical therapy with no recurrent symptoms for gastroesophageal reflux disease	0.63	SF36
7	2004-01-00375	Program/ Organizational Interventions	Hepatocellular cancer	0.10	Time trade off
			Liver biopsy for severe complications in HCV patients	0.20	Author Judgment
			Variceal bleeding	0.28	Time trade off
			Hepatic encephalopathy	0.30	Time trade off
			Ascites	0.35	Time trade off

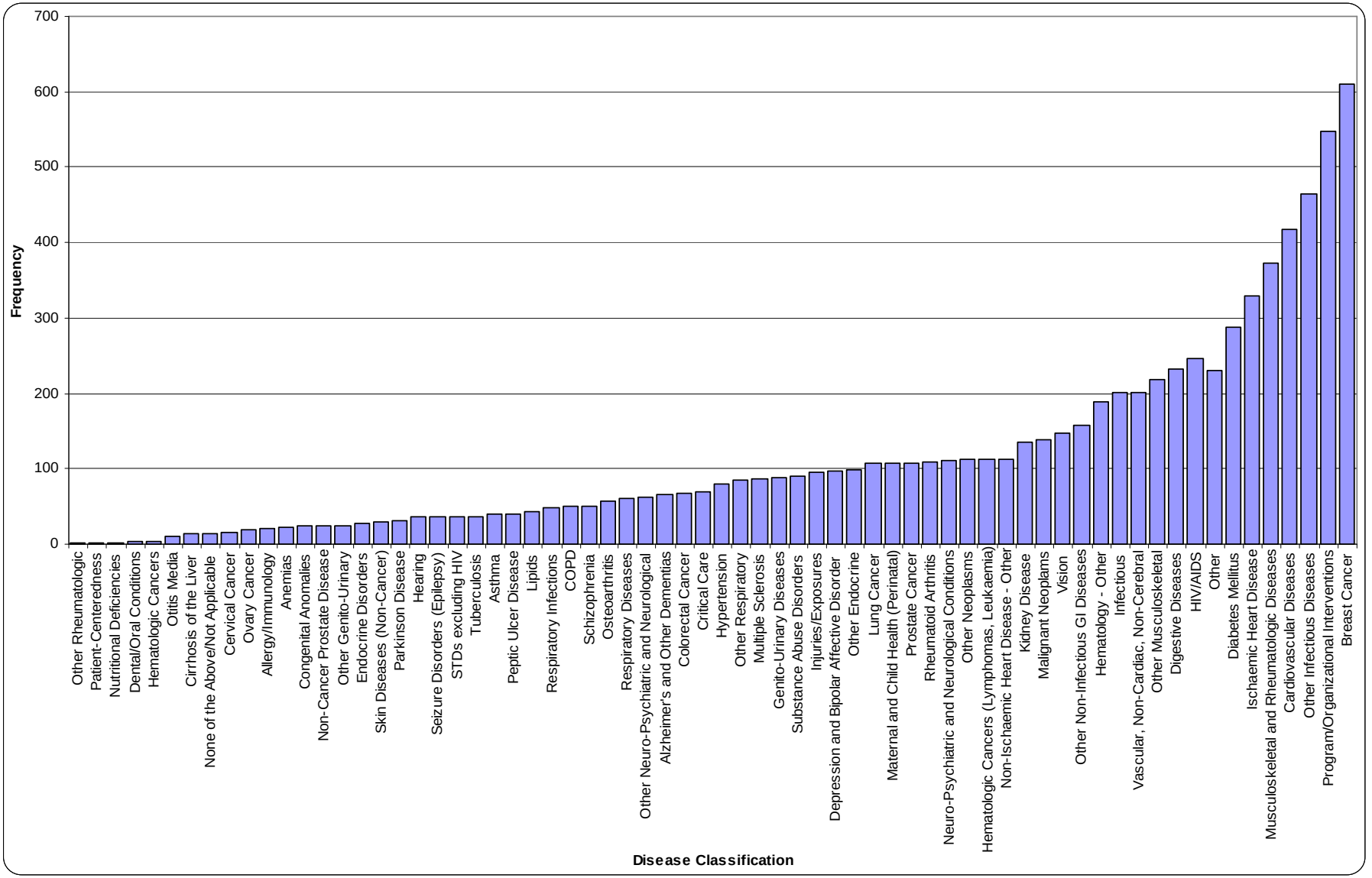
			Cirrhosis	0.44	Other
			Liver transplant in HCV patients during first year	0.50	Time trade off
			Side effects of HCV treatment	0.50	Unknown/NA
			Chronic hepatitis C	0.89	Other
			HCV Treatment without side effects	0.89	Other
			Liver transplant in HCV patients during second or subsequent years	0.90	Other
			Successful drug treatment for HCV	0.95	Other
8	2005-01-01406	Program/ Organizational Interventions	Neurologic disability due to bacterial meningitis	0.06	HUI
			Multiple amputations due to bacterial meningitis	0.61	HUI
			Single amputation due to bacterial meningitis	0.71	HUI
			Hearing loss due to bacterial meningitis	0.72	HUI
			Skin scarring due to bacterial meningitis	1.00	Author Judgment
9	2007-01-02969	Digestive Diseases	Successful revision of dynamic graciloplasty (year 1)	0.45	Author Judgment
			Successful revision of primary artificial bowel sphincter (year 1)	0.58	Author Judgment
			Successful revision of dynamic graciloplasty (years 2-5)	0.65	Author Judgment
			Successful revision of primary artificial bowel sphincter (years 2-5)	0.66	Author Judgment
			End stoma for fecal incontinence	0.69	SF36
			Successful dynamic graciloplasty	0.84	SF36
			Successful primary artificial bowel sphincter	0.91	SF36
10	2007-01-03447	Diabetes Mellitus	Diabetes in the first year when the end stage renal failure occurs	0.64	QWB
			Diabetes in the first year when the heart failure occurs	0.69	QWB
			Diabetes in the first year when the stroke occurs	0.72	QWB
			Diabetes in the first year when the retinopathy occurs	0.75	QWB
			Diabetes in the first year when the myocardial infarction occurs	0.76	Author Judgment
			Diabetes in the first year when the lower extremity amputation occurs	0.80	QWB
			Diabetes in the event-free health states	0.80	Unknown/NA
11	2007-01-03493	Colorectal Cancer	Hospitalization (except neutropenia)	-0.50	Author Judgment
			Neutropenia, hospitalization	-0.45	Unknown/NA
			Diarrhea (no hospitalization)	-0.36	Unknown/NA
			Neuropathy (no hospitalization), grade 2/3, disease-free	-0.30	Unknown/NA
			Neuropathy (no hospitalization), grade 2/3, after relapse	-0.23	Unknown/NA
			Neutropenia, no hospitalization	-0.23	Unknown/NA
			Nausea, vomiting (no hospitalization)	-0.19	Unknown/NA
			Survivor of colorectal cancer with recurrence	0.20	HUI

			Survivor of colorectal cancer	0.85	HUI
12	2008-01-03654	Ischemic Heart Disease	Alive with HF and Stroke	0.22	Author Judgment
			Alive with major disabling stroke	0.36	Unknown/NA
			Alive with HF	0.62	Time trade off
			Good health post AMI	0.90	Unknown/NA
13	2008-01-03657	Program/ Organizational Interventions	Infant neurologic	0.51	Time trade off
			Infant respiratory (hospitalization)	0.58	Time trade off
			Anaphylaxis	0.60	Author Judgment
			Severe cough illness	0.81	Time trade off
			Pneumonia	0.82	Time trade off
			Infant respiratory (outpatient)	0.85	Author Judgment
			Moderate caugh illness	0.85	Time trade off
			Mild caugh illness	0.90	Author Judgment
			Systemic reaction	0.93	Time trade off
			local reaction	0.95	Time trade off
14	2008-01-03826	Diabetes Mellitus	Complication: amputation	0.51	EQ5D
			Severe complications	0.52	Author Judgment
			Complication: renal failure	0.58	Author Judgment
			Complication: nonfatal stroke	0.62	EQ5D
			Complication: heart failure	0.68	EQ5D
			Complication: angina	0.70	EQ5D
			Complication: blind in one eye	0.71	EQ5D
			Complication: nonfatal myocardial infarction	0.73	EQ5D
			Weel: no long-term complication	0.79	EQ5D
15	2008-01-03830	Digestive Diseases	Active + fistula	0.40	Author Judgment
			Non-responding active	0.40	Author Judgment
			Post-surgery complications	0.50	Author Judgment
			Active	0.55	EQ5D
			Active + fistula closure	0.55	EQ5D
			Post-surgery remission	0.67	Unknown/NA
			Remission + fistula	0.68	Author Judgment
			Surgery	0.73	Unknown/NA
			Remission	0.83	EQ5D
			Remission + fistula closure	0.83	EQ5D

16	2008-01-04015	Digestive Diseases	Untreatable adenocarcinoma	0.40	Standard Gamble
			Surgical complications	0.50	Author Judgment
			Surgical treatment	0.55	Author Judgment
			Symptomatic adenocarcinoma	0.68	Standard Gamble
			Well after regression from Barrett's oesophagus	0.80	EQ5D
			Barrett's oesophagus	0.81	Standard Gamble
			High-grade dysplasia(HGD)	0.81	Standard Gamble
			Low-grade dysplasia(LGD)	0.81	Standard Gamble
			Well after surgery	0.86	Standard Gamble
			Diagnosed with adenocarcinoma	0.88	Standard Gamble
17	2008-01-04292	Malignant Neoplams	Disease progression of unresectable gastrointestinal stroma tumors (GIST)	0.58	EQ5D
			During the 4 weeks with the treatment of each cycle of sunitinib	0.71	EQ5D
			During the 2 weeks without treatment of each cycle (rest weeks) of sunitinib	0.77	EQ5D
			Best supportive care (BSC) no progression	0.78	EQ5D
			Spanish patients with metastatic and/or unresectable gastrointestinal stroma tumors (GIST) after progression or intolerance with imatinib	0.79	Author Judgment
18	2008-01-04297	Ischaemic Heart Disease	Systemic complications	0.72	Time trade off
			After failed cardiac rehabilitation	0.83	Author Judgment
			After non-fatal cardiac event	0.83	EQ5D
			Pre-rehabilitation	0.83	EQ5D
			After successful cardiac rehabilitation	0.98	EQ5D
19	2008-01-04509	HIV/AIDS	Pancreatitits	0.50	Author Judgment
			Lipoatrophy	0.87	Unknown/NA
			Neuropathy	0.94	EQ5D
20	2008-01-04522	Digestive Diseases	Ulcerative colitis in remission-difference between no maintenance 5 Aminosalycylic acid therapy vs. maintenance	0.01	Author Judgment
			In patient flare	0.61	Unknown/NA
			Post pouch excision/ileostomy	0.73	Unknown/NA
			Outpatient flare	0.77	Time trade off
			After colectomy with ileal pouch	0.84	Unknown/NA
			Ulcerative colitis in remission-no maintenance 5 Aminosalycylic acid therapy	0.92	Time trade off
			Ulcerative colitis in remission-maintenance 5 Aminosalycylic acid therapy	0.92	Time trade off
21	2009-01-04903	Digestive Diseases	Very severe	0.43	Standard Gamble
			Severe	0.69	Standard Gamble

			Moderate	0.80	Standard Gamble
			Remission	0.86	Author Judgment
22	2009-01-05169	Digestive Diseases	Distal Cancer (Dukes D)	0.25	EQ5D
			Regionalized Cancer (Dukes C)	0.59	EQ5D
			Localized Cancer - Dukes (A/B)	0.74	EQ5D
			Between stage I and stage II of ileal pouch anal anastomosis	0.80	Author Judgment
			Long term after ileal pouch anal anastomosis	0.92	EQ5D
			Permanent ileostomy	0.92	EQ5D
			Ulcerative colitis in remission (before ileal pouch anal anastomosis)	0.94	Author Judgment

Figure 10. Frequency of the disease classification for all the health states on the TUFTS database



The biggest challenge with this approach was that the description of the health states were vague and often overlapping, such that it was difficult to summarise utilities across different diseases to ensure ‘like’ was compared with ’like’. I tried to overcome this problem by referring back to the relevant publication in an attempt to define the health state more precisely, but this was not as straightforward as I had originally hoped it would be. It was incredibly time consuming and raised other issues around the quality of the utility values reported in the literature and subsequently reported in the database. Without being able to accurately define the health states, it was difficult to select which health states should be chosen for the hierarchy. In addition, the whole process was complicated by the shear volume of the database. I do not think that the size of the database is ultimately a bad thing. However, I do have concerns about the quality of the some of the values reported and the vague health states described. It is the size which means that it would take more time than I had available to accurately define the health states for the given utilities and to asses the quality of the reported values, to select a meaningful sample to produce such a hierarchy as I intend.

Appendix 13: Analysis of NICE appraisals

As discussed previously in chapter 8 and appendix 12, the TUFTs database did not provide an appropriate source of utilities and therefore an alternative source of utilities was required. I therefore considered other sources of utilities where I could borrow strengths from previous work and identified NICE appraisals as on e such source. The advantage of NICE appraisals was that i) the health states are reasonably tightly defined, and ii) NICE committees review the quality of the appraisals. Therefore, I decided it would be reasonable to assume that these utilities would offer the best estimates currently available in the literature, which allowed me to account for the variations in quality.

I identified the NICE appraisals from the website - www.nice.org.uk/Guidance/TA/Published. At the time the search (June 2010) there were 191 published technology appraisals available. I entered this information (ref number, title, date issued, and review date) into an Excel spreadsheet for further analysis. Once in Excel my first task was to edit the list. Many of the appraisals were updates of an earlier appraisal so I removed any that had been superseded by a more recent review. My second task was to categorise the appraisals by assigning a disease topic to each of the appraisals. I ended up with 138 appraisals (table 1), which covered 78 disease topics (see figure 1).

Next, I needed to start identifying the utility values. I surveyed the list to pick out conditions that on the face of it would cover a wide range of diseases/ sub-diseases, varying from psoriasis to motor neurone disease for example. Those selected are shown in bold in table 1 and illustrated in pink in figure 1. This was still a time consuming process as not all the NICE appraisals state the baseline utility score, often they state just the QALY gain between the comparative treatments/ interventions. In these cases, I sourced the corresponding NICE Evidence Review Group (ERG) report and/or the NICE Technology Assessment Report (TAR) to gather the required information. Both the ERG report and TAR can be found via the advanced search function under published HTA report (http://www.hta.ac.uk/project/htapubs.asp), from here, there is a link to the corresponding NICE report and access to the ERG report and TAR. Further details on the utility values identified are given in chapter 8, page 233.

Table 1. A list of the NICE technology appraisals used to form the basis of identifying utility values for given health states

Ref	Topic	Title	Date Issued
TA167	Abdominal aortic aneurysm	Abdominal aortic aneurysm - endovascular stent-grafts	Feb-09
TA182	**Acute coronary syndrome**	**Acute coronary syndrome – prasugrel**	**Oct-09**
TA47		**Acute coronary syndromes - glycoprotein IIb/IIIa inhibitors (review)**	**Sep-02**
TA98	**ADHD**	**Attention deficit hyperactivity disorder (ADHD) - methylphenidate, atomoxetine and dexamfetamine**	**Mar-06**
TA111	**Alzheimer's disease**	**Alzheimer's disease - donepezil, galantamine, rivastigmine (review) and memantine**	**Sep-07**
TA142	Anaemia	Anaemia (cancer-treatment induced) - erythropoietin (alpha and beta) and darbepoetin	May-08
TA73	**Angina and myocardial infarction**	**Angina and myocardial infarction - myocardial perfusion scintigraphy**	**Nov-03**
TA52		**Myocardial infarction – thrombolysis**	Oct-02
TA143	Ankylosing spondylitis	Ankylosing spondylitis - adalimumab, etanercept and infliximab	May-08
TA95	Arrhythmia	Arrhythmia - implantable cardioverter defibrillators (ICDs) (review)	Jan-06
TA35	Arthritis	Arthritis (juvenile idiopathic) – etanercept	Mar-02
TA138	**Asthma**	**Asthma (in adults) - corticosteroids**	**Mar-08**
TA131		**Asthma (in children) – corticosteroids**	**Nov-07**
TA133		**Asthma (uncontrolled) – omalizumab**	**Nov-07**
TA38		**Asthma (older children) - inhaler devices**	**Mar-02**
TA10		**Asthma (children under 5) - inhaler devices**	**Aug-00**
TA88	Bradycardia	Bradycardia - dual chamber pacemakers	Feb-05
TA23	Brain cancer	Brain cancer – temozolomide	Apr-01
TA121		Glioma (newly diagnosed and high grade) - carmustine implants and temozolomide	Jun-07
TA116	Breast cancer	Breast cancer - gemcitabine	Jan-07
TA112		Breast cancer (early) - hormonal treatments	Nov-06
TA108		Breast cancer (early) – paclitaxel	Sep-06
TA109		Breast cancer (early) – docetaxel	Sep-06
TA107		Breast cancer (early) – trastuzumab	Aug-06
TA34		Breast cancer – trastuzumab	Mar-02
TA94	Cardiovascular disease	Cardiovascular disease – statins	Jan-06
TA89	**Cartilage**	**Cartilage injury - autologous chondrocyte implantation (ACI) (review)**	**May-05**
TA183	Cervical cancer	Cervical cancer (recurrent) - topotecan	Oct-09
TA69		Cervical cancer - cervical screening (review)	Oct-03
TA100	Colon cancer	Colon cancer (adjuvant) - capecitabine and oxaliplatin	Apr-06
TA176	Colorectal cancer	Colorectal cancer (first line) – cetuximab	Aug-09
TA118		Colorectal cancer (metastatic) - bevacizumab & cetuximab	Jan-07

TA105		Colorectal cancer - laparoscopic surgery (review)	Aug-06
TA93		Colorectal cancer (advanced) - irinotecan, oxaliplatin and raltitrexed (review)	Aug-05
TA61		Colorectal cancer - capecitabine and tegafur uracil	May-03
TA152	**Coronary artery disease**	**Coronary artery disease - drug-eluting stents**	**Jul-08**
TA187	Crohn's disease	Crohn's disease - infliximab (review) and adalimumab (review of TA40)	May-10
TA40		Crohn's disease – infliximab	Apr-02
TA97	**Depression & anxiety**	**Depression and anxiety - computerised cognitive behavioural therapy (CCBT)**	**Feb-06**
TA59		**Electroconvulsive therapy (ECT)**	**Apr-03**
TA151	Diabetes	Diabetes - insulin pump therapy	Jul-08
TA113		Diabetes (type 1 and 2) - inhaled insulin	Dec-06
TA60		Diabetes (types 1 and 2) - patient education models	Apr-03
TA53		Diabetes (types 1 and 2) - long acting insulin analogues	Dec-02
TA114	Drug misuse	Drug misuse - methadone and buprenorphine	Jan-07
TA115		Drug misuse – naltrexone	Jan-07
TA177	Eczema	Eczema (chronic) - alitretinoin	Aug-09
TA81		Atopic dermatitis (eczema) - topical steroids	Aug-04
TA82		Atopic dermatitis (eczema) - pimecrolimus and tacrolimus	Aug-04
TA79	**Epilepsy**	**Epilepsy (children) - newer drugs**	**Apr-04**
TA76		**Epilepsy (adults) - newer drugs**	**Mar-04**
TA110	Follicular lymphoma	Follicular lymphoma – rituximab	Sep-06
TA179	Gastrointestinal stromal tumour	Gastrointestinal stromal tumours – sunitinib	Sep-09
TA86		Gastro-intestinal stromal tumours (GIST) - imatinib	Oct-04
TA188	Growth failure	Human growth hormone (somatropin) for the treatment of growth failure in children (review)	May-10
TA64		Growth hormone deficiency (adults) - human growth hormone	Aug-03
TA128	Haemorrhoid	Haemorrhoid - stapled haemorroidopexy	Sep-07
TA172	**Head & neck cancer**	**Head and neck cancer (squamous cell carcinoma) - cetuximab**	**Jun-09**
TA145		**Head and neck cancer – cetuximab**	**Jun-08**
TA166	Hearing	Hearing impairment - cochlear implants	Jan-09
TA120	Heart failure	Heart failure - cardiac resynchronisation	May-07
TA173	Hepatitis b	Hepatitis B - tenofovir disoproxil fumarate	Jul-09
TA154		Hepatitis B - telbivudine	Aug-08
TA153		Hepatitis B - entecavir	Aug-08
TA96		Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a	Feb-06
TA106	Hepatitis c	Hepatitis C - peginterferon alfa and ribavirin	Aug-06

TA75		Hepatitis C - pegylated interferons, ribavirin and alfa interferon	Jan-04
TA189	Hepatocellular carcinoma	Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line)	May-10
TA83	**Hernia**	**Hernia - laparoscopic surgery (review)**	**Sep-04**
TA44	**Hip**	**Hip disease - metal on metal hip resurfacing**	**Jun-02**
TA2		**Hip disease - replacement prostheses**	**Apr-00**
TA132	Hypercholesterolaemia	Hypercholesterolaemia – ezetimibe	Nov-07
TA117	Hyperparathyroidism	Hyperparathyroidism – cinacalcet	Jan-07
TA164	Hyperuricaemia	Hyperuricaemia - febuxostat	Dec-08
TA168	Influenza	Influenza - zanamivir, amantadine and oseltamivir (review)	Feb-09
TA158		Influenza (prophylaxis) - amantadine, oseltamivir and zanamivir	Sep-08
TA77	Insomnia	Insomnia - newer hypnotic drugs	Apr-04
TA71	Ischaemic heart disease	Ischaemic heart disease - coronary artery stents	Oct-03
TA122		Ischaemic stroke (acute) – alteplase	Jun-07
TA174	Leukaemia	Leukaemia (chronic lymphocytic, first line) - rituximab	Jul-09
TA119		Leukaemia (lymphocytic) – fludarabine	Feb-07
TA70		Leukaemia (chronic myeloid) – imatinib	Oct-03
TA29		Leukaemia (lymphocytic) – fludarabine	Sep-01
TA190	**Lung cancer**	**Lung cancer (non-small-cell) - pemetrexed (maintenance)**	**Jun-10**
TA162		**Lung cancer (non-small-cell) - erlotinib**	**Nov-08**
TA124		**Lung cancer (non-small-cell) - pemetrexed**	**Aug-07**
TA184		**Lung cancer (small-cell) – topotecan**	**Nov-09**
TA181		**Lung cancer (non-small cell, first line treatment) - pemetrexed**	**Sep-09**
TA137	Lymphoma	Lymphoma (follicular non-Hodgkin's) - rituximab	Feb-08
TA155	**Macular degeneration**	**Macular degeneration (age-related) - ranibizumab and pegaptanib**	**Aug-08**
TA68		**Macular degeneration (age-related) - photodynamic therapy**	**Sep-03**
TA78	Menstrual bleeding	Menstrual bleeding - fluid-filled thermal balloon and microwave endometrial ablation	Apr-04
TA135	Mesothelioma	Mesothelioma - pemetrexed disodium	Jan-08
TA20	**Motor neurone disease**	**Motor neurone disease – riluzole**	**Jan-01**
TA171	Multiple myeloma	Multiple myeloma – lenalidomide	Jun-09
TA129		Multiple myeloma – bortezomib	Oct-07
TA127	**Multiple sclerosis**	**Multiple sclerosis – natalizumab**	**Aug-07**
TA32		**Multiple sclerosis - beta interferon and glatiramer acetate**	**Jan-02**
TA65	Non-hodgkins lymphoma	Non-Hodgkin's lymphoma – rituximab	Sep-03
TA165	Organ preservatin	Organ preservation (renal) - machine perfusion and static storage	Nov-08

TA160	**Osteoporosis**	**Osteoporosis - primary prevention**	**Oct-08**
TA161		**Osteoporosis - secondary prevention including strontium ranelate**	**Oct-08**
TA102	Other	Conduct disorder in children - parent-training/education programmes	Jul-06
TA49		Central venous catheters - ultrasound locating devices	Sep-02
TA91	Ovarian cancer	Ovarian cancer (advanced) - paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan (review)	May-05
TA55		Ovarian cancer - paclitaxel (review)	Jan-03
TA159	Pain	Pain (chronic neuropathic or ischaemic) - spinal cord stimulation	Oct-08
TA25	pancreatic cancer	Pancreatic cancer – gemcitabine	May-01
TA156	Pregnancy	Pregnancy (rhesus negative women) - routine anti-D (review)	Aug-08
TA101	prostate cancer	Prostate cancer (hormone-refractory) - docetaxel	Jun-06
TA180	**Psoriasis**	**Psoriasis - ustekinumab**	**Sep-09**
TA146		**Psoriasis – adalimumab**	**Jun-08**
TA134		**Psoriasis – infliximab**	**Jan-08**
TA125		**Psoriatic arthritis (moderate to severe) - adalimumab**	**Aug-07**
TA103		**Psoriasis - efalizumab and etanercept**	**Jul-06**
TA104		**Psoriatic arthritis - etanercept and infliximab**	**Jul-06**
TA136	Psychosis	Structural neuroimaging in first-episode psychosis	Feb-08
TA178	Renal cell carcinoma	Renal cell carcinoma	Aug-09
TA169		Renal cell carcinoma – sunitinib	Mar-09
TA48	**Renal failure**	**Renal failure - home versus hospital haemodialysis**	**Sep-02**
TA99	Renal transplantation	Renal transplantation – immunosuppressive regimens for children and adolescents	Apr-06
TA85		Renal transplantation - immuno-suppressive regimens (adults)	Sep-04
TA186	**Rheumatoid arthritis**	**Rheumatoid arthritis - certolizumab pegol**	**Feb-10**
TA141		**Rheumatoid arthritis (refractory) - abatacept**	**Apr-08**
TA130		**Rheumatoid arthritis - adalimumab, etanercept and infliximab**	**Oct-07**
TA126		**Rheumatoid arthritis (refractory) - rituximab**	**Aug-07**
TA84	Sepsis	Sepsis (severe) – drotrecogin	Sep-04
TA139	sleep apnoea	Sleep apnoea - continuous positive airway pressure (CPAP)	Mar-08
TA123	Smoking	Smoking cessation - varenicline	Jul-07
TA185	Soft tissue carcinoma	Soft tissue sarcoma – trabectedin	Feb-10
TA92	Teeth	Tooth decay – HealOzone	Jul-05
TA1		Wisdom teeth – removal	Mar-00
TA74	Trauma	Trauma - fluid replacement therapy	Jan-04
TA163	Ulcerative colitis	Ulcerative colitis (acute exacerbations) - infliximab	Dec-08

TA140		Ulcerative colitis (subacute manifestations) - infliximab	Apr-08
TA90	Vascular disease	Vascular disease - clopidogrel and dipyridamole	May-05
TA170	**Venous thromboembolism**	**Venous thromboembolism – rivaroxaban**	**Apr-09**
TA157		**Venous thromboembolism - dabigatran**	**Sep-08**

Figure 1. Distribution of disease topics across the 138 NICE appraisals