Including Health Spillovers in Economic Evaluations

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Abstract

Patient chronic illness and disability impacts the health of family members and household members who experience psychological distress and care burden. These impacts, known as 'health spillovers', are typically ignored in economic evaluations, despite being relevant to ensuring maximum health benefits from scarce resources. This thesis explores methods for including health spillovers in economic evaluation. Three empirical studies were carried out. The first study generated evidence supporting the validity of the EQ-5D-5L and SF-6D for measuring health spillovers. The second study examined the health spillover from a behavioural intervention on related household members' outcomes. Further trials are warranted which measure household member outcomes for patient health interventions. The third study demonstrated and applied a methodology which could be used to include health spillovers in a cost-utility analysis. The general conclusion is that family member costs/outcomes should be systematically accounted for in extra-welfarist economic evaluations, and though there remains uncertainty about the best way to achieve this, the findings from this thesis show that this is possible and advance the methods forward.

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Overview of thesis

This thesis aims to address methodological challenges to including health spillovers (health effects in family members of patients) in a cost-utility analysis (CUA). To address this aim, the thesis has the following objectives.

1) To establish how health spillovers have been conceptualised in the research literature and included to date in CUA;

2) To test the validity and responsiveness of different generic health status measures for measuring health spillovers;

3) To conduct a case study collecting primary data on health spillovers generated through a behavioural intervention targeted at patients;

4) To establish and apply methods for including health spillover data in a within-trial cost-utility analysis.

These investigations were carried out in order to address a lack of understanding in health economics about the best way to measure health spillovers, the appropriate methods for including health spillovers in a cost-utility analysis, and the types of health spillovers that behavioural health interventions produce.

Two case studies were used to explore the research questions: a study where a secondary dataset of the family members of meningitis patients was analysed (used to address the second research objective), and a study where survey data was collected and analysed on the health status of household members of COPD trial patients (used to address the third and fourth research objectives). The first two chapters review the medical and economic literature on health spillovers (addressing the first research objective). Chapters 3 to 7 describe the 3 empirical studies that were carried out for the thesis. Chapter 8 draws

together the thesis with main findings and implications for future research and practice. More details of each chapter are provided below:

Chapter 1: Health Spillovers of Illnesses

This chapter first provides a definition of health spillovers, and then reviews the medical and psychological literature on health spillovers. The objective of Chapter 1 was to identify how family members' health is impacted by patient chronic illness/disability. Impacts that were identified on family members' health included anxiety, depression, stress, back pain, sleep disturbance and reduced immunity. This literature review also enabled a model of the determinants of family members' health status to be generated, as a basis for the empirical study in Chapter 3.

Chapter 2: Incorporating spillovers in economic evaluation

Chapter 2 is a review of the economic evaluation literature on spillovers (both health and non-health related spillovers). Although the economic literature sometimes refers to spillovers in terms of the externalities generated through business transactions or industrial research and development (e.g. pollution, the creation of new knowledge), the concept of spillovers in this study relates to the inclusion of caring about and caring for the patient effects in economic evaluation. The chapter concludes with a systematic literature review of all the cost-utility analyses which have included health spillovers. The systematic review aims to help us understand the methods which have been used for including health spillovers in

economic evaluation to date. The studies identified were used to inform the methods used for the economic evaluation study in Chapter 7.

Chapter 3: A comparison of the validity and responsiveness of the EQ-5D-5L and SF-6D for measuring health spillovers: a study of the family impact of meningitis: methods

This chapter describes the methods of the first empirical study of the thesis. The study compares the validity of the EQ-5D-5L and SF-6D for measuring health spillovers, by using a secondary dataset of 1587 family members of meningitis survivors. Two types of validity are assessed: construct validity and responsiveness. A literature review of factors associated with spillover effects was undertaken to identify constructs related to the caring context and patient health predicted to be associated with impaired health of family members.

Chapter 4: Results of a comparison of the validity and responsiveness of the EQ-5D-5L and SF-6D for measuring health spillovers: a study of the family impact of meningitis

Chapter 4 presents the results and discussion for the study of validity and responsiveness. Statistical tests were carried out to assess associations between a range of constructs and family members' health outcomes (assessed by the EQ-5D-5L and SF-6D).

Chapter 5: Investigation of the impacts of a COPD telephone coaching intervention on the health and health behaviours of household members: methods

This chapter presents the methods for the second empirical study of the thesis. The study assesses the health spillovers generated from a COPD telephone coaching intervention. A literature synthesis of the existing evidence on COPD family impact was carried out. A randomised controlled trial of a COPD telephone coaching intervention was used as a case study. Data on the health and health behaviours of responding household members (n=153) was collected at baseline and after 12 months. Qualitative free-text responses were also collected to enable understanding of how COPD indirectly impacted family members.

Chapter 6: Results of an investigation of the impacts of a COPD telephone coaching intervention on the health and health behaviours of household members

Chapter 6 presents the results and discussion of the study analysing the health spillovers generated from a COPD telephone coaching intervention. Assessments were made about whether the telephone coaching intervention produced statistically significant improvements in physical activity, smoking, mental health, and the EQ-5D-5L scores of patients' household members.

Chapter 7: Including health spillovers in the economic evaluation of a COPD telephone coaching intervention

This chapter is the third empirical study of the thesis. The study undertakes a range of approaches for including health spillovers in the cost-utility analysis of the COPD telephone coaching intervention. In this study, an illustration of how household member QALYs may be included in a trial-based economic evaluation is provided. Factors that were examined were the threshold adopted, number of household members included and the inclusion of household member primary care costs.

Chapter 8: Overall discussion

The final chapter reflects on the main findings of the thesis which explores how health interventions produce health spillovers, and what the best practice is for measuring and including health spillovers in a cost-utility analysis. Recommendations for future areas of research are provided.

CHAPTER 1: HEALTH SPILLOVERS OF ILLNESSES

The impact of illness is not confined to the patient. Patients are not isolated individuals and their illness or disability can also be a tragic experience for their family members. Family members may experience both health and non-health impacts to their life from patient illness or disability. Health spillovers refer to the impacts of illnesses (and associated health interventions) specifically on the *health* of family and social networks of patients.

The overarching aim of this thesis is to increase understanding of the methods which are appropriate for including health spillovers in a cost-utility analysis. The rationale for this doing this is that health spillovers are potentially important to include in cost-utility analyses, but this is rarely done. In order to achieve the aim, various objectives were met. Objective 1 was to establish how health spillovers have been conceptualised in the research literature, and how health (and non-health) spillovers have been included in economic evaluations such as cost-utility analyses (CUAs). For objective 1, two literature chapters were produced. The first literature review chapter (Chapter 1) provided a review of the medical, psychological and sociological literature on the health spillovers which are generated from patient chronic illness and disability. The second literature review chapter (Chapter 2) provided a review of the health economics literature by setting out the various ways in which health and non-health effects in family members can be incorporated into an economic evaluation. The systematic review at the end of Chapter 2 presented a narrower focus of the ways that health spillovers have been included in CUAs to date, through a comparison and critique of the methods which have been used to include health spillovers in these studies, as well as identification of how many CUAs have included health spillovers.

Objective 2 was to assess what instruments are valid for measuring health spillovers. For objective 2, a comparison of the validity of EQ-5D-5L and SF-6D was conducted using a large dataset of family members of meningitis survivors, which is reported in chapters 3 and 4. Objective 3 was to conduct a case study collecting primary data from family members alongside the randomised controlled trial of a behaviour change intervention for patients. This objective was addressed in Chapters 5 and 6, where the impact of a behaviour change health intervention on the EQ-5D-5L scores of patients' household members was evaluated, which provided a basis for calculating QALYs for the secondary analysis of the economic evaluation of the intervention in Chapter 7. Furthermore, data on the household members' own health behaviours and psychological wellbeing was also collected and evaluated. The fourth objective of the thesis (addressed in Chapter 7) was to identify and apply various techniques for including health spillover data in a within-trial CUA. These techniques were informed by the methodological literature, as well as drawn from the cost-utility analysis studies from the systematic review in Chapter 2 which included health spillovers.

The medical literature on health spillovers is discussed in this chapter, with the objective of identifying health outcomes for families and social networks of patients, the mechanisms by which they arise and the groups that are affected. The methods of including spillover in economic evaluation, and the economic principles underlying their incorporation are the focus of Chapter 2. Before addressing how health spillovers intersect with economic evaluation in health care, the primary objective of this first chapter is to identify the nature and scope of health spillovers by reviewing key studies from the medical and psychological literature.

Section 1.1 provides a definition of health spillovers and also provides a brief description of the non-health spillovers that family members may also experience. Section 1.2 goes on to document the health outcomes of family members of those with illness, with explanation of the potential physical and mental health effects of illness on those close to patients. Section 1.3 discusses the different individuals who are likely to experience health spillover, including spousal carers, young carers and those who share a house with the patient, as it is important to identify the individuals who are at most risk of pathology. Section 1.4 then separately discusses the literature about the concordance of health behaviours within social networks resulting in health spillovers, motivating the PhD study which examines the wider effects of a COPD behaviour change intervention. Section 1.5 surveys the literature on the health outcomes generated from health interventions, as the ultimate interest of this work is to capture the health outcomes of interventions beyond the direct recipients of the intervention, to inform resource allocation decisions. Section 1.6 concludes the chapter.

1.1. Conceptualising health spillovers

A patient's illness can have a variety of impacts on the family which result from the psychological suffering induced from 'caring about' a patient, and the provision of informal care, i.e. 'caring for' a patient. These two causal pathways are discussed at length in section 1.2.6. The spillover concept relates to the impact that the illness of a patient and interventions for that patient has on the social network of a patient, while the patient is still alive (5). For example, people who are emotionally and physically close to the patient (e.g. family and household members) are likely to be affected by the illness. This is because family members may take on a 'carer' role to provide care for the sick patient- imposing various

effects on these family members. Family members who do not take on carer responsibilities may also experience spillover effects from the anxiety and distress of having a loved one that is ill(6). Around six million (one in ten) people in the UK are informal carers, and many more people are affected by a loved one's ill health, even if they do not provide informal care for them. Some individuals may not be blood-related to the patient, or live with the patient, yet may still incur spillovers- e.g. a friend, or a neighbour that assumes carer responsibilities. The spillover outcomes can be further dichotomised into two types- health spillovers (the effects of illness on the *health* of individuals other than the patient), and non-health spillovers (this distinction is set out further in section 1.1.3). Wittenberg et al (2013) define health spillovers as:

'The mental and physical health effects of illness that extend beyond the solitary patient' (p.1) (5).

I will use this definition of health spillovers for the rest of the thesis, but with an extended component, to address the health effects not only of illnesses, but also of *health interventions*, beyond the individual patient. Before investigating health spillovers it is also important to set out that the health spillovers that are the focus of this PhD do not relate to the concepts of infectious diseases spreading from one patient to another, the genetic transmission of hereditary diseases, or the health experiences of individuals who experience a bereavement which are distinct to the health effects experienced from having a loved one with a chronic illness or disability (5).

1.1.1. Evolution of research into health spillovers

A number of studies were carried out in the 1960s on the heightened risk of mortality of older individuals following the bereavement of a spouse (termed as the 'widower effect') (7-10). However since the 1980s, academic research has shifted focus away from bereavement effects to spillover effects relating to the physical and mental health of family carers of the chronically ill or disabled. A large number of studies have been carried out in this area, with a particular focus on Alzheimer's disease and dementia(11) as dementia caregiving is recognised as being a distinctly challenging experience, as will be described in section 1.3. However, the spillover of illness on non-caregiving family members (family members who are not active caregivers) remains a neglected area of research, and yet it is important to explore the nature of the physical and psychological health effects of patient illness on these non-carers as they may be substantial. Moreover these effects may also apply to carers that 'care about' the patient's wellbeing (12).

This PhD aims to build on the existing body of research by investigating health spillovers among both caregiving and non-caregiving family members, with the specific aim of addressing key issues in enabling health spillovers to be included in economic evaluation. Including the wider health effects of interventions is necessary in economic evaluation to guide decision makers towards judgements that maximise population health, rather than just patient health (13).

1.1.2. Setting health spillovers in the context of other spillover effects of illness

Family members experience a number of spillovers of illness. These effects may extend beyond their health status, such as the financial losses for family members having to reduce or give up their employment to care for the patient, reduced participation in social activities and being confined to the house (14). The family members who often experience spillovers of illness are those who provide care for the patient- known as family (informal) carers. Informal care tasks may include cleaning and food preparation for someone who is incapacitated, assistance with health care, and lifting and transporting a disabled person (14). The need to provide informal care for a chronically ill person can impose substantial financial and time costs on a family carer for many years (14, 15). Family carers are usually referred to as 'informal carers' - as the care they provide is unpaid, although some informal carers may receive social security benefits related to their care work such as Carer's Allowance(16). Many informal carers spend large amounts of time providing unpaid care that may also prevent them from undertaking paid work. Additionally the time burden resulting from informal care means that many carers live very restricted lives and have little time for themselves outside of work and providing informal care (14, 17). The ONS (Office for National Statistics) estimates that there are 5.8 million unpaid carers in the UK (18), including 1.4 million providing over 50 hours of unpaid care per week(18). The total value of the care that informal carers provide in the UK is valued at £132 billion per annum (19). Therefore, even if a small proportion of these carers were unable to continue providing care due to their own health impairment, the loss to the UK economy could still be substantial.

This indicates that there may be a substantial economic cost from neglecting to account for the health of carers in resource allocation decisions. It may also be important to account for health effects experienced among non-caregiving family members who may experience lasting feelings of isolation, anxiety, distress and loss, from the chronic illness of a family member (6, 14).

Although there is clearly a potential to explore spillover of illness more broadly to include non-health effects such as financial impact; this thesis focuses more narrowly on the health spillovers of illness, and the inclusion of these in economic evaluation. The justification for this narrower focus lies in the form of economic evaluation most commonly used, and is set out in Chapter 2. Therefore the focus of this literature review is only on the health effects of illness beyond the patient.

1.1.3. Scope of health spillovers considered within PhD

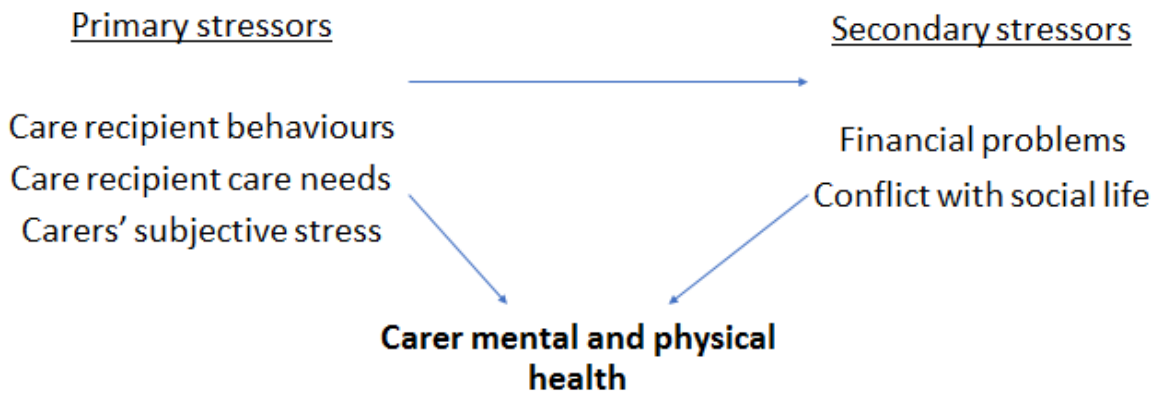
Definitions of health spillovers do not usually refer to the impact of bereavement on the health of family members(5). However there will be a short discussion in this chapter on these bereavement effects on family members, as there may also be justification for the inclusion of these effects in economic evaluation (20). Spillovers on formal carers (those who are paid to provide care for people), are important to capture as a health or social care resource cost in applied economic evaluations (21), but the health effects to formal carers are not considered as health spillovers as they are paid for their services.

Therefore the focus of the PhD is on assessing the health effects (or health spillovers) of illness on unremunerated social networks of patients, while the patient is still alive. The health spillovers on family members are not only the result of providing care for the patient. Seeing a loved one suffering with an illness is also a cause of psychological distress(6). The health outcomes of both carers and non-carers will therefore be documented in this chapter. This review also examines the literature on the concordance of health behaviours within family networks and social networks where an improvement in an individual's health behaviours such as their smoking and exercise may induce the same health behaviour change in surrounding individuals (22). This mechanism may also confer health spillovers from one individual to another.

1.2. **Impacts of illness on the health of patients' family members**

The following section reviews the literature on the health impacts of living with the illness of a family member. This provides an understanding of the health symptoms which are experienced by family members (carers and non-carers) of people with illness or disability. Pearlin's seminal model illustrated how the provision of informal care may directly cause the carer to experience physical and mental health impairment through strain, as well as indirectly cause the carer's health to be impaired as a result of the carer experiencing financial losses and having less time for their social and family life (Figure 1.1) (23).

Figure 1.1: Pearlin's model of the factors that cause health spillovers in carers (23).



Sections 1.2.1 to 1.2.5 review the literature on the physical health, health behaviours, stress, depression and psychosocial health of family members of people with illnesses respectively. Section 1.2.6 discusses the key 'predictors' of family member health impairment. Section 1.2.7 assesses the size of health spillovers of different health conditions.

1.2.1 Impact of illness on the physical health of family members

This section gives an overview of the evidence on the physical health impacts of patient illness on family members. Physical health is defined as relating to the condition of the human body, as distinguished from the mind (or mental health) (24). Caring for a loved one with an illness can result in impacts to carers' physical health, ranging from the physical strain from providing care, having less time to look after one's own physical health, and the physiological responses to the mental health effects of living with someone with an illness.

24% of informal carers who provide over 50 hours of care per week experience physical strain, which is a much higher prevalence than the 10% of carers who provide 20 to 50 hours per week and 3% of carers who provide less than 20 hours per week (25). One impact on the physical health of informal carers is related to the broad area of back pain, although there are few studies that have explored this. Lower back problems are likely to result from continuous lifting from anomalous postures; especially if a patient requires frequent assistance in transfers (e.g. from wheelchair to bathroom, or from house to car), due to the patient having physical disabilities and mobility problems, resulting in back pain among carers of patients with conditions such as a stroke, spinal injury, or cerebral palsy (11, 14, 26-29). The onset of care provision may exacerbate existing lower back problems that an individual may have(27). Carers that experience lower back pain may as a result also experience subsequent mental health problems such as depression (11, 27).

1.2.2 Impact of illness on the health behaviours of family members

Health behaviours refer to behaviours that may promote or damage health, such as physical activity, smoking, accessing health care services and treatments, and sleep. There are a limited number of studies that look at the association between patient illness and the health behaviours of family members that may ultimately cause the health of family members to be affected (30-32). It has been assessed that the burden of caring means that some carers have less time and energy to partake in self-care activities such as resting and exercise (14, 31, 33), although carers have reported continuing to access health care services and treatments such as flu immunisations despite the constraints on their time (31).

Moreover a heightened attention to self-care may result from living with a patient because witnessing illness can make one more determined to avoid having one's own health problems (14). For example in a qualitative study, one participant described that he changed his behaviour to regularly apply sunscreen as a result of his father's skin cancer diagnosis(14). A heightened attention to self-care may only be realised once one is relieved of the burden of care responsibilities: a study of former carers found that after the caring role finished, individuals visited the doctor twice as much and also experienced significant improvements in health (32).

Many illnesses result in sleep disturbances for patients, such as cancer, lung disease, fibromyalgia and nocturia (34). As the patient will often cohabit with other family members, family members may also be woken up from the patient's own sleep interruptions. A number of studies report a strong positive association between care burden (i.e. perceived demands of care or the hours of care provided by the individual) and sleep disturbance

among carers(25, 35). Maher and Green (2002) found that that 47% of informal carers providing over 50 hours of care per week, 24% providing between 20 to 50 hours of care per week, and 7% of carers providing less than 20 hours per week, experience disturbed sleep (25). Loss of sleep appears to not only be caused by not having as much time to rest, but also by the physical and mental strain of providing care(35). These findings suggest that moderate or high burden informal carers are much more likely to experience disturbed sleep compared with family members who do not provide such care.

Sections 1.2.3 to 1.2.5 discuss the evidence relating to the impact of illness on the mental health of family members by causing stress, depression and impaired psychosocial health. Mental illness refers to illness relating to the mind, which may prevent an individual from being able to realise his or her own potential (24, 36). Illness may result in family members experiencing depression, stress or anxiety resulting from the strain of care provision, and the anxiety and distress of having someone close being ill(37). It is important to recognise that spillovers of patient illness on the mental health of family members are more frequently reported than spillovers on physical health (14, 17, 30, 38, 39). Moreover, mental health spillovers are generally more negative than physical health spillovers in terms of their contribution to the total health losses of carers measured in QALYs (5, 30, 40, 41). This is because patient illness is mostly a psychosocial experience for the patient's family members rather than a physical experience. However physical and mental health spillovers are often interlinked to some degree; for example carers that experience physical health problems are also more likely to suffer from depression (11, 27).

1.2.3. Impact of illness on the stress of family members

Research has shown that moderate to high burden carers appear to experience higher levels of stress, higher blood pressure, and lower antibody production compared to matched non-carers (42-44). The higher stress levels of carers may directly cause carers to have higher blood pressure and lower antibody production, although lifestyle changes brought about by caregiving such as reduced exercise may offer a complementary or alternative explanation of the changes in carers' blood pressure and antibody production (11, 30). Carers who experience altered immune responses may be more susceptible to diseases such as diabetes and Alzheimer's (42, 45). The effect of stress in terms of impact on the immune system appears to persist even after the caring situation has terminated (e.g. when the care recipient dies) (45). However it appears that overall high-burden carers experience reduced stress and improved quality of life when a care recipient dies, due to relief from the burden of caring, that outweighs the negative feelings resulting from the bereavement in the long-run (46).

1.2.4. Impact of illness on the depression of family members

Informal carers are at risk of depression as a result of being distressed by a close person's illness and the significant demands of providing care (47, 48). One large UK survey found that 24% of informal carers who live with the patient reported feeling depressed, compared with just 9% of carers who do not live in the same house as the patient (25) (49). Cancer is

an illness that results in high rates of spillover on mental health; with estimates of prevalence of depression among carers of people with cancer ranging from 30-65% in most studies(50-52), to as high as 82% in one Korean study(53). Variation in these estimates may be the result of differences between types of cancer, stages of cancer, and the instruments that are used to measure depression, as the CES-D, HADS and BDI instruments are used across studies (50-52).

Regional context may be an important predictor of the risk of a carer having depression. For example, carers of parents in East Asia experience markedly high prevalence of depression of between 70-80%, due to cultural traditions of children having a duty to care for their parents when they are older, declining birth rates in these countries meaning that there are fewer siblings to shoulder the burden of care, and a very limited supply of long-term care institutions in these countries (53-55). Carers are also more likely to experience depression if they feel that providing care had taken over their lives, inhibiting them from their self-development and participation in other activities (47).

Several studies have observed that family members of chronically ill/disabled patients experience even higher rates of psychological suffering such as depression, anger and loss of interest in daily activities, than the associated care recipients(52, 56). One carer of a parent with arthritis reflects that: 'It's almost worse for the caretaker than for the [ill] person because they have to see them in this pain' (p.7) (14).

The mechanism by which carer depression is induced was explored in a large empirical study of dementia carer-patient dyads. The authors assessed the impact of carer distress on carer depression(48). Distress was theoretically modelled as two states; the carer's sense of

purpose and self (termed ‘existential distress’), and ‘emotional distress’ (feelings of sadness, crying). Existential distress was associated with higher use of antidepressants among the carers but emotional distress was not associated with antidepressant use. Higher levels of patient suffering were associated with higher levels of existential and emotional distress. These associations were tested in multivariate linear regressions, whilst controlling for the burden of care (i.e. patient physical and cognitive impairment). These findings indicated that patient suffering independently triggers family member distress, and clinical depression, independent of how severe the patient’s condition is. These findings may also translate to non-dementia caring situations, and also non-caregiving situations where family members nonetheless feel distressed and experience depression from seeing a loved one suffering.

1.2.5. Impact of illness on the psychosocial experience of family members

It is debatable whether psychosocial spillovers such as guilt and stigma are health conditions in themselves, or are alternatively considered as non-health spillovers which may for some people contribute towards them experiencing a mental illness such as anxiety or depression. Family members may experience feelings of guilt from patient illness for a variety of reasons: for not being able to provide what they perceive as a sufficient amount of care for the care recipient, for not enabling the condition to be diagnosed earlier (e.g. in dementia cases), and for some parental carers, not being able to spend a sufficient amount of time with their other healthy children(57). Feelings of guilt and personal responsibility for the illness may also be felt in parental carers of children with genetic illnesses (17). Family members may

also experience feelings of anger if an illness or disability was compounded by medical or human negligence (56).

The stigma of illness may not only be experienced by a patient (primary stigma), but also the families of patients (known as 'courtesy stigma' or 'stigma-by-association') (58). One study found that illnesses where patients experience primary stigma and are felt to be responsible for the illness (such as drug dependence), are more likely to result in courtesy stigma, due to public perceptions that family members are also responsible for the illness and are therefore less deserving of sympathy(58). HIV, tuberculosis and mental illness are illnesses that result in entire families experiencing shame, secrecy and withdrawal from society as a result of courtesy stigma, particularly in developing countries, and family members may also stigmatise the patient (59-62). Family members who experience courtesy stigma and social isolation are associated with higher rates of depression, stress and lower subjective wellbeing (63-65).

1.2.6. Factors that moderate the health spillover of illness on family members

This section discusses the evidence on factors that moderate the health spillover of illness. Most of the studies only use samples of family members who are carers. The studies predictably show that larger care burdens correlate with poorer carer health. Also, the type of care that is being provided may influence the way it is experienced psychologically by both the carer and the care recipient. Socioeconomic and demographic factors also modify the size of spillover.

Amount of care provided

The evidence relating to the association between the amount of informal care provided, and carer health, suggests that the association is not linear. Many studies report a general association between greater hours of care/number of caring tasks (or simply being a carer relative to not being one), and poorer carer health and wellbeing(11, 17, 25, 31, 66, 67). This is likely due to the increasing strain of providing care affecting mental and physical health, and the heightened emotional impact of seeing a loved one that is more severely ill(6). However, a recent large UK census study found that individuals who reported providing persistent moderate to heavy informal care (20 or more hours per week over several years), were 33% more likely to report a better health status than individuals not providing any informal care (68). Several studies report a non-linear relationship in observing that carers with low burden experienced lower rates of mortality and greater happiness when matched with non-carers, although these effects diminished or reversed as caregiving hours increased (40, 69).

These findings seem to indicate that the positive impacts of caring on carer health and wellbeing may outweigh the negative aspects when carers are providing a low and manageable level of care for a patient with less severe illness. However, there may be reverse causality which provides a further explanation for why low burden carers experience better health than non-carers. This is because individuals who take on informal care responsibilities may do so because they are physically healthy enough to undertake informal care(70). Nevertheless, positive health and wellbeing spillovers on family members have been documented in the qualitative literature that include; a strengthening of relationships, a greater determination to look after one's own health, and caring making one feel useful

(14, 71, 72). Furthermore informal carers may enjoy the active processes of providing care, and also experience pleasure from seeing a loved one experiencing better health as a result of their actions (73).

Care burden and spillover may also decline over time, as care becomes more routine and efficient, family members come to terms with the illness after the initial shock of illness subsides, relationships strengthen from facing the adversity of illness together and providing compassionate care, and an increased understanding of conditions (particularly those that are widely misunderstood in society such as depression) after diagnosis (14, 17). On the other hand, family members of patients with chronic and progressive conditions (such as dementia) are likely to experience greater care demands and impairment in physical and mental health as the patient's health deteriorates (11, 45).

Type of care provision

A high care burden is not only associated with the hours that are spent providing care, but also the nature and intensity of the care provision. Providing assistance with activities of daily living (ADLs) like bathing, shaving and toileting is associated with lower carer health in several studies, as it is often experienced as degrading to both the carer and care recipient (74-76). A strong association between patients' behavioural impairments and lower carer physical and mental health is observed in both carers of dementia patients and of ill and disabled children with behavioural problems, including situations where the child's behaviour problems are not directly attributable to their illness (11, 67, 77, 78). This suggests that the utility that a carer derives from providing care is largely influenced by the carer's

ability to sustain an emotional bond with the care recipient, and in the process derive enjoyment and satisfaction from the process of caring.

Sharing a house with the patient

There is a convincing association between a carer living in the same household as the care recipient, and having a higher care burden, more demanding caring experience and greater impairment in health (25, 66, 79, 80). For example, a large UK study found that a higher proportion of carers sharing a house with the patient reported experiencing health problems than carers not sharing a house such as depression (24% vs 9%), physical strain (13% vs 3%) and disturbed sleep (31% vs 6%) (25). This may be explained by the study also finding that 63% of co-resident carers reported providing over 20 hours of care per week compared with just 11% of carers not co-residing with the patient, and also finding that the co-resident carers were much more likely to provide assistance with physical tasks like walking and personal tasks like washing. Another study estimated a 33% higher risk of mortality among non-caregiving co-residents of dementia patients compared with caregiving co-residents, which the authors speculated may be the result of immune dysregulation brought about from stress of witnessing a degenerative condition which was somewhat mitigated for the carers through improved relationships (81).

Socioeconomic and demographic factors

Having a better socioeconomic and employment status is associated with better carer health in several studies, suggesting that holding gainful employment is an important determinant of carer wellbeing (17, 39, 67, 79). Conversely single parents and those with limited familial and community support systems are more likely to experience practical and financial burden in managing care (17), although one study indicates single parent carers do not necessarily experience worse health than their two-parent counterparts(82). Several studies have found that another important coping mechanism for carers is their faith and religious belief, with carers that practise a religion being associated with better wellbeing (17, 83).

Bereavement

This thesis focuses on spillovers arising from illness in living patients, but as noted earlier in the chapter health spillovers were first documented in response to the death of a patient(8, 10). Bereaved family members may experience acute grief, and if the family member of the patient is aged 60 or over at time of bereavement, they are associated with a subsequent increased short-term risk of a cardiovascular event, (84). Such a cardiovascular event is the result of a surge of stress hormones that results in what has been termed as the 'broken heart syndrome'(7). An unexpected bereavement (as compared with when there was known morbidity in a patient), results in an even greater stress reaction to a bereavement and a more marked risk of having a cardiovascular event such as a heart attack or stroke(84).

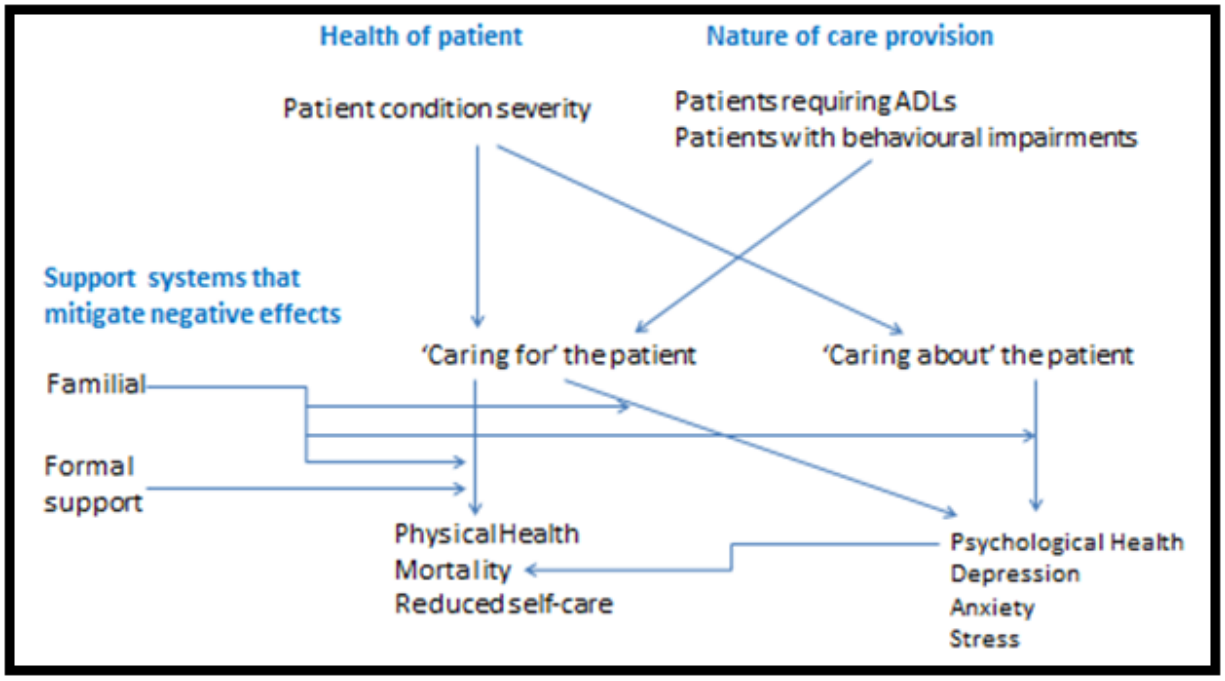
Bereaved widows also experience a greater risk of mortality in the long-run compared to non-bereaved individuals (odds ratio=1.20 over a 9 year period following a

bereavement)(85). This may be the result of depression or social isolation resulting from a bereavement resulting in a weakened immune response, or may also be attributed to an individual's possible lack of ability (or motivation) to care for themselves and maintain their health following the death of a spouse, even after the acute grief subsides (86).

One situation where bereavement appears to have an overall positive impact on a family member's health is when an older care recipient dies. This was explored in a meta-analysis of 17 studies that found that after the initial grief resulting from a bereavement subsided, the (former) informal carers experienced long-lasting positive outcomes from bereavement due to relief from the burden of caring and end of the patient's suffering (46). The overall positive impact was particularly observable among the adult children who had lost their parent but less noticeable for the bereaved spouses. Nevertheless, former carers may continue to experience negative mental and physical health spillover effects such as depression, sleep disturbance and back pain, after the patient has died (87).

Using the evidence in this review, a model of the causal pathways of family member physical and psychological health was developed, depicted in Figure 1.2 below.

Figure 1.2: Model of factors associated with family member physical and psychological health impairment resulting from living with a sick or disabled person



The model in Figure 1.2 provides a conceptual framework for thinking about the likely scale of health spillovers in a particular context. For example, the model predicts that having formal support (such as Carer's Allowance) may mitigate some of the financial and practical challenges that carers face, but is not predicted to be an effective substitute for familial support in providing care that also helps to offset the emotional challenges of 'caring about' a patient that is ill. Providing informal care for a person with behaviour impairments or assisting with a patient's activities of daily living (ADLs) is expected to be particularly stressful to a carers' health. Also, family members who experience mental health problems such as stress or depression may consequently be at a higher risk of mortality, for example through the effects of stress on blood pressure and immune responses which are discussed in section 1.2.3. The model draws particularly from a study by Bobinac et al (2011) who

describes health spillovers as the product of two primary mechanisms that are: family members 'caring about' the wellbeing of the patient resulting in anxiety and distress, and family members providing care for ('caring for') the patient resulting in physical and mental strain(6).

1.2.7. Magnitude of the health spillovers from different conditions

Several studies have been carried out to examine the relative size of the health spillovers which are generated from different health conditions. From these studies there appears to be an indication that patients with mental illness have a greater spillover effect on family members' health than many other conditions (5, 85, 88). This appears to be because of the behavioural problems which are associated with mental illness, and also family members often blaming themselves as a cause of the patient's mental illness by attributing it to relational conflict and genetic inheritance (14, 60). However as these studies measure health in different ways by the use of generic health instruments, mortality statistics and simple scales in relation to general health, it is difficult to consolidate findings across studies to assess the relative magnitude of health spillovers across different conditions (5, 85, 88). Also, the studies focus on different sub-populations of individuals affected by health spillovers: e.g. carers(88), spouses(85) and all household members (5). Furthermore, studies use different classification methods for diseases that make it even more challenging to consolidate findings. For example some studies classify mental illness and circulatory illness broadly(5, 88), whereas other studies look specifically at more severe and long-term illnesses within those broad areas, such as strokes, and hospitalisation from psychiatric illness(85, 88).

Studies also vary in terms of quality- for example one study does not report the sample size of carers that was used to estimate prevalence of spillover across different diseases(88), whereas other studies clearly specify the large samples that they used (n>20,000) (5, 85).

Nevertheless, once the different classifications of illness are accounted for, there is some indication that conditions that severely reduce the quality of life of patients through significant disability and impairment such as stroke, dementia and psychiatric conditions, produce a greater spillover on family members and carers (5, 85, 88). Therefore, it follows that the greater the severity of a condition, the greater the spillover on family members. This has also been empirically observed in a number of smaller studies that have identified a positive association between carer health and patient health (37, 89). Also, some smaller studies produce richer insights into the different aspects of a condition and the context of caring that are strong determinants of impairment in carer health, as were described in section 1.2.6.

1.3. The different individuals that experience health spillovers

This section identifies the different groups that are affected by a patient's health condition, the health outcomes of individuals in these groups, and the mechanisms by which their health is affected. Sections 1.3.1 and 1.3.2 look at different groups of carers and non-carers respectively that are affected by health spillovers.

1.3.1. Health spillovers in groups of carers

Different individuals can become informal carers, although the UK General Household Survey (GHS) estimates that most informal carers who provide over 20 hours of care per week are either spouses caring for a partner (60%) or (adult) children caring for a parent (20%) (90). This section focuses on specific groups of carers (young carers, female carers, spousal carers and parental carers) that face their own distinct challenges from caregiving that are important to recognise.

Young carers

One survey estimates that there are as many as 700,000 young people with substantial caring responsibilities in the UK, usually provided for a parent(91). Furthermore 18% of young carers provide intimate care (76). Providing intimate care for a parent can be considered to be socially unacceptable, and evidence suggests it is also the most disliked type of care work for both the young carer and the parent(92, 93). Young carers are also

likely to experience feelings of isolation and lack of social interaction with their peers, may feel pressure to conform by hiding their caring circumstances from classmates and teachers, and experience anxiety of being separated from their parents should their caring circumstances be revealed to the authorities(93, 94). No large study to date has been carried out to establish the prevalence of health issues among young carers (95). A small survey of 41 former young carers found that 70% experienced long-term psychological effects into adulthood, and this was assessed to be particularly substantial among young carers of parents with alcoholism or mental illness, suggesting that the psychological distress experienced among young carers of a parent with mental illness is particularly profound (94).

Beyond the health impacts of caring to a young carer's health are the impacts to their educational attainment, which is a non-health spillover. A large panel study of 9,000 young carers found that young carers were associated with an educational attainment at GCSE that is 'nine grades lower than their peers' (p.5), e.g. the difference between 9 Bs and 9 Cs, affecting their long-term prospects (96).

Female carers

UK census figures from 2011 report that 58% of informal carers are female(18). Not only are carers more likely to be female, but female carers also spend more hours providing care than male carers, and also do more manual and grooming tasks than male carers, whereas male carers are more likely to do financial and administrative tasks that are less

straining(79). However although female carers report longer hours spent providing care and do more straining informal care tasks, the association between care burden and impairment in carer health is weaker among female carers compared to male carers(11, 97). This suggests that female carers on average may be more resilient and better equipped in meeting the caring burden. However, studies of COPD carers have found that female carers experience higher levels of anxiety despite having the same care burden as their male counterparts (98, 99).

Spousal carers

When the onset of chronic illness or disability affects an adult in a cohabiting relationship, the main duty of care usually falls on the partner/spouse. However, it is important to note that in some non-Western cultures (e.g. in South America and Asia) there are strong traditions of filial piety in which children (and adult children) are expected to become the main care providers when a parent falls ill (55, 100).

Illness can result in a large shift in the dynamics of a spousal relationship, as the spouse has to readjust their role in the relationship and their expectations of the partner who is ill. Spouses of patients may experience feelings of loss of a relationship particularly if a partner is suffering from cognitive impairment (e.g. resulting from a stroke or dementia) (101). Spouses may also be overwhelmed by the demands of caring and a shifting in the weight of financial and household responsibilities that the ill partner can no longer undertake (101). Spouses may have to undertake substantial new tasks within the household and also experience a loss of shared activities with the partner, resulting in a very broad range of health and non-health spillover effects (14). However in many cases of illness, spillover onto

the partner is likely to decrease over time because many relationships are able to adjust to the new situation after the initial shock of illness subsides (14).

The spouses of patients with dementia will often become the primary carer for the patient, and are particularly vulnerable to impairments in both their mental and physical health (11, 102). This is because a raft of stressors to health are likely to be experienced by these carers including: a high severity of patient illness, the carer being more likely to be elderly and frail, shifts of financial and household responsibilities, losses in shared activities with partner, carer blaming themselves in situations where early diagnosis could have been achieved, facing behavioural challenges such as verbal and physical aggression, and assisting with activities of daily living(11, 14, 75, 83). Furthermore, sustaining an emotional bond with a care recipient has an important mediating effect from the stress of caring; however in some dementia cases there may be little possibility for the patient to exchange in meaningful conversation with the carer (103).

Carers of children (parental carers)

Parental carers (parents that provide informal care for ill or disabled children) face substantial challenges from the combined demands of working, parenting and providing informal care. Parental carers also experience the emotional challenges of seeing their child suffer particularly as parents are often more invested in their children's welfare than even their own. Parents of children with illnesses that are potentially life-threatening struggle emotionally with the knowledge that they might outlive their child (104). Several studies have also suggested that parental carers frequently experience physical health problems

such as pain and discomfort (14, 39). However another study found little evidence of physical health impairment in parental carers of children with chronic illnesses (17).

As discussed earlier, women are generally more likely to take on caring responsibilities than men, but this particularly seems to be the case in caring for children. The result is a clear consensus that mothers are much more likely to experience impaired health than fathers of ill children (105-107). Furthermore, studies of the experiences of parental carers often use mostly (or exclusively) samples of female carers, suggesting that mothers are specifically recruited in these studies (17, 39, 67, 108).

Several studies have identified specific factors that determine the wellbeing of carers of chronically ill children (17, 39, 67). One mixed-methods study found that single parents of ill children were more likely than married parents to experience financial pressures due to not being able to work full time, coupled with the expenses of providing care, and therefore experienced stress (17). Predictably, caring for multiple children with genetically-induced disabilities was found to be a more mentally and physically straining task compared to caring for only one child with a genetic disability(17). Carers of children with genetic illness also reported feelings of guilt and personal responsibility for the child having their condition (17). Family and social support was identified in a range of studies as providing important emotional support and practical assistance to carers of children (17, 23, 67). Less clear is the existence of association between the age of informal carers of children and carer health, with studies reporting contradictory findings (39, 109).

The experiences of informal carers of children are also shaped by the type of condition that a child has. Informal carers of children with physical disabilities are specifically likely to feel

confined to their house because of the difficulties of travelling with and accommodating a disabled child, as well as the demands of providing care (14). The parents of adult children with mental illness experience specific worries about the patient's future when they are no longer around to monitor the patient's wellbeing (60). Carers of children with behavioural problems (such as those on the autism spectrum) often experience alarm at their child's erratic and sometimes violent behaviour, and also experience social stigma resulting from the lack of understanding of their child's behaviour(33). Stigma may also lead to parents of disabled children becoming isolated from members of the extended family who hold a prejudice towards disability (110).

One case study of the PhD focuses on the health spillovers on family members from meningitis, an illness which predominantly occurs in young children and results in a range of physical, mental and behavioural impairments.

1.3.2. Health spillovers in groups of 'non-carers'

Non-carers are individuals who do not provide additional caring tasks, but may nevertheless care about, and share a strong emotional bond with the patient, thus experience distress from witnessing the patient's suffering. Health spillovers may occur in non-carers for other reasons. Individuals may also imitate the harmful health behaviours of their peers (111), leading to the transmission of negative health outcomes from peer to peer (discussed further in section 1.4). Non-carers that are affected by health spillovers may be family members or household members of the patient, or they may be part of the wider social

network of the patient. The health spillovers of individuals within these two groups are discussed in this section.

Families and households

Individuals experience anxiety and distress as a result of caring about a person that is ill(6). These individuals may be family members, or they may be friends of the patient. Although household members of a patient may be physically close to witness the illness of a patient, they may not necessarily be emotionally close (e.g. if the patient shares a house with acquaintances rather than family) (112). For example, although in many cases of illness household members are likely to be the individuals most affected by health spillover, it has also been qualitatively documented that family members of patients with severe mental illness may choose to live separately from the patient as living with the patient creates a burden not only on themselves but also the rest of the family (such as young children) (60). Therefore the identification of the individuals who are most impacted by spillover may need to take into account that physical proximity to the patient does not necessarily correspond to emotional closeness (or caring responsibilities).

Bobinac et al's (2011) empirical analysis identified two causal pathways by which health spillovers are generated. The first pathway is the burden of providing care for a patient that only affects informal carers ('caring for' a patient), and the second is the emotional distress of witnessing a loved one experiencing suffering that affects both carers and non-carers (or 'caring about' a patient)(6).

Some studies use mixed samples of carers and non-carers (13), but only a very limited number of studies have carried out a focused examination of the specific experiences of non-caregiving family members (or 'non-carers') who also in theory experience health impacts from a relative's illness resulting from 'caring about' a patient (6, 14). One qualitative interview study of 32 carers and 17 non-carers of chronically ill patients found that non-carers were less likely to report stress/anxiety and sadness/depression than carers, but were also more likely to report worry/fear than carers(14). This surprising finding that non-carers more frequently reported worry/fear than carers may be because by observing illness but not being able to support or be involved in the practical issues of care, means that non-carers may feel more powerless and distant than a carer in fighting the illness, although this finding would require further examination in a larger quantitative study. Indeed non-carers or carers that only provide partial or limited support to the patient have reported feelings of guilt from feeling that they are not doing as much as they can to help the patient (60). Conversely, some non-carers may not provide active care for a patient, but may nevertheless be burdened by having to overcompensate for household tasks that patients are no longer able to do because of their illness(14).

Another mechanism for health spillovers in families and households may result from the deterioration of health of a parent leading to poorer health outcomes of children and dependents. This association is particularly observed in developing countries (113, 114); even though it may also be relevant to developed countries, this has not been empirically documented(11). In a developing country setting, the illness of a parent and the associated medical costs that they may incur, can mean the difference between the parent being and not being able to provide basic nutrition and care for their young dependents (114). There

are challenges in studies aiming to establish an association between parent health and child health caused by spillovers for a variety of reasons. Both children and parents may be exposed to the same environmental factors that determine health, and transmission of infectious diseases from parents to children may explain an association between parent health and child health outcomes (infections are not considered a spillover). Also, respondent bias may be generated from studies in which surveyed parents both self-report their own health, and also give proxy assessments of the child's health that are influenced by their views of their own health (114).

Social networks

As explained in the 'families and households' section above, individuals do not have to be family members of the patient or live with a patient, but may yet experience health spillovers from being part of the patients' social network. For example neighbours and friends may be emotionally close to the patient, and are even sometimes known to provide informal care for patients (90).

All members of a patient's social network (without exclusions) may be exposed to another important mechanism of health spillover concerning the 'peer effects' of illness and health interventions. Peer effects are the imitation and concordance of health *behaviours* across individuals in social networks(115). Section 1.4 goes further in discussing the evidence on the peer effects of health behaviours and behavioural health interventions, of relevance to the core empirical work for the PhD.

1.4. Behavioural (peer) effects in social networks

This literature chapter focuses primarily on health spillovers resulting from the emotional and physical stresses arising from caring about a loved one and caring for (i.e. providing informal care for) a patient. However, there is a third separate mechanism that may result in health outcomes of individuals within social networks of ill patients to be affected and is important to consider- known as 'peer effects' or 'social interaction effects' (116). Peer effects refer to the situation where people are influenced by the behaviour of people in their social and family network, to behave in a similar way(115). Therefore interventions that improve health behaviours, may confer benefits beyond the intervention population by making harmful behaviours less socially acceptable in wider social networks.

1.4.1. The concept of peer effects

Peer effects refer to the influence of an individual's behaviour on the actions of another individual(111). Although peer effects are sometimes discussed exclusively in regards to interactions among friends and members of the same community (as opposed to within families and family dyads), the mechanisms of peer effects are likely to also apply to relationships in families(117). In the literature, peer effects may also be referred to as social interaction effects(118). In the discussion of health behaviours, social interaction effects are almost always explored in terms of a specific health behaviour (e.g. cigarette smoking) influencing the same health behaviour in another individual, and these interactions are mostly positive, e.g. individuals who become cigarette smokers may in theory increase

(rather than decrease) the probability that another member of their social network will either take up smoking or increase their smoking.

Social interaction effects broadly fall into four different categories: physical, learning, stigma, and taste-related interactions(118). Physical social interactions relate to the tangible benefits (e.g. money, time) of participating in a behaviour if others are also partaking in that behaviour. For example in a household, an individual may be more likely to eat healthily if the rest of the family is doing so, because of the economies of scale involved in meal preparation for the whole family rather than eating junk food separately, and the convenience of eating the food that is available in the house instead of doing an extra shop. In terms of exercise, individuals may also experience physical social interaction effects as exercise may be more enjoyable when done with a friend/family member, or another example is an individual's purchase of an exercise bike, that may be a better investment if other members of a household also use the bike.

Learning-related social interactions involve learning about the effects of a behaviour through witnessing someone else's participation in the behaviour or through direct communication with that individual. For example, if a smoker sees a family member with COPD experience better health from reducing their smoking, they may also then feel motivated to avoid damaging their own health by smoking. Also smokers that are able to successfully reduce their consumption may then pass on this advice and knowledge to their family members/friends, which is one reason why former smokers are better at supporting family members to quit smoking compared to individuals who have never smoked(119).

Stigma-related interactions relate to whether one likes or dislikes the individual that is participating in a behaviour that may be stigmatised (or glamorised) (118). For example, one may be more likely to take up smoking if other people who the individual likes or admires also smoke, and the converse is true. Taste-related interactions relate more to the direct imitation of behaviours, for example some people are psychologically more likely to imitate others and conform to the environment around them than others(120).

The evidence of these social interaction effects in empirical studies of health behaviours will be discussed in the next sections; firstly in relation to interaction effects between spouses, and subsequently in terms of peer effects between friends and in social groups, before finally discussing the contextual factors that appear to moderate the existence/size of interaction effects.

1.4.2. Peer effects on spouse/partner

The peer effects of smoking behaviours may be strongly realised within relationships in households, particularly in regards to smoking and smoking cessation behaviours between couples. The evidence of smoking peer effects between spouses varies between studies. (119, 121, 122). For example, one study found that only male smokers were substantially more likely to quit smoking if in a relationship with someone who also quit smoking compared to being with someone who had never smoked (122), but in another study both genders were substantially more likely to quit smoking when in a relationship with an ex-smoker compared to being with someone who had never smoked (121). Furthermore, it has

been suggested that former smokers are better than current smokers or those that have never smoked at supporting their partner to quit, as well as acting as 'role models' for quitting (119).

Interaction effects between couples have been explored in studies relating to behaviour change in order to achieve weight loss. Studies have found that not only does having a motivated, encouraging and engaged partner play a substantial role in facilitating an individual's weight loss, such partners also achieve improvements in their own lifestyle, particularly as dietary patterns are likely to be similar and shared within households (123), and also by the partner learning more about their own weight and lifestyle and feeling more motivated to manage it (124). Conversely evidence also suggests that when one spouse is more determined than their partner to increase their physical activity, the partner may feel left out, and therefore act in a way that creates tension in the relationship and discourages their spouse from increasing their exercise activities (125, 126). Spousal concordance in health behaviours such as smoking and exercise also appears to translate to resultant concordance in health outcomes such as high blood pressure, coronary heart disease, and strokes (127).

One other context of concordant behavioural changes between spouses where there is a growing body of evidence is alcohol drinking, with several studies documenting concordance in drinking patterns between couples, including in stopping drinking (121, 128). However stopping drinking may or may not be beneficial to one's health, depending on the amount of alcohol that was being consumed prior to stopping (121). Furthermore drinking alcohol (and misusing drugs) may result in another potential mechanism of spillover, with individuals

under such influences being more likely to be violent to others, with intimate partners a particular risk group (129).

1.4.3. Peer effects beyond couples

The imitations of health behaviours such as smoking and physical exercise are not just limited to couples. Broadly speaking, the evidence indicates that the acceptability of smoking within society as a whole is a key determinant of the likelihood of one taking up smoking (130). However, the evidence of peer effects of cigarette and cannabis smoking among friends and peers is mixed (111, 131-133). For example some studies suggest that there are peer effects associated with cigarette/cannabis smoking(111, 132), but other studies find no evidence of a peer effect(131), or the potential existence of a 'negative' peer effect by which knowing a peer that smokes tobacco/cannabis puts one off the idea of smoking(111). Nevertheless it is also recognised that individuals are often introduced to cigarette smoking through their peers, habits that later on develop into addictions(134). There is also a category of 'social smokers', by which smokers mostly or completely limit their cigarette smoking to environments where other friends are participating in these activities(134). It is also relevant to note is that passive smoking is also a health spillover.

Several studies have also observed that increases in physical activity spread beyond the individual; for example between friends(135) and even from children to parents(136). However, it can be difficult to empirically ascertain the magnitude of these peer effects, as people frequently select into friendships with people who have similar health behaviours, and because of the role that external (environmental) factors play, for instance in areas

which facilitate an unhealthy or sedentary lifestyle for many members of the social network (137).

1.4.4. Factors that moderate imitation of health behaviours

Gender appears to be an important factor in moderating the imitation of health behaviours. A number of studies have suggested that men are more likely to be influenced by their peers and family members to participate in both health promoting and health damaging activities than women are (122, 131, 136), although in some conservative cultures in a spousal relationship women are more likely to act in a more imitative way to their husbands regarding their health behaviours (124, 127). Female non-smokers may be more likely than male non-smokers in attempting to influence their partner's smoking in some cultural settings (122), though not all (119). The smoker's gender may influence the desirability of a peer taking up smoking; for example it has been documented that male smokers are perceived as sophisticated, and female smokers perceived as 'trashy' (111, 134). There is no consensus in the literature on whether binge drinking peer effects are isolated among men, or also extend to women (111, 131).

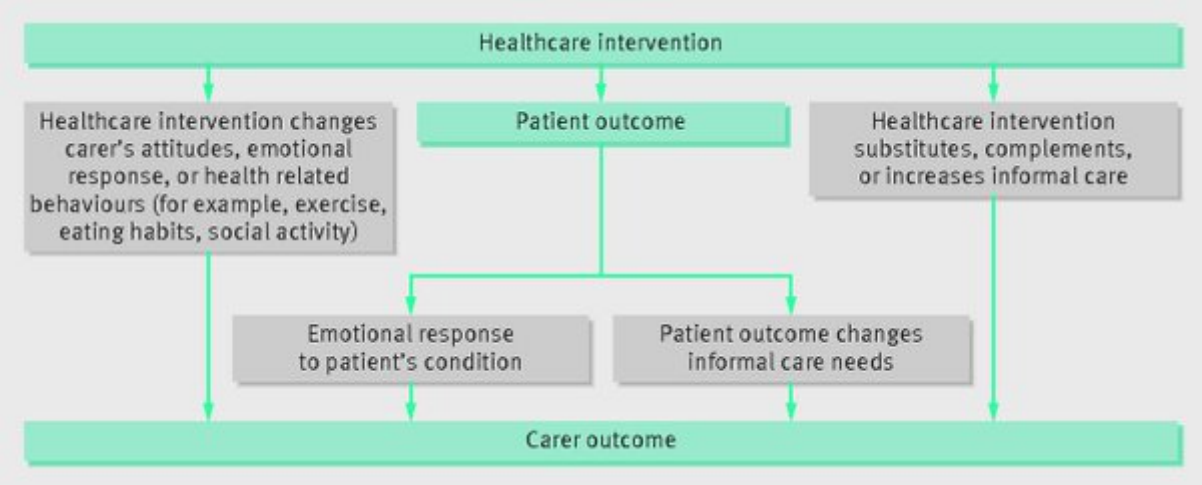
Education and learning is another potential moderator of peer effects between individuals, as noted in a number of empirical studies relating to the peer effects of health behaviours such as smoking and diet (122, 138, 139). This appears to be because more educated individuals are potentially both better at delivering information to others to persuade them to change health behaviours, and also in understanding information presented to them

about health behaviours, and enabling behavioural changes to be incorporated into their lifestyle(118).

1.5. Health spillovers of interventions

The causes of health effects in family members from health interventions broadly fall into four pathways: i) the alleviated distress from caring about someone who is close if their health improves from the intervention ii) the reduced burden of being an informal carer if the patient's health improves from the intervention so the patient can function more independently, iii) the concordance of improved health behaviours of a patient resulting from a health behaviour change intervention, with surrounding individuals, and iv) the effect of interventions that are more directly aimed at supporting carers by adjusting their attitudes, behaviours and reducing their care load (e.g. from the provision of formal care support) (Figure 1.3) (116).

Figure 1.3: Mechanisms by which health effects in family members are generated by health interventions (taken directly from Al Janabi et al (116)).



1.5.1. Mechanisms by which interventions generate health spillovers

As discussed throughout this chapter, interventions which improve patient health are likely to also alleviate family member distress and carer burden. However, there are at least two scenarios by which improvements in patient health may potentially result in a higher burden on informal carers. The first scenario is where a patient's condition prevents a patient's premature death but means that they require intensive informal care for the remainder of their lifetime(140). The second scenario is where health interventions which improve patient's health prevents the patient from being admitted into a hospital or institution, resulting in additional caregiver burden (141, 142). However, although both scenarios would result in a higher burden on informal carers who 'care for' the patient, family members may experience positive health effects from 'caring about' the patient. Under the first scenario family members would potentially feel happier that the patient is living longer. Under the

second scenario family members would again feel happier that the patient's health is better, and furthermore some family members experience process utility from being the carer for the patient, as opposed to handing over the care to formal providers and experiencing guilt and uncertainty over doing so (143). Overall it therefore appears that interventions that lead to a greater improvement in patient health, will often generate better health outcomes in family members.

A limited number of randomised trials of patient health interventions have collected data on family member outcomes (116). The few trials which have done so show that interventions which demonstrate some effectiveness for patients do not offer much evidence of an improvement in carer burden (144) or carer mental health (3, 145). However, observational studies have documented positive diet and physical activity spillovers being generated from behavioural interventions (136, 146). These appear to be the result of the interaction effects discussed in section 1.4, as well as patients being coached as part of the intervention to recruit their family members to also partake in healthier behaviours (146).

1.5.2. Interventions which generate health spillovers

Interventions which provide formal care services to patients may substitute the burden of care away from the informal carer to the paid carer/s (116). These interventions may include the delivery of meals to elderly people's houses (also known as 'meals-on-wheels') and home care services where paid carers visit the older person or patient regularly to provide care (147). On the other hand, the National Health Service and Community Care Act of 1990

was a systems-level intervention that appeared to increase informal care, due to a shift of community care resources away from people with informal carers and towards people deemed as having a greater need, including older people who do not have an informal carer and therefore were perceived as needing a greater level of formal support (147). Prior to 2014, carers in the UK did not have a legal right to receive state sudsidised support from paid carers and this support was only offered on a discretionary basis. However, the Care Act of 2014 provided carers with the same legal rights as patients (148). This was done by providing a legal entitlement for informal carers to an assessment of their needs and wellbeing, and receipt of an according level of subsidised home care support from the local authority.

Carers' attitudes and skills may be promoted by certain carer interventions, resulting in better carer health. For example, there is evidence of limited quality that carer support groups and psycho-educational skill building interventions for carers are effective in improving carers' psychological health (149, 150). Carer support groups may involve the exchange of advice and tips between carers which result in more efficient and effective care provision, which also benefits the person being cared for. A number of interventions have been developed that jointly target carers and patient; for example multi-faceted psychosocial interventions (such as counselling) received jointly by patients and carers (3, 151, 152). Financial grants for carers such as Carer's Allowance, may mitigate financial hardship and consequently reduce carer stress (23).

1.6. Conclusion

The chapter outlines the concept and scope of health spillovers, drawing on medical, psychological and sociological literature. It presents evidence that the impact of illness extends to affect the health of both caregiving and non-caregiving family members, although limited studies have been carried out on the health experiences of non-caregiving family members. The impact of patient illness is more pronounced on the mental health, rather than the physical health of family members, although some informal carers are at risk of neglecting their own physical health in order to attend to the needs of the patient. Young carers, single parent carers, and elderly and frail carers are among the most vulnerable caring groups, because each of these groups are less equipped in their own distinct ways to deal with care challenges. Becoming a carer can change an individual's life in good and bad ways, but the negative effects of being a carer frequently strongly outweigh the positive effects, particularly for the millions of informal carers in the UK providing a large number of hours of care each week. These negative effects include impacts to a carer's physical and mental health at a considerable cost to the NHS and to society. As the informal care sector continues to grow in an ageing society, it becomes even more important to take into account the health spillovers on informal carers (and possibly also non-caregiving family members) in decision making in health care.

The role of these health spillovers in economic evaluation and resource allocation decisions will be set out in Chapter 2. This will review different methods and perspectives that may be adopted for including health spillovers in economic evaluations of health interventions. Later

chapters outline empirical studies to test measures for capturing health spillovers and efforts to capture and include health spillovers in economic evaluation.

CHAPTER 2: INCORPORATING SPILLOVERS IN ECONOMIC EVALUATIONS

This chapter extends the discussion from Chapter 1, by exploring how health spillovers may be included in the economic evaluations of health interventions. Section 2.1 begins by describing the different types of economic evaluations of health interventions, and the potential role for including spillovers in these evaluations. Economic evaluations are comparisons of costs and benefits, and the presence of spillovers mean that there are potentially important costs and outcomes of interventions that are normally unmeasured. Sections 2.2-2.4 then explore the practical methods for including spillovers in economic evaluation. These sections focus on the inclusion of spillovers through either costs or outcomes, or both costs and outcomes simultaneously in an economic evaluation.

Section 2.5 then goes on to address how decision makers such as NICE have addressed health spillovers in their existing guidelines for economic evaluation, and the potentially evolving role of health spillovers in these guidelines. Section 2.6 presents a systematic review of cost-utility analyses which have included health spillovers. Section 2.7 concludes the chapter.

2.1. Economic evaluations in health care

2.1.1. Different perspectives for economic evaluations

Economic evaluations in health care enable a solution that optimises the dispersion of a limited health care budget, when deciding between different interventions to implement for a particular clinical or health problem. This may, for instance, enable a decision to be made about whether to implement a newly developed drug versus an existing drug for treating a particular disorder (153). Economic evaluation essentially is a trade-off between the costs and benefits of an intervention. Costs that may be included in an economic evaluation are direct costs such as drug and treatment costs and the costs of primary and secondary care utilisation of patients. Indirect costs may also be included in an economic evaluation such as the productivity losses generated from patient illness and alleviated through intervention (153), although this may be considered as a benefit rather than a cost depending on the perspective for economic evaluation that is used (154). The benefits of a health intervention may be captured in terms of a monetary valuation that the patient places on the treatment. Alternatively, self-report measures such as a quality of life questionnaires or objective measures such as number of cancer cases detected may be used to assess benefit.

The underlying objective of an economic evaluation depends on the perspective that is being adopted by the decision maker undertaking the evaluation. The perspective that some economists would argue as the 'ideal' or perfect resolution to the decision problem would be the adoption of a societal outlook to arrive at a decision that maximises social welfare (or

aggregated utility across all individuals in the society) - referred to as a *welfarist* approach to decision making (155). The intervention that would be chosen under this societal (or welfarist) perspective for a decision problem is the one that maximises utility across society by maximising the difference between the full benefits of the intervention and the full costs of the intervention aggregated across all of the individuals affected by the intervention. Both costs and benefits are measured to provide a full valuation of all of the costs and outcomes associated with the interventions, without excluding any outcomes or any individuals who are affected by the intervention either directly or through spillover (156). This decision-analytic framework carried out under a welfarist perspective is known as a cost-benefit analysis.

An alternative perspective that a decision maker may adopt when undertaking economic evaluation is an *extra-welfarist* perspective. An extra-welfarist perspective for economic evaluation is distinct from a welfarist perspective in four key ways (155). Firstly, an extra-welfarist perspective allows relevant key outcomes of an intervention to be selected, whereas utility aggregated across individuals is the only relevant outcome in a welfarist perspective. Secondly, extra-welfarism allows (but does not mandate) that different weights may be assigned to outcomes of an intervention (e.g. according to age or socioeconomic status of the affected individuals). Thirdly, extra-welfarism allows for individuals outside the intervention population to be an 'external' source for valuing outcomes. Finally, extra-welfarism enables interpersonal comparisons of outcomes to be made between individuals affected by an intervention, whereas in practice welfarism does not possess a satisfactory measure of individual utility to enable these comparisons to be made.

Most economic evaluations carried out under an extra-welfarist perspective aim to maximise some *aspect* of welfare, rather than attempt to maximise welfare per se in a cost-benefit analysis. In economic evaluations within an extra-welfarist framework, the aspect of welfare considered most relevant and important to capture and maximise (subject to a limited health care budget) are health effects. In the health care context, the term 'extra-welfarism' may be seen as poorly phrased, because health is actually an integral component of a person's welfare, and not 'extra' to welfare. The assessment of these health effects are usually restricted to patients affected by the intervention, as evidenced in the systematic review in section 2.6. This however may not be an appropriate limit to set, as illnesses and interventions also have the ability to have substantial and variable effects on the health of family members of patients (78, 157).

2.1.2. Economic evaluations of health interventions under an extra-welfarist perspective

Economic evaluations in health care under an extra-welfarist perspective in most cases involve the comparison of costs and health outcomes of a health intervention compared with an alternative (153). There are 3 main types of economic evaluations that that an extra-welfarist decision maker may carry out in order to decide whether to implement a new health intervention – either a cost-consequence analysis, cost-effectiveness analysis, or a cost-utility analysis.

In a cost-consequence analysis of a health care intervention, benefits are measured according to several observable and important health outcomes relating to the objective of the intervention (153), which may potentially include health spillover outcomes of family members (e.g. the anxiety and depression scores of carers and non-carers). These benefits are listed in a tabulated form separately to the costs of the intervention, and in a cost-consequence analysis there is no subsequent aggregation of these costs and benefits.

Cost-effectiveness analysis on the other hand is distinct from cost-consequence analysis, because one 'primary' outcome of the intervention is identified as being the most important within the evaluation; for example it could be the number of cancer diagnoses produced as a result of screening (153). In a cost-effectiveness analysis, the differences in the estimated costs and benefits between different intervention strategies (i.e. incremental costs and benefits) are subsequently combined into a ratio in the analysis, this ratio is defined as an 'incremental cost-effectiveness ratio' (or ICER).

Cost-utility analysis is a subset of cost-effectiveness analysis(156). In a cost utility analysis of a health intervention, the benefits of the intervention being evaluated are consolidated into a single measure of *health-related utility* (156). In the cost-utility analysis of a health intervention, the unit of utility that is usually used to measure health is quality adjusted life years (or QALYs). Measuring intervention effects in terms of QALYs allows for capturing gains and losses resulting from an intervention in terms of life expectancy, and health-related quality of life. Different measurement instruments can be used to elicit the health-related quality of life of individuals including patients and their family members, and they are usually administered directly to the individual in the form of a questionnaire for completion, so

health-related quality of life is self-reported. A proxy report of health-related quality of life may alternatively be elicited if a person is unable to complete a questionnaire due to being too young, cognitively impaired, ill or fatigued. The quality of life scores that are elicited can then be used to calculate QALYs by combining quality of life with life expectancy. This is done by multiplying health-related quality of life score with the number of years spent with that quality of life. As with a cost-effectiveness analysis, the incremental costs and effects (QALYs) of the intervention are subsequently combined into an ICER. In a cost-utility analysis, the ICER is subsequently compared against a decision threshold to evaluate the cost-effectiveness of the intervention. This threshold acts as a cut-off value for establishing the cost-effectiveness of an intervention. The threshold used in a cost-utility analysis performed by the National Institute of Health and Care Excellence (NICE) is £20,000 per QALY (158). An ICER that falls below the threshold indicates that the intervention is likely to be cost-effective and the opposite also holds true.

The EQ-5D and SF-6D are the two frequently used instruments for measuring health-related quality of life (159, 160). The EQ-5D is the recommended instrument for measuring QALYs in NICE economic evaluations, administered to individuals who self-report their own health-related quality of life. The instrument is designed to capture both the physical health and mental health of an individual (161).

2.1.3. Externalities within the health care setting

Although all health effects are relevant to economic evaluation in principle, there is a tendency to focus on the direct health effects on the patients and the health spillover may therefore be akin to an externality. Economic theory usually refers to 'externalities' as the impact of market transactions on 'third parties'; third parties being any individuals who are neither the consumers nor the producers of a market good (162). Externalities may however be visible within a non-market setting such as a health care setting. However, the literature on the family impacts of illness has chosen to move away from this market based definition of externalities to 'spillovers', therefore the term 'spillovers' is used for the majority of this thesis. One reason for this changing terminology is because it may not be appropriate to characterise illness itself as producing an externality, as illness is not the product of a transaction. However health care interventions may be viewed as a transaction, where patients are the consumers of health care and the health care providers are the producers of health care. Thus the delivery of a health intervention may generate externalities in the form of third party spillover effects. Another important distinction between externalities and spillovers is that externalities encompass a wider definition of the effects in societies resulting from health care provision, such as the productivity gains from having a healthier workforce.

Some economic theorists may regard informal care not as an isolated spillover (or even an altruistic behaviour), but as part of a process of reciprocal giving and receiving within the structure of the family (163). Children may for instance provide care for their elderly parents as a hard-wired evolutionary response that facilitates mutual cooperation within families; for

example responding to the care they received growing up, and/or the financial provisions they expect to receive when their elderly dependents die (163, 164). In spite of this the approach that is taken more generally within health economics is to treat the spillovers of interventions on family members as a type of externality, that are therefore important to capture in broader perspectives for economic evaluations of interventions that alleviate patient illness (12, 165).

2.2. Current practice of including spillover impacts in economic evaluation

A systematic review carried out in 2010 by Goodrich et al identified all studies that had included informal care in applied economic evaluations (166). The review reported 30 eligible studies, with only 23 of these studies relating to spillover, i.e. the interventions that were being evaluated were directly targeted at the patient, with resulting spillover impacts on informal carers. However a subsequent review by Krol et al in 2013 suggested that there may be a growing literature of economic evaluations that include informal care (167). Krol et al found that 23 of the 100 of the economic evaluations carried out between 2009 and 2013 for Alzheimer's disease, rheumatoid arthritis, metastatic colorectal cancer and Parkinson's disease, had included informal care. The following sections 2.3 and 2.4 will discuss the different methods that have been used in studies for incorporating spillovers on informal carers into estimates of intervention costs, intervention outcomes, or both costs and outcomes within the same economic evaluation.

2.3. Measuring costs of family members for economic evaluation

Economic evaluations may incorporate spillovers of patient interventions on informal carers into assessments of costs. This may be done by estimating the time that the informal carer spends on providing care, across the different interventions that are being evaluated. The majority of studies that have measured carer costs in economic evaluations have done so solely in terms of the time losses that informal carers incur (166, 168). The time that informal carers spend providing care is characterised as a 'time loss' (or 'time cost') because it is time spent providing unpaid care that could instead be spent doing paid work and leisure activities. Since non-carers do not incur any obvious time costs (or any other monetary costs) resulting from patient illness as they do not provide active care, they would not be included in these cost estimates in economic evaluations.

The time losses that informal carers incur are subsequently converted into monetary costs. A systematic review by Goodrich et al identified two conversion methods reported in the 25 studies that measured carer costs (166). The first was the opportunity cost method, which uses information on the carer's previous or current employment that they had to terminate or scale back in order to provide care, to calculate the work related financial losses to carers. This is determined using the gross wage of the carer, as the gross wage reflects the financial loss to both the individual and to the rest of society (141, 169). This cost is added to other sacrifices that the carer makes in terms of their leisure and volunteering activities in order to provide care. Both leisure time and volunteering time can be converted into monetary valuations by using a local tariff from a value of time study (21).

The other method that was used to convert time costs to monetary costs from the studies included in Goodrich et al's review was the proxy good method(166). This method estimates the time cost incurred to the informal carer in monetary terms, according to the remuneration that a paid carer or appropriate substitute for the specific task (e.g. cleaner) receives within the marketplace for providing the same amount and type of care that the informal carer is providing. The care provided by a (paid) home carer may be very similar in nature to types of informal care provided (170).

A disadvantage of both the opportunity cost and proxy good method for valuing carer time losses, is that neither of these methods takes into account process utility (or disutility) from providing informal care. Process utility here refers to the utility (or disutility) that the carer derives from the process of providing informal care (143). Process utility is illustrated in one study that found that on average carers indicated a preference for being the care provider as opposed to enlisting the services to someone else that would provide the care free of charge(143). The motivation for providing long-term informal care for any individual is influential in determining how process utility is generated. In many situations, caring is an altruistic behaviour that is motivated by love that as a result generates positive feelings, but in other cases caring is motivated by a sense of duty or societal expectation (e.g. filial piety) so that it generates process *disutility* as caring is experienced more as a burden (54, 163). Measurement of outcomes of carers in economic evaluation may instead allow for process utility to be captured, for example by using self-reported quality of life measures or the willingness-to-pay methods that are discussed in section 2.4.

Aside from these methodological shortcomings in valuing carer time losses, it would arguably only be appropriate to value carer time costs in economic evaluation, if time costs to patients are also accounted for in the evaluation, for example the income losses that are incurred by patients that are absent from work as a result of their illness (153). Further costs to family members that have been used in the economic evaluations are health care costs (167). This is because family members (carers and non-carers) may utilise health care services for the health spillovers that they experience (e.g. prescriptions for anti-depressants). Another cost is the out-of-pocket costs that carers may incur in the process of care such as transportation costs which have been included in some economic evaluations (168, 171). However, it may be difficult to disentangle patient out-of-pocket costs from carer out-of-pocket costs, for example if patients and carers share the methods or costs of transportation to a health care appointment. Complexities also arise in disentangling the cost of paid 'home carers' in economic evaluation where the cost is split between the NHS and the patient's family (172).

2.4. Measuring outcomes of family members for economic evaluation

The spillovers of change in patient health on the outcomes of family members who are carers or non-carers may also be estimated, in addition to, or instead of costs (173). Three alternative approaches for measuring outcomes of family members will be discussed in this section. Firstly, the approach that aims to elicit a full (or complete) valuation of outcomes of

family members resulting from spillover of patient illness through a willingness-to-pay method will be discussed. The alternative approaches, using a partial valuation of family member outcomes through a care-related or health-related quality of life measure, will be discussed in sections 2.4.2 and 2.4.3 respectively. A full valuation aims to value the benefits (and harms) of the intervention across all areas of a family member's life. A partial valuation only values the outcomes generated from the intervention in relation to an aspect of life, in this instance, referring to the outcomes associated with care provision (care-related quality of life), and the health outcomes of family members (health-related quality of life).

2.4.1. Willingness-to-pay valuation of family member outcomes

Willingness-to-pay (WTP) methods may be used to fully value outcomes of not just carers but also family members who are non-carers. Willingness-to-pay values outcomes in monetary terms, which enables them to be included in (welfarist) cost-benefit analyses of health interventions.

There are two willingness-to-pay methods that are commonly applied in the health sector to value health interventions. The first is contingent valuation, which uses a questionnaire to ask participants to state the maximum amount they would be willing to pay to experience particular benefits of a health intervention, or the minimum amount they would be willing to accept to forego the same benefits of the intervention (or to bear some harm) (174). The specific benefits of the health intervention are described in the survey in order to enable respondents to fully imagine what it would be like to experience these benefits. For

instance, a contingent valuation survey could simply ask patients the maximum amount they would be willing to pay for a hypothetical treatment that alleviates the symptoms of the illness for a specific duration of time. The other method is a discrete choice experiment that enables an indirect calculation of an individual's willingness-to-pay for a health intervention. This is elicited through a complex survey design requiring individuals to repeatedly choose their preferences between many different sets of attributes (175). These attributes may be defined in the context of spillover as the different areas of an informal carer's life that are impacted from providing care (176).

Two existing willingness-to-pay studies that have been administered to carers or family members as part of a cost-benefit analysis were identified in the review by Goodrich et al (166). However, the main objective of these studies was to value changes in the wellbeing of patients rather than carers. Both were contingent valuation studies administered to carers as the patients in these studies were affected by dementia and were therefore incapable of self-reporting their willingness-to-pay for the intervention (166, 177). However, evidence suggests that it may be sufficient to administer contingent valuation studies to patients in order to account for spillovers on family members (178). This is because willingness-to-pay studies administered to patients may elicit both the impact of illness on the patient themselves, as well as the value of the spillovers experienced by the patient's loved ones, that the patient altruistically accounts for as one's own disutility in a valuation (179).Nevertheless, the disutility that the carer actually experiences may be different to the disutility that the patient perceives the carer as experiencing. For instance, the patient may over-estimate the carer's disutility due to feelings of guilt and/or being a burden, by undervaluing the satisfaction and sense of accomplishment (process utility) that carers may

experience from providing care (143). On the other hand, they may under-estimate the disutility if the carer actively disguises the stress they experience as a result of caring.

A number of methodological shortcomings of contingent valuations have been noted in various studies (180). These include systemically higher elicited valuations for the same good when the minimum willingness-to-accept for the good is elicited instead of the maximum willingness-to-pay, when the valuation question is closed-ended compared with open-ended, and when the good is delivered through the private sector instead of the public sector (181-183). Nevertheless, in the context of willingness-to-pay for informal care greater consistency has been noted in observing that the reported minimum willingness-to-accept for informal care by informal carers is similar to the maximum willingness-to-pay (184).

Discrete choice experiments (DCEs) have grown in use in health economics in recent years (185). This growth may reflect a perception that DCEs are a more valid alternative to contingent valuations for valuing health interventions as they enable participants to consider more thoroughly the different attributes of interventions that they place value on. Despite this some empirical studies have questioned the external validity of DCEs in noting a lack of consistency between the preference indicated by respondents in DCEs and their actual realised behaviours (186, 187). Another drawback of DCEs are that they are much more intensive to design, and also for participants to complete than contingent valuations, and may as a result obtain low response rates (188).

2.4.2. Care-related quality of life of family members

An alternative to using willingness-to-pay (WTP) is to use care-related quality of life instruments. The instrument is administered to carers to measure the effect to a carer's wellbeing (or quality of life) resulting from providing care, and then a social tariff of index values is applied to changes in quality of life.

Two main instruments exist that aim to estimate a valuation of the welfare changes of carers resulting from providing care, defined as 'care-related quality of life'. A third instrument, the ASCOT measure, is primarily intended to elicit the social care related quality of life of care recipients rather than the carers, although it consists of some domains relevant to carers (189). The first instrument that will be discussed is the Carer Experience Scale (CES). The CES is composed of six attributes: activities, formal support, informal support, fulfilment, control, and relationship to care recipient(176, 190). Qualitative research was used to extract the major themes that encompass the 'carer experience', that were then selected as items for the instrument. The tariff for the instrument was obtained from a best-worst scaling experiment administered to 200 carers in the UK (176). The experiment asked participants to repeatedly rank their most and least preferred items in the scale in order to determine the relative importance of these items in determining the carer's experience (or welfare).

The second instrument that is available to estimate a valuation of a carer's welfare changes from providing care is the CarerQol instrument(191). This instrument consists of 7 attributes and a visual analogue (happiness) scale. Specific attributes of the CarerQol that are distinct from the CES are items relating to the financial situation of the carer, and specifically framed questions about the physical and mental health of the carer. A tariff for the measure was

recently constructed based on a discrete choice experiment administered to 1000 members of the Dutch general adult population(192).

Table 2.1 below compares care-related quality of life instruments and the EQ-5D instrument for capturing different areas of carer spillover:

Table 2.1: Attributes of quality of life instruments for carers

	CES	CarerQoL	EQ-5D
Physical Health		✓	✓
Mental Health		✓	✓
Fulfilment from caring	✓	✓	
Relationship to care recipient	✓	✓	
Finances		✓	
External support	✓	✓	
Daily activities	✓	✓	
Feelings of control	✓		

Although broader instruments have been developed that are sensitive to many of the changes in a carer's quality of life resulting from providing care such as the CES and Carer QoL, aggregation of estimates of care-related quality of life with patient health-related quality of life in an economic evaluation is not simple. Even though estimations of health-related quality of life and care-related quality of life can both be converted into standardised measures on a 0 to 1 scale, these measures are different in terms of the type of quality of life they are measuring (176). Therefore, they cannot be combined in a straightforward way, and may have to be assessed separately as part of a cost-consequence analysis. Alternatively, there has been some discussion of a way of calibrating measures of care-related quality of life with patient health-related quality of life, by assigning normative

weights about the relative importance of these aspects of quality of life (179). These weights could be estimated by collecting data about how much patients value health-related quality of life in relation to their overall quality of life, and comparing this with how carers value their care-related quality of life also in relation to their overall quality of life (179).

Furthermore, these instruments are only appropriate to implement with household members or family members who are carers, as they were designed based on qualitative research involving carers and validated among populations of carers, and as a result they ask questions about providing informal care.

The following section 2.4.3 explores an alternative approach for capturing the outcomes of family members affected by spillover. This section explores the measurement of health outcomes of family members, for inclusion in economic evaluations that have the underlying objective of maximising population health. This approach is particularly interesting to decision makers like NICE that pursue this objective, and is the core focus of the PhD.

2.4.3. Valuation of carer and family member health outcomes in economic evaluation

This section focuses on an approach for measuring the health spillovers of family members resulting from patient interventions. This approach is aligned with decision makers that aim to maximise health across a population (153). In order to do this, decision makers need to measure the spillover impacts of interventions on the physical and mental health of family members.

Health outcomes of family members can be measured in terms of QALYs by using generic preference-based measures of health, for example the EQ-5D-5L, SF-6D, or the HUI-3 instruments (174). These measures can be used to generate a utility score on a 0 to 1 scale that can then be used to adjust life year data to estimate the incremental QALYs gained or lost through an intervention for family members (as well as patients). In a NICE health technology assessment, it may be argued that the EQ-5D-5L is the most appropriate instrument to measure health status changes in family members, because this is also the preferred instrument for measuring the health of patients in these appraisals. However, if the EQ-5D-5L performs poorly in terms of lacking sensitivity in detecting health spillovers when tested in a population of family members of patients, another instrument may be needed for measuring the health outcomes of family members. It is plausible that alternative instruments that are more socially oriented or offer more detailed elicitations of mental health, such as the SF-6D, may be better at capturing aspects of health spillover that carers and non-carers experience (14, 193).

A total estimate of health outcomes of an intervention across patients and family members can be made by simply summing the QALYs accrued across all of the individuals within the intervention arm, as depicted in the ICER formula below (78):

$$\frac{\textbf{Incremental costs of intervention}}{\textbf{Patient} + \textbf{ family member QALYs generated from intervention}}$$

This summation of QALYs across patients and family members is an appropriate method of aggregating direct patient health effects with spillover effects on the health of family members, if the underlying normative assumption that a QALY is a QALY holds. This

assumption implies equal weighting of QALY gains and losses across all individuals, irrespective of whether the gains and losses fall on patients or on family members(12). The underlying objective of an extra-welfarist framework that includes health outcomes of family members is thus to maximise the health of all individuals (patients and family members) who experience important health gains from an intervention. This moves away from existing approaches that in practice focus only on maximising the health of a subset of the population (usually patients), rather than the whole population.

2.4.4. Measuring both costs and outcomes in the same evaluation

Instead of only incorporating spillover effects into either costs or outcomes of an economic evaluation, another option is to include both costs and outcomes of family members in economic evaluations. The rationale for doing this is also the same for including family members in economic evaluations in the first place; the more appropriate evidence that can be included in decision making about the impacts of interventions, the better. Furthermore, there are a range of costs and outcomes that fall on family members. The potential spillover costs and outcomes on family members that could be included in economic evaluation are listed in Table 2.2 below:

Table 2.2: Costs and outcomes of family members

		Carers	Non-carers
Costs	Work time	✓	
	Volunteering time	✓	
	Leisure time	✓	
	Out-of-pocket (e.g. transport)	✓	
	Health care (e.g. anti-depressants)	✓	✓
Outcomes	Health-related quality of life	✓	✓
	Care related quality of life	✓	
Costs&outcomes	Willingness-to-pay to avert spillover	✓	✓

However, measuring both costs and outcomes of carers in the same evaluation can lead to a problem known as 'double counting'. Double counting refers to the situation where individuals report losses and gains of the same factor in their assessments of both costs and outcomes, even though the same factor should only be counted once in an economic evaluation. For example double counting is likely to happen if carer costs are reported from lost time from work, and if a valuation method such as the CarerQoL instrument is used to measure outcomes, as the CarerQoL instrument includes a dimension specifically relating to the financial impact of caring. In fact a valuation of carer utility by using a care-related quality of life instrument or a willingness-to-pay survey implies no further inclusion of impacts to carers on the cost side of an economic evaluation (21).

The possibility of double counting is less of an obvious problem in economic evaluations where family member outcomes are limited to health-related quality of life. These economic evaluations potentially allow for two important areas of spillovers on family members to be captured separately on the cost and outcome side of an economic evaluation. The first area is the health outcomes of family members resulting from strain of caring and witnessing illness. The second area is the value of the time that carers could spend doing other activities

if they did not have to spend that time providing informal care (e.g. time spent in work, volunteering and leisure as a general typology of other potential activities) (21). The inclusion of both carer time costs and carer health-related QALYs within the same evaluation is consistent with US guidelines for cost-utility analysis (194).

However, there may remain less obvious risks of double counting by including time costs alongside health outcomes of family members in economic evaluation. One risk concerns the fact that value of time studies are used to value one hour of sacrificed leisure time in order to provide informal care to enable leisure time to be included as a cost, and these value of time studies often elicit this value through survey methods (21, 195). However, respondents in value of time studies may consider the health benefits they may experience from having more leisure time in producing their valuations, such as reduced stress and increased participation in exercise. These effects may also be strong determinants of the health spillovers experienced by many carers, leading to double counting.

Nevertheless, extra-welfarist decision makers often restrict costs in economic evaluations to those incurred by health care providers (by using a 'payer' perspective). For example NICE applies a NHS and PSS (personal social services) cost perspective for economic evaluations, that deliberately excludes costs incurred to patients and other individuals (158). This is because the underlying objective of NICE economic evaluations is to maximise health gains within a population from a fixed NHS and PSS budget (158). Therefore, only the impacts of interventions on family members in terms of *health outcomes* rather than time costs, are likely to be compatible with the extra-welfarist economic evaluations carried out by NICE.

It is also the case that the possibility of double counting is only an obvious problem for elicitations from carers. This is because non-carers are unlikely to experience losses in terms of work and leisure time from patient illness as they are not spending time providing care, so work and leisure time losses would not be measured on the cost side of an economic evaluation for non-carers anyway.

2.5. Including spillovers in economic evaluations at the decision making level

2.5.1. Economic evaluations conducted by NICE

NICE (National Institute for Health and Care Excellence) is the major public body in the UK that recommends the adoption or rejection of new health interventions into clinical practice, and requires all health interventions that are appraised to undergo economic evaluation (by way of cost-utility analysis). Since NICE's inception in 2000, the organisation has undertaken over 400 single or multiple health technology assessments (HTAs) to form 674 recommendations (196). 19% of these recommendations instructed that the technology should not be introduced into clinical practice in the NHS.

NICE guidelines for economic evaluations that form part of a HTA recommend the inclusion of 'direct health effects' of interventions to both the patient, and the carers of a patient,

using the EQ-5D questionnaire (158). However the health effects to informal carers are rarely included in these evaluations(166). This may be because spillover effects may be more appropriately characterised as indirect health effects extending from changes in the patient's health. Moreover, no consensus has yet been reached on a general methodology for measuring health spillovers and incorporating them into economic evaluations (12, 78, 197). Goodrich et al (2012) drafted a reference case for a NICE HTA that includes health spillover only for the primary carer(166). However in some cases it may be difficult to identify a primary carer, for example in the case of parents providing care for chronically ill children, where duties may be shared more or less equally between parents(198). Also including the health outcomes of non-carers that are affected by 'caring about' the patient, would require further modifications of the reference case by Goodrich et al, and also implies the inclusion of all household members, and potentially non-household members who experience health spillover. If a patient has a close knit and/or large family, the overall total health spillover to family members could theoretically be much larger than the isolated health effect to the patient. However it may be important to restrict primary data collection of spillover to a limited number of the closest family members to the patient for feasibility reasons, that are discussed later in this section.

Discussions were held by NICE in 2014 to adjust economic evaluation guidelines to incorporate the wider benefits of an intervention, under proposed 'value based assessments' (formerly 'value based pricing') (199). The inclusion of 'wider societal impacts' in NICE appraisals, appeared to offer the opportunity to include measurements of the health effects of an intervention on informal carers (200). However, the most recent plans to introduce value based assessments into NICE economic evaluations were shelved in late

2014 as they were considered to be unworkable in the short-term, reflecting challenges in expanding NICE's current reference case (201).

2.5.2. Implications of including spillovers on the NICE cost-effectiveness threshold

It is also important to consider the implications of the regular inclusion of health spillovers in NICE economic evaluations on the budget constraint (or threshold) that NICE uses. NICE currently uses a range for its decision threshold of £20,000-30,000 per QALY. NICE considers interventions that cost the NHS less than £20,000 per QALY gained as cost-effective, and interventions that cost the NHS between £20,000 to £30,000 per QALY gained as cost-effective if certain additional conditions are met (158). If the ICER for an intervention exceeds £30,000 per QALY, funding the intervention is considered to generate a lower patient health benefit compared with the benefit generated if the funds are reallocated somewhere else in the NHS (158). As explained earlier, NICE economic evaluations are carried out under an extra-welfarist perspective, and currently aim to maximise the health outcomes of those directly affected by interventions (usually patients), although this thesis argues that there is potential to expand this perspective of the health gains of interventions to individuals whose health is indirectly affected by spillover.

Systematic inclusion of health spillovers in NICE economic evaluations may reduce a number of intervention ICERs from above the NICE threshold of £30,000 per QALY to below the threshold. This is because interventions that are more effective so that they lead to greater

improvements in patient health, may result in a greater improvement in family member health as well, by further reducing the burden of care and distress that family members experience. Therefore including health spillovers may reduce the ICERs of these more expensive and more effective interventions, so that they fall below the NICE threshold (167). Although NICE is unlikely to adjust its cost perspective to include costs other than those directly incurred by the NHS (such as patient or carer productivity costs), if carer costs were also included alongside family member outcomes in economic evaluations, this is also likely to reduce the ICERs for interventions that are more effective in improving patient health. This is because better patient health means the patients are less dependent on the carer, thus reducing the time and financial burden on the carer (202).

As a result, including spillovers in economic evaluations without any lowering of the threshold would place a greater strain on the limited NHS budget. Therefore, a modified reference case for NICE economic evaluations that instructs the routine inclusion of health spillovers should also specify a lower cost-effectiveness threshold to accommodate this change. The overall impact on the cost-effectiveness of a more expensive intervention would therefore depend on whether the intervention alleviates the health burden on family members substantially enough so that it outweighs a reduction in the threshold (78). Deciding exactly how much to reduce the NICE decision threshold is an important question that needs to be resolved to enable inclusion of health spillovers in the NICE reference case. This may be done by applying a multiplier to the threshold that reflects the ratio of health spillovers to patient QALYs from health interventions in general (78).

2.5.3. Appraisals beyond NICE

In a number of countries, a societal perspective is advocated in national guidance for the economic evaluations of health technologies, such as Australia, Netherlands, France and the USA (194, 203). These guidelines in their current form do not address what methods should be used for incorporating spillovers. Health spillovers may be a relevant outcome for economic evaluations conducted under a societal perspective. These evaluations may compare societal costs against health outcomes aggregated across patients and family members. As discussed in section 2.2, it may be possible under a societal perspective to include health outcomes of family members alongside non-health (time) costs incurred by family members who are providing informal care, with small risk of double counting.

Also, decision makers other than NICE may adopt a more flexible approach to including the wider health benefits of an intervention. For example the JCVI (Joint Committee on Vaccination and Immunisation) recently approved a meningitis B vaccination to be administered in a routine immunisation programme (204). In doing so the JCVI considered evidence from the economic evaluation which estimated the benefits of a vaccination programme across the family network of the patient(20).

2.5.4. Ethical considerations for including health spillovers in decision making

The inclusion of health spillovers in applied health economic evaluations for informing decisions implies stronger preferences for interventions affecting patients that have larger families thus conferring spillover on a larger family/household network. However it may

firstly be ethically problematic to give greater priority for health resources to individuals on the basis of them having many family members (140). Furthermore by including spillovers, lower preferences may also be given to single parent households (e.g. single parents of ill children or young carers of single parents) who are already among the more disadvantaged and impoverished groups in society, therefore resulting in even more social disadvantage in these groups. On the other hand, measurement of health spillovers should be able to capture the additional strain that is placed on family members who lack the support of a spouse or an additional parent to offset the care load. One could also argue that the position before health spillovers are taken into account exacerbates existing inequalities in NHS funding allocation where mental health services are underprovided. This is because this position gives lower priority to treatments affecting mental illness because it does not take into account the potentially substantial health spillover benefits of mental health interventions.

In any case in terms of taking equality considerations into account in economic evaluation, others may argue that in order to pursue a goal of maximising health, economic evaluations use a positive process of evaluation rather than a normative process, and therefore inequitable outcomes are an inherent part of this process(162). For instance regular economic evaluations imply 'sexist' outcomes that discriminate against men; for example life-saving treatments for women will receive greater preference than life-saving treatments for men, as women on average live longer than men so would receive more life year gains as a result of treatment (205). However, economic evaluation is used to inform population level decisions about whether treatments should be funded rather than decisions about whether one patient or another should get it (taking their family network into account). It might be

more appropriate to use normative considerations such as equality as a separate strand of decision making processes for adopting health interventions, alongside, rather than formally integrated with the evidence from economic evaluations (206).

2.6. Systematic review of cost-utility analyses that have included health spillovers

This section assesses the extent to which existing cost-utility analyses (the most common form of economic evaluation) have included health spillovers. Although two systematic reviews have been conducted in the area of spillover, these reviews were limited to carers in both reviews, four chronic diseases in one review, and the reviews only included studies up to 2013 (166, 168). A better understanding of the limitations in existing practice of including health spillovers in economic evaluation helps to identify areas where further research is most needed.

The first objective of the systematic review was to identify all cost-utility analyses of patient interventions that have included QALYs of family members. These family members include, in principle, all significant others such as spouses or friends. The second objective was to determine the methods that have been used in these studies to measure health spillovers and to include them in the cost-utility analysis.

The following section documents the findings of the review. The methods of the review are presented in appendix 2.1. The key areas which are documented are the number of cost-utility analyses that have included health spillovers, the disease areas in which health

spillovers have been accounted for, the methods used to estimate health spillover and incorporate them into decision analyses, and the impact of including health spillovers on the cost-effectiveness of the interventions. Tables summarising key characteristics of the included studies are also provided in this section (tables 2.3 and 2.4). Further detail on the included studies is provided in data extraction forms (appendix 2.2).

Study selection

The search identified 2765 studies after duplicates were removed. Titles and abstracts were screened, and 132 full texts were identified as needing to be assessed for eligibility. Of those, 29 studies were included in the final review. The reasons for excluding the remaining 103 studies in the full text screen are provided in Figure 2.1.

Figure 2.1: Prisma flow diagram

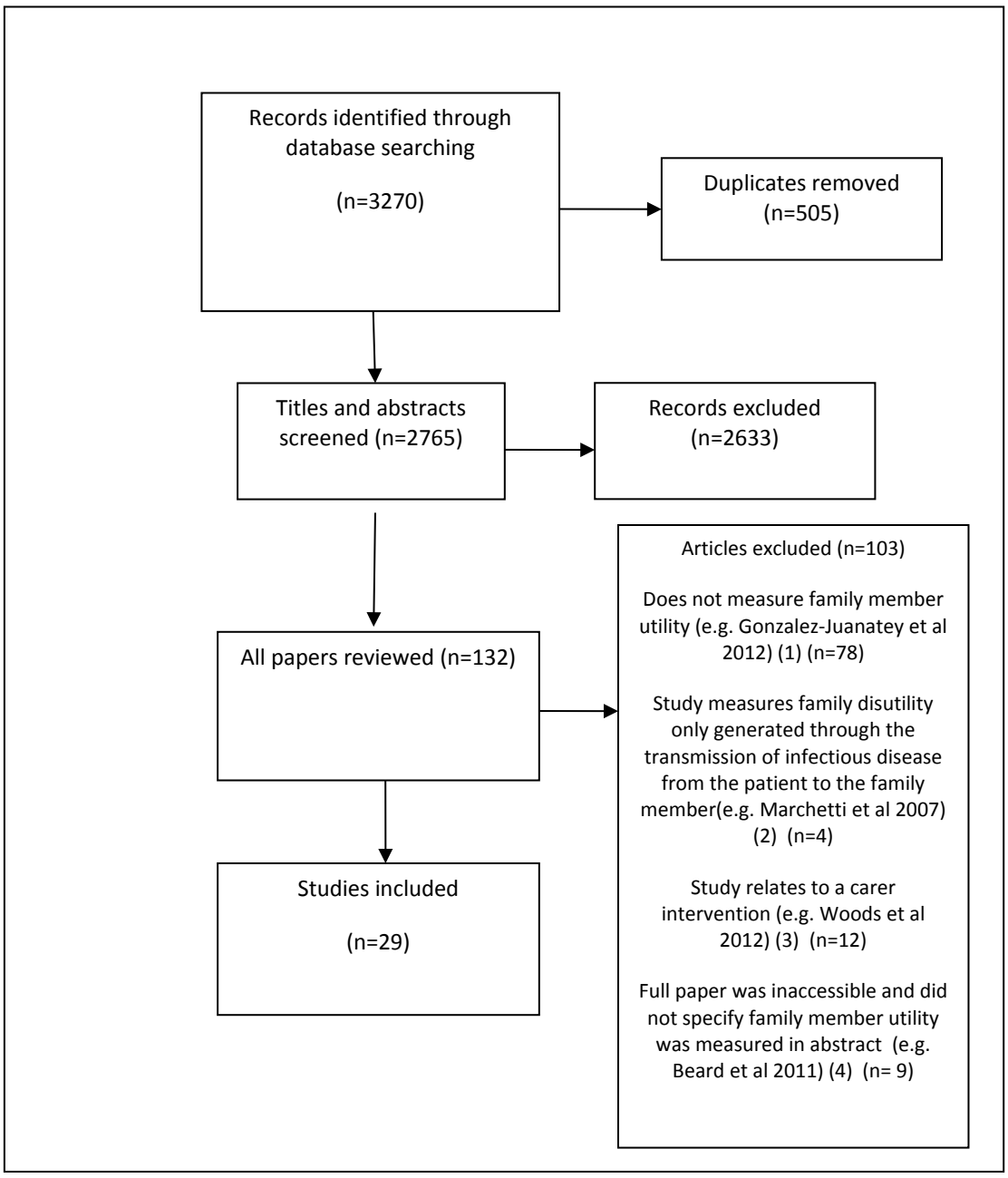


Table 2.3: Characteristics of included studies

Author	Year	Country	Underpinning condition	Intervention
Bilcke et al	2009	Belgium	Rotavirus	Vaccination
Christensen et al	2014	UK	Meningitis	Vaccination
Creswell et al	2015	UK	Anxiety disorder	Mother anxiety treatment
Fisman et al	2012	Canada	Rotavirus	Vaccination
Flood et al	2005	UK	Frail older patients	Occupational therapy
Gani et al	2008	UK	Multiple Sclerosis	Natalizumab
Getsios et al	2010	UK	Alzheimer's	Donepezil
Getsios et al	2012	UK	Alzheimer's	Early assessment & donepezil
Greer et al	2011	Canada	Pertusiss	Pertussis vaccination
Hartz et al	2012	Germany	Alzheimer's	Donepezil
Hornberger et al	2012	USA	Cancer (leukemia)	Rituximab
Itzler et al	2011	Taiwan	Rotavirus	Vaccination
Jit et al	2009	5 countries	Rotavirus	Vaccination
Jit et al	2007	England and Wales	Rotavirus	Vaccination
Little et al	2005	USA	Herpes Simplex	Acyclovir prophylaxis
Meeuwsen et al	2013	Netherlands	Dementia	Memory clinic care
Melliez et al	2008	France	Rotavirus	Vaccination
Milne et al	2009	New Zealand	Rotavirus	Vaccination
Neumann et al	1999	USA	Alzheimer's	Donepezil
Newall et al	2007	Australia	Rotavirus	Vaccination
Perez-Rubio et al	2011	Spain	Rotavirus	Vaccination
Pham et al	2014	Canada	Terminally ill	Palliative team care, patient planning
Poirier et al	2009	Canada	Pneumococcal	Pneumococcal conjugate vaccination
Salize et al	2013	Germany	Alcoholism	Alcohol dependence treatment
Schawo et al	2015	Netherlands	ADHD	Osmotic release oral system
Shim et al	2009	USA	Rotavirus	Vaccination
Sturkenboom et al	2015	Netherlands	Parkinson's	Occupational therapy
Tilson et al	2011	Ireland	Rotavirus	Vaccination
Tu et al	2012	Vietnam	Rotavirus	Vaccination

Table 2.4: Methods for accounting for health spillovers on family members (FMs) in included studies

Author	Year	Study design for measuring family member health	Number of FMs included in primary analysis	FMs included in synthesis of benefits?	Outcome measured	Data collection dates
Bilcke et al	2009	Observational	1	Yes	EQ-5D	2005
Christensen et al	2014	Observational	4	Yes	EQ-5D	2012
Creswell et al	2015	RCT	1	Yes (no patients)	EQ-5D	2008-2013
Fisman et al	2012	Observational	Not stated	Yes	EQ-5D	2005
Flood et al	2005	RCT	Not stated	No	EQ-5D	2000-2001
Gani et al	2008	Not stated	1	Yes	Not stated	Not stated
Getsios et al	2010	RCT (pooled estimate)	1	Yes	SF-36	Not stated
Getsios et al	2012	RCT (pooled estimate)	1	Yes	SF-36	Not stated
Greer et al	2011	Observational	2	Yes	Direct elicitation	1997-1998
Hartz et al	2012	RCT (pooled estimate)	1	Yes	SF-36	Not stated
Hornberger et al	2012	Unclear	1	Yes	Direct (time trade-off)	1986-1994
Itzler et al	2011	Observational	1.9 (average)	Yes	EQ-5D	2005
Jit et al	2009	Observational	1	Yes	EQ-5D	2005
Jit et al	2007	Observational	2	Yes	EQ-5D	2005
Little et al	2005	Observational	1	Yes	Direct elicitation	1997-1998
Meeuwsen et al	2013	RCT	1	Yes	EQ-5D	2007-2010
Melliez et al	2008	Observational	1	Yes	EQ-5D	2005
Milne et al	2009	Observational	1	Yes	EQ-5D	2005
Neumann et al	1999	Observational	1	Yes	HUI:2	1996-1997
Newall et al	2007	Observational	1	Yes	EQ-5D	2005
Perez-Rubio et al	2011	Observational	2	Yes	EQ-5D	2005
Pham et al	2014	Observational	1	Yes	EQ-5D	2004
Poirier et al	2009	Not stated	1	Yes	Not stated	Not stated
Salize et al	2013	Observational	1	Yes (no patients)	WHO-BREF	2005-2008
Schawo et al	2015	Observational	4	Yes	EQ-5D	2012
Shim et al	2009	Observational	1	Yes	EQ-5D	2005
Sturkenboom et al	2015	RCT	1 / 2	Yes	EQ-5D	2011-12
Tilson et al	2011	Observational	1	Yes	EQ-5D	2005
Tu et al	2012	Observational	1	Yes	EQ-5D	2005

2.6.1. Study characteristics

Included studies were published between 1999 and 2015. In one 2012 study (207), family member QALYs were estimated using an external study which used data recorded between 1986 and 1994 (140). One study was a cost-utility analysis carried out in five different European countries (208), and seven of the studies were specifically conducted in or within the UK (209-215). The studies identified were quite geographically dispersed across Europe, Asia, Australasia and North America, although none of the studies were from South America or Africa. Six studies did not appear to state a rationale for including health spillovers in the analysis (212, 216-220).

Most cost-utility analyses included in the systematic review concerned interventions for chronic illness of patients, including a number of interventions for chronic illnesses in older people such as Alzheimer's disease (209, 211, 221-223). However also included were twelve cost-utility analyses undertaken across different countries for vaccination of rotavirus, including Vietnam, Taiwan, Spain, France, Belgium, New Zealand and Australia. Rotavirus is an acute disease that occurs in infants, and was found to cause a brief but sizeable loss in quality of life in both infants and their caregiving parents(224). The other studies included in the review evaluated vaccination interventions for both acute and chronic illnesses (215, 217), interventions for health conditions characterised by behavioural impairments in patients such as alcoholism and ADHD(225, 226), interventions for cancer(207), multiple sclerosis(210), eight end of life care interventions (227), and some complex multi-faceted interventions involving mothers and their child/neonate that also factored in health spillovers (214, 228).

2.6.2. Models versus trials

Many of the economic evaluations identified in the systematic review used estimates of family QALYs from an external study to incorporate into a decision model, while at the same time used a different study or methodology to estimate the QALYs of the patients(207, 210, 215, 219, 226-228). Furthermore in several economic evaluations, the external study that provided an estimate of health spillovers was related to a different condition (207, 210, 226, 228). For example one economic evaluation used a study on the health spillovers of meningitis to estimate family QALYs for ADHD (226). Meningitis encompasses a broader range of symptoms beyond behavioural impairments that create health spillovers, such as limb amputations. Another economic evaluation used a study on the health spillovers of Alzheimer's disease to estimate family QALYs for multiple sclerosis (210). Alzheimer's disease is predominantly a cognitive illness affecting older patients, whereas multiple sclerosis is predominantly a physical illness.

In just three studies, family QALYs were measured in the intervention and control arms of a trial-based economic evaluation (209, 221, 223). However there was considerable missing data on family QALYs in one of these trial-based economic evaluations, with only 113 carers sampled compared with 321 patients as a result of missing data at both baseline and follow-up, leading to greater uncertainty about the magnitude of carer QALYs, and inhibiting their inclusion in a base-case analysis (209). In this study, informal carers were only approached to take part if they were present at the participant recruitment interview (229). However in another study that surveyed patients and carers separately there was very little missing data on family QALYs relative to patient QALYs, but the authors instead encountered problems in

obtaining complete and valid data on informal care hours, as carers found it tricky to conceptualise the amount of extra informal care that they provided resulting from the patient's illness (223).

In combining patient and family QALYs, one trial-based economic evaluation only included patient-carer dyads that had produced a complete set of EQ-5D scores for both the patient and carer at baseline and follow-up stages of the trial (223). There was a similar amount of data for both patient and carer self-reported health in this trial. Only a slightly lower number of carer respondents compared with patient respondents were obtained, which was attributed to patients either not having an informal carer, or informal carers not being available or willing to participate in data collection (223).

Empirical studies 2 and 3 of the thesis provide a practical case study of the missing data which may be associated with collecting spillover data, and the methods which may be used for including health spillovers in a trial-based economic evaluation.

2.6.3. Outcome valuation technique

In the systematic review, a range of direct and indirect approaches were identified for measuring family member QALYs (although in two studies the technique for measuring health spillovers was unspecified). 24 studies used indirect methods for eliciting health status through use of a health instrument; 19 of these studies used the EQ-5D to measure family member QALYs, 3 studies used the SF-6D (211, 230, 231), one study used the HUI:2

(222), and one study used the WHO-BREF (225). Unlike the EQ-5D, SF-6D or HUI, the WHO-BREF was originally designed as a broader quality of life measure rather than a health-related quality of life measure (232), and comprises of four domains: physical health, psychological well-being, social relationships and environment (232). Nevertheless the WHO-BREF may be considered as a health-related quality of life measure as there is a substantial conceptual overlap between the measure and the World Health Organisation's definition of health as a "state of complete physical, mental and social wellbeing" (233). The authors of the economic evaluation that used the WHO-BREF to measure the QALYs of family members, used the NICE reference case for cost-utility analysis as a framework for their analysis (234), although it may be considered unlikely that a NICE economic evaluation would use evidence from a broad measure such as the WHO-BREF.

In the rotavirus vaccination economic evaluations, and donepezil economic evaluations published post 2010, the instrument that was used to measure family member QALYs was not the same instrument that was used to measure patient QALYs. However, in the rotavirus vaccination studies, the authors of the external study which used different measures for patient QALYs and carer QALYs justified doing this on the basis that the standard EQ-5D would only be an appropriate measure of the carers' health but not appropriate for measuring the health of the infant patients(158, 224).

Despite the evidence in this review of the extensive use of the EQ-5D to measure health spillovers for a cost-utility analysis, Chapter 3 of the thesis details the first empirical study in the literature to assess the relative performance of EQ-5D-5L compared with the SF-6D for detecting health spilovers.

Direct elicitations of family member health (dis)utility (including standard gamble and time trade-off techniques) were used in three economic evaluations that referred to external studies for these estimates (207, 219, 228). For example in one of these external studies, the time trade-off technique was used to ask the wives of patients with prostate cancer the maximum number of years of life expectancy they would give up in order to avoid the worries, burden and stress arising from their husband's illness (235). Direct utility elicitation methods may lead to overestimates of health spillovers and potential double counting in a cost-utility analysis (12). This is because it may be difficult for family members in these elicitations, to disentangle spillover of the patient's illness on their health, with the disutility experienced by the patients themselves from the illness.

2.6.4. Individuals included in analysis

Cost-utility analyses of interventions that were identified mostly included one or two family members identified to be substantial care providers such as parents of ill children or the spouses of chronically ill patients. Two cost-utility analyses appeared to have made a specific adjustment to the number of parents affected by spillover according to data on the proportion of single parent households (219, 236). Four cost-utility analyses that included health spillovers also included utility decrements experienced by bereaved family members (207, 215, 227, 228). Two cost-utility analyses only included family member QALYs generated through spillover and excluded patient QALYs (214, 225), although in one of the studies the authors stated that they planned to combine family member and patient QALYs in a future related study (214), and in the other study the authors justified excluding patient QALYs on account of not having collected data from the patients themselves (225).

The studies that included health spillovers varied by the number of family members of the patient included in estimates of QALYs. Many evaluations included health spillover of only one family member of the patient who was established to be the primary carer. In the cases of childhood illness, it was considered appropriate in some studies to include health spillover for both parents (216, 219), although in one key external study for rotavirus vaccination it was not clear whether the authors estimated QALYs for one parent or for both parents (224, 237). Other economic evaluations used an estimate from an external study of the health spillovers accumulated across the four closest family members of the patient (20, 226).

2.6.5. Impact of including health spillovers in the analysis

In the studies included in the review, there was considerable variation in the impact that including health spillovers had on cost-effectiveness of interventions. Estimates of health spillovers when estimated for a single primary carer were variable; in some clinical and economic evaluation studies QALY gains for the primary carer were similar to or even exceeded patient QALY gains (208, 223, 238) or the intervention was cost effective by applying carer QALYs alone (while excluding patient QALYs)(225). This was also the case for the twelve rotavirus vaccination studies which were all based on an external Canadian study which found that the average carer QALYs lost to rotavirus were similar to the average patient QALYs lost(224). However in this study, the estimation of carer QALYs lost was more uncertain than the estimation of patient QALYs lost with a much wider 95% confidence interval reported (224). This indicates that it may be insufficient to only look at mean estimates and ICERs when judging an economic evaluation which has incorporated health

spillovers, and it is also important to take into account the uncertainty of the health spillover parameter. Contrastingly in other studies primary carer QALYs gains were less than 10% of patient QALY gains (210, 217, 222, 227, 231). Also in one economic evaluation, the authors used an external study to estimate that the primary carer actually lost QALYs as the patient's health and life expectancy improved due to a longer imposition of care burden (207). In three studies it was not possible to assess the impact of including health spillovers, because QALYs for patients and family members were not presented in a disaggregated form (218, 219, 228).

A number of methodological decisions undertaken by authors influenced the impact of including health spillovers in the analysis. The number of family members included in the economic evaluation was influential; for example including two carers in a base-case analysis resulted in greater inflated total QALYs compared to just one carer (208, 216). Another factor was whether interventions caused patient deaths- for example rotavirus vaccination was projected to prevent 1660 deaths in Vietnam but only one death in Belgium, so the inclusion of health spillovers on carers had less impact in the economic evaluation in Vietnam where bereavement effects on family members were excluded from the analysis (239, 240). This also raises the question of whether it is possible to introduce health spillovers routinely into economic evaluation without accounting for health effects in family members resulting from patient deaths. Including health spillovers routinely in economic evaluation while excluding 'bereavement spillovers' could result in more unfavourable assessments of health interventions that save lives, which may be undesirable.

Health spillovers were frequently included in base case analyses; but were also often isolated for sole inclusion in scenario analyses. Also in some studies health spillovers were only included in a scenario analysis on the premise of carer costs being excluded to prevent double counting, so the overall impact of including health spillovers was lessened by simultaneously and deliberately excluding informal care costs (240-242). On the other hand, the three studies published between 2010 and 2012 which evaluated donepezil for the treatment of Alzheimer's disease included both carer costs (in terms of productivity losses) and carer QALYs in the same analysis (211, 212, 230). These studies found that including carer productivity losses had a much greater impact on reducing the cost-effectiveness ratios than including carer QALYs.

None of the studies in the systematic review reduced the cost-effectiveness threshold in order to account for health spillovers, although it is recommended in the methodological literature that this is done (78), and doing so would reduce the overall impact of including (positive) health spillovers on cost-effectiveness. One study identified in the review did explicitly acknowledge that including health spillovers is controversial (236), and reducing the cost-effectiveness threshold may be necessary to alleviate any controversy.

In summary, the cost-utility analyses identified in the systematic review illustrated a general lack of evaluations that have included health spillovers, and a lack of consistency in the methods used across studies for measuring and including health spillovers in the analysis.

2.7. Conclusion

Based on the literature reviewed in Chapter 2, there are a number of unresolved methodological issues about including health spillovers in economic evaluation. The aim of this PhD is to address the following gaps in relation to the inclusion of health spillovers in applied economic evaluation:

1. Uncertainty about the relevance and performance of different health-related quality of life measures for picking up health spillovers. No empirical study has yet been carried out that has directly compared different health instruments for measuring health spillovers (12, 243, 244). However, some health instruments may be more sensitive in detecting the psychosocial dimensions of impaired health of family members, and it is important to accurately measure these health spillovers.

2. The systematic review illustrated the focus of existing economic evaluations is on measuring and valuing spillover associated with chronic and infectious diseases. There is a notable absence of investigations into the production of spillover from health behaviour change interventions, and the potential role that peer effects may play in producing a spillover here.

3. Data is rarely collected prospectively from family members. The systematic review of this chapter demonstrated there are only three trial-based economic evaluations which have collected data on family members' health status within the trial, thus providing evidence on the feasibility issues which might emerge when collecting spillover data. The review also demonstrated that a household perspective has yet to be adopted in any existing trial-based economic evaluation which has included health spillovers. However, a household

perspective may be the most feasible way of collecting data from family members, and may also be a reasonable approximation for the individuals who are most affected by spillovers (5). A household perspective may also be preferred rather than restricting data collection to just the primary carers of patients, because such an approach may neglect in capturing variability in health spillovers according to family size, as some illnesses are more likely to occur in larger families and households, with more individuals affected by spillovers from 'caring about' the patient (157).

4. A lack of consistency in the methods for including health spillovers in existing economic evaluations, and uncertainty over methodological choices in representing spillover in economic evaluation.

This thesis now presents a series of empirical studies to tackle these gaps. These comprise of:

1. A study of validity and responsiveness of the EQ-5D-5L and SF-6D for measuring the health spillovers of meningitis on carers and non-carers. Since meningitis results in a diverse range of physical, mental and behavioural impairments in patients resulting in various mechanisms of spillover on family members, the findings from this study are of relevance to chronic illness more generally.

2. Assessment of the health outcomes of household members generated in the randomised controlled trial of a COPD telephone coaching intervention. Although there is a theoretical and empirical basis for several mechanisms by which behavioural health interventions generate benefits on surrounding family members, it remains to be seen whether such

benefits are substantial and reach statistically significant levels within a trial intervention period.

3. The secondary analysis of an economic evaluation of a COPD telephone coaching intervention incorporating health spillovers on household members, to showcase a methodology that could be used for future practice.

CHAPTER 3: A COMPARISON OF THE VALIDITY AND RESPONSIVENESS OF THE EQ-5D-5L AND SF-6D FOR MEASURING HEALTH SPILLOVERS: A STUDY OF THE FAMILY IMPACT OF MENINGITIS: METHODS

Chapter 2 described how routinely including health spillovers in economic evaluations in health care can better guide health technology assessment decisions towards judgements that maximise health across patients and their family networks rather than for just the patients themselves (13). However, it remains unresolved about what health status measure should be used for measuring health spillover effects to inform economic evaluations. This chapter describes the rationale and methods of a study that was carried out to compare the psychometric properties of two widely used health status measures (the EQ-5D-5L and SF-6D) for measuring health spillovers. This study was published in May 2017 (245):

Bhadhuri, A., Al-Janabi, H., Jowett, S. and Jolly, K. (2017). A comparison of the validity and responsiveness of the EQ-5D-5L and SF-6D for measuring health spillovers: a study of the family impact of meningitis, Medical Decision Making.

Chapter overview

Section 3.1 provides background about generic health status measures and theory of validity analysis. The existing evidence in this area is also discussed with particular focus on the

evidence related to measuring health spillovers. Section 3.2 presents the methods for the study by describing the rationale for looking at the validity of these two measures, the dataset that was used, the overarching framework used for the analysis (caring 'about' and 'for' the patient), the process of identification of hypotheses for the validity testing, and the statistical tests that were performed. The results and discussion of the study are presented in the next chapter (Chapter 4).

3.1. Background

The inclusion of health spillovers in economic evaluation requires some data to be collected on health status changes of family networks in response to an intervention. The performance of various health status measures has been assessed for patient sub-groups, but we know little about the performance of these measures in family members.

3.1.1 Generic preference-based health status measures

As discussed in Chapter 2, cost-utility analysis is a common form of economic evaluation in health care which usually adopts quality-adjusted life years (QALYs) as the relevant outcome. QALYs are calculated by combining length of life with health-related quality of life. Various methods can be used to elicit an individual's health-related or disease-related quality of life. Disease-specific measures can be used to measure disease-related quality of life for patients with the disease (153). Alternatively, generic health status measures may be used to

measure the health-related quality of life of any individual. The advantage of generic health status measures over disease-specific measures is that they enable comparability across conditions and interventions. The EQ-5D (EuroQol), SF-6D (Short form 6 dimension) and HUI (health utility index) measures are the most widely used generic health status measures (246). The patient/family member self-completes the measure (i.e. questionnaire) to generate a profile. This profile is then scored on a 0-1 scale to enable the calculation of QALYs. The conversion of a profile to a health status score from 0 to 1 is often done by using a tariff which has been derived from an external valuation study.

The EQ-5D is a widely used generic health status measure and there are two versions of the measure: a 3 level (EQ-5D-3L) and a newer 5 level (EQ-5D-5L) version which became available in 2011. The EQ-5D-5L is considered an improvement on the EQ-5D-3L due to its better psychometric performance (247). The EQ-5D consists of 5 items relating individual's mobility, pain and discomfort, anxiety and depression, ability to perform usual activities, and ability to wash and dress oneself (248). Each of the dimensions of the EQ-5D-5L consists of five levels of severity: no problems, slight problems, moderate problems, severe problems and extreme problems. Prior to the publication of a UK tariff, the crosswalk algorithm was often used as a method for mapping EQ-5D-5L responses to the EQ-5D-3L tariff in order to calculate EQ-5D index scores for a British sample (160). The range of scores elicited using the EQ-5D-5L measure using the crosswalk algorithm range from -0.281 (worst health) to 0 (death state) to 1 (full health) (249). A UK tariff of the EQ-5D-5L measure was published in January 2016 (250). The tariff is now the standard algorithm for computing EQ-5D-5L index scores for UK based research.

The SF-6D instrument is an alternative generic measure of health status which is composed of 8 domains of health relating to perceived general health, mobility, social functioning, bodily pain, vitality and mental health, and impact of (i) physical health and (ii) emotional health on ability to carry out daily activities (251). There are long-form and short-form versions of the SF-6D; the long-form version came first and consists of 36 items (SF-36), and the subsequent short-form version consists of 12 items (SF-12 version 2) (159). Each item of the SF-12v2 includes a progressive scale of either 3 or 5 levels ranging from no/minimal problems to severe problems for a particular aspect of health (159). Data collected from the SF-12 questionnaire can be converted into a SF-6D utility score to calculate Quality Adjusted life Years (QALYs) (159). There are various different country-specific value sets available (including a UK tariff) which may be used to calculate SF-6D utility scores from SF-12 responses (159). SF-6D utility scores range from 0.29 to 1 (full health) (252).

The HUI (Health Utility Index) is a further available generic health status measure(253). The HUI measure conceptualises health as a sensory experience. There are different forms of the HUI instrument and include the HUI:2 instrument and the HUI:3 instrument. The HUI:3 was developed to correct the perceived flaws of the HUI:2 instrument, and comprises of eight domains which relate to dexterity, vision, hearing, speech, ambulation, emotion, cognition, and pain(253). Other health status measures which are less commonly used for clinical or cost-effectiveness studies are the AQOL (Assessment of Quality of Life) and QWB (Quality of Well-being Scale) (253).

The EQ-5D is the most commonly used instrument to measure the health status of patients in cost-utility analysis in order to calculate QALYs, and is the recommended instrument for

National Institute of Health and Care Excellence (NICE) technology appraisals in the UK (158, 161). However the EQ-5D may not be an appropriate instrument for measuring health spillovers of interventions on family members. Previous studies suggest that it is predominantly the mental health of carers and family members that suffers when a loved one is ill, as discussed in Chapter 1 (5, 14). For example, Wittenberg et al's qualitative study in 2013 described a high prevalence of worry/fear among non-caregiving family members, and high prevalence of stress/anxiety and sadness/depression among carers (14) . Another study by Schulz et al (2008) observed that carer depression was associated with patient suffering, independent of care burden, which indicates that non-carers may also experience depression (48) . A study by Bobinac et al (2010) found that half of the negative impact of illness on carers' wellbeing was induced by 'caring about' the patient, and the other half was from 'caring for' the patient (37).

These findings suggest that only one item of the EQ-5D ('anxiety and depression') may be suitable to capture changes in family members' health status arising from the illness of a patient (5). Alternatively, the SF-12 version 2 measure offers a more detailed measure of the individual's emotional/mental health status and consists of specific items relating to the individual's calmness, energy levels, low feelings, and how the emotional and physical health impacts an individual's work life and social activities (159). The EQ-5D-5L and SF-6D are presented in Figures 3.1 and 3.2 respectively.

Figure 3.1: The EQ-5D-5L questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about	☐ 1
I have slight problems in walking about	☐ 2
I have moderate problems in walking about	☐ 3
I have severe problems in walking about	☐ 4
I am unable to walk about	☐ 5

SELF CARE

I have no problems in washing and dressing myself	☐ 1
I have slight problems in washing and dressing myself	☐ 2
I have moderate problems in washing and dressing myself	☐ 3
I have severe problems in washing and dressing myself	☐ 4
I am unable to wash and dress myself	☐ 5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

I have no problems doing my usual activities	☐ 1
I have slight problems doing my usual activities	☐ 2
I have moderate problems doing my usual activities	☐ 3
I have severe problems doing my usual activities	☐ 4
I am unable to do my usual activities	☐ 5

PAIN/DISCOMFORT

I have no pain or discomfort	☐ 1
I have slight pain or discomfort	☐ 2
I have moderate pain or discomfort	☐ 3
I have severe pain or discomfort	☐ 4
I have extreme pain or discomfort	☐ 5

ANXIETY/DEPRESSION

I have no anxiety or depression	☐ 1
I have slight anxiety or depression	☐ 2
I have moderate anxiety or depression	☐ 3
I have severe anxiety or depression	☐ 4
I have extreme anxiety or depression	☐ 5

Figure 3.2: The SF-12 version 2 questionnaire

In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	↓	↓	↓
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
Climbing several flights of stairs	☐1	☐2	☐3

During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	↓	↓	↓	↓	↓
Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5

During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
<u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

During the <u>past 4 weeks</u>, how much did your <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all ↓	A little bit ↓	Moderately ↓	Quite a bit ↓	Extremely ↓
☐1	☐2	☐3	☐4	☐5

These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> . . .

	All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
Have you felt downhearted and low?	☐1	☐2	☐3	☐4	☐5

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
☐1	☐2	☐3	☐4	☐5

There are also a variety of measures which may be used to capture different concepts of quality of life of family members. These include care-related quality of life measures such as the CarerQoL instrument and Carer Experience Scale (CES) (21), and broad measures of wellbeing such as the ICECAP-A capability measure (254). The ICECAP-A measure may be more suitable for capturing non-health spillover effects in family members such as career, lifestyle, happiness and relationship impacts (254). However, these types of measures are not included in current NICE guidelines for health technology appraisal (158).

3.1.2. Assessing the properties of health status measures

In order to compare health status measures in terms of their relative merits and drawbacks, assessments of the measures can be made in terms of their reliability, validity, feasibility and ceiling (or floor) effects (255).

Instrument validation involves assessing the ability of an instrument to measure what it is intended to measure. In the Trinitarian model of validity, there are three different types of validity that may be examined: content validity, criterion validity, and construct validity (255). These will now be described, along with responsiveness, reliability, feasibility and ceiling effects.

Different types of assessment of health status measures

Types of assessment	Sub-types
Reliability	Test-retest, alternate form, internal consistency, inter-rater
Validity	Criterion, content, face, construct, responsiveness
Other assessments	Feasibility, ceiling effects

Reliability

Reliability measures the consistency of an instrument by assessing the degree to which repeated elicitations from the instrument for measuring the same thing are correlated (255). There are four forms of reliability which are commonly tested for: test-retest reliability, alternate form reliability, internal consistency reliability and inter-rater reliability (256). Test-retest reliability involves computing correlation coefficients between an initial measurement and one or more repetitions of the measurement (257). The test-retest reliability of health status measures has been evaluated in the previous literature. In these studies, the EQ-5D and SF-6D were administered to respondents on more than one occasion several weeks apart, under the assumption that the participants' health was unlikely to change over this period (258, 259).

Alternate form reliability involves assessing how well different presentations of the same measure correlate (256). This could for example involve assessing correlations between different presentations of the levels of a health status measure, e.g. an initial response where items are presented from most severe problems to least severe, compared with 2

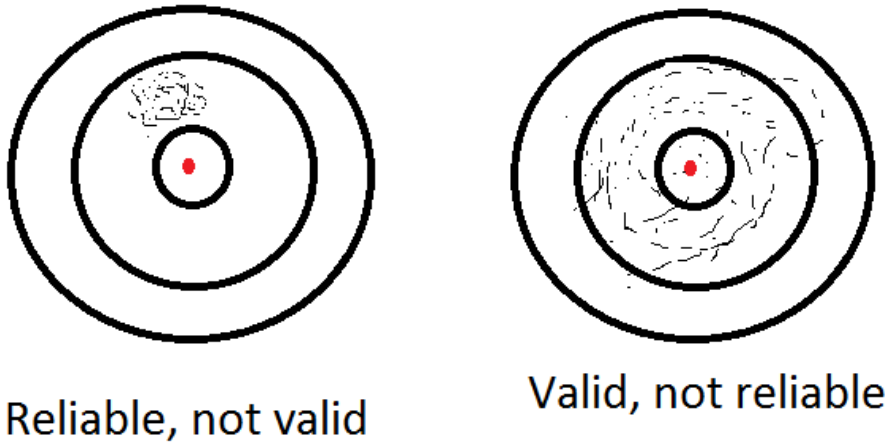
week follow-up response where the items are instead presented from least severe to most severe problems (256).

Internal consistency reliability involves assessing how strongly correlated similarly themed items of a measure are(260). This could for instance, involve assessing the correlation between items of the SF-12 which relate to feeling down-hearted, calm and energetic as aspects of a person's emotional health(256). Correlation coefficients which exceed 0.9 may however indicate that items are measuring exactly the same thing rather than different aspects of something(255).

Inter-rater reliability assesses the degree to which multiple ratings of a measure correlate (256). For example, in order to assess the inter-rater reliability of proxy reports of the EQ-5D-5L across a range of conditions, one could assess the degree to which 2 or 3 respondents presented with a description of various patient illnesses, produce similar EQ-5D-5L proxy assessments of those illnesses.

Reliability analysis determines how consistent a measure is, but does not provide information about the relevance of the instrument for measuring what it is supposed to, which is what validity and responsiveness analysis aims to determine (Figure 3.3).

Figure 3.3: The 'target metaphor' which shows how a measure may or may not exhibit reliability and validity, adapted from Trochim et al (2015) (261)



Content validity

Content validity uses a qualitative process for determining whether an instrument comprises of items (or domains) which are relevant for measuring a particular concept. For measuring spillover effects using a health status measure, content validity may be assessed by asking 'experts' (e.g. family members of chronically ill patients) the extent to which each item of an instrument is pertinent to the way their physical and mental health has been affected by the patient's illness(256). Family members may also be asked whether there are other important areas in which their health has been impacted by the patient's illness, but not described within the domains of the instrument. Face validation is a type of content validity assessment which simply involves an individual making a subjective assessment of whether an instrument comprises of relevant domains for measuring a particular concept (255, 256). For instance, on 'face value' it may seem that the SF-6D comprises of more relevant items

than the EQ-5D for capturing health spillovers, although we can't be too sure that this is true, hence why a more rigorous qualitative approach for assessing content validity will often be favoured by academic researchers.

Criterion validity

Criterion validation assesses the degree to which a proposed instrument is associated with an existing measure (255). There are two types of criterion validity: concurrent validity and predictive validity (255). Concurrent validation involves assessing the correlation between the proposed measure and an existing measure which is considered the 'gold-standard' for measuring a concept, when the measures are administered simultaneously to a sample of respondents (256). The gold-standard measure will exhibit a very high degree of accuracy; for example, this measure could be an invasive or laboratory-based diagnostic test. However, a proposed measure may subsequently be favoured over the gold standard measure if the measures are reasonably well correlated and the proposed measure is a less cumbersome, expensive or invasive alternative to the gold-standard measure (for example a questionnaire may be criterion validated against a more invasive diagnostic test or a longer questionnaire) (256). Alternatively, predictive validity involves the assessment of the correlation between a proposed measure and a future measure of the same outcome. An example of predictive validity assessment is the use of a survey instrument for measuring voters' preference prior to an election, and then seeing whether the instrument is well correlated with the actual realised voting behaviours (256).

Construct validity

Guion (1977) notes that "all validity is at its base some form of construct validity" (p.410) (262). Construct validation in health is "a series of procedures for assessing the extent to which an instrument correlates with other hypothesised measures or indicators of the health concept or concept of interest" (p.43) (263). Construct validity is mostly relevant for testing instruments which measure non-tangible concepts (like quality of life) rather than readily observable concepts (255). Analysis of construct validity is usually only undertaken using cross-sectional data (255).

The process of construct validation involves exploration at one point in time whether the variability in the values elicited from an instrument is compatible with existing knowledge about how the instrument should or is likely to vary according to some other observable variables (255). Variability in the measurement scale is tested against other variables from the same sample of respondents. Health status measures that are compatible with existing hypotheses about how health is expected to vary according to predicting factors (e.g. age, presence of disease), may be seen to exhibit a high level of validity for measuring health, and vice versa. Similarly, care-related quality of life measures exhibit construct validity if they demonstrate the ability to detect associations with variables relating to caregiving which are predicted to generate quality of life differences (e.g. informal care hours, providing activities of daily living care) (97).

An evidence-based approach for construct validation needs to be taken by using empirical studies to identify the range of variables which are expected to have an association with the concept we are interested in measuring (264). Statistical tests are subsequently carried out

to evaluate whether most (or all) of the theories regarding how a concept is expected to vary according to observed variables A…J, emerge to be correct. Usually, only univariable statistical tests are performed in assessing the relationship between a measure and a factor for a construct validity analysis, although other research has performed multivariate OLS regressions to compute R squared values of the models in order to determine the strengths of associations (265).

Assessing instrument validity requires the process of consolidating evidence from multiple studies and hypotheses tests performed over several years (256). During this process, researchers can further their understanding not only about the validity of the measure, but also about how robust the theories are regarding the relationships between outcome B (which could be a health status score), and various factors $A_{1.}$ to $A_{n,}$ that predict outcome B (260).

The magnitude of associations, assessed through standardised effect sizes, may be used as a guide for assessing the construct validity of a measure (266). However, a statistically significant weak effect size with a factor may not necessarily correspond to a low level of measure validity, particularly if the measure is not expected to detect large effects from change in a factor (267).

Responsiveness

Responsiveness is the ability of an instrument to respond to a meaningful or clinically important external change over time (255). A clinically important change here may be characterised as one which exceeds the threshold of a minimal important change (268).

Responsiveness may be distinguished from the concept of sensitivity-to-change, which instead refers to an instrument's ability to respond to external change, regardless of whether the external change is meaningful or not (269). Within the context of health intervention trials, health economists are particularly interested in the responsiveness of a measure, as the aim is to assess the change in a measured outcome over time as a response to a drug or treatment. Also it is not enough to just assess construct validity given that instruments which exhibit construct validity may not necessarily be responsive (270). This is because changes in an outcome over a limited time period may be small, and one may wish to assess the ability of an instrument to detect small changes.

An anchor-based analysis may be performed to assess responsiveness. The objective of an anchor-based analysis is to examine whether scores on the measure of interest change in the expected direction when compared with changes in the scores of a related construct or measure (the 'anchor' measure) (271, 272). Here, the anchor measure is usually grouped into an ordinal scale to reflect whether the anchor measure has meaningfully increased, not meaningfully changed, or meaningfully decreased. Where relevant anchors are not available, a distribution-based analysis may instead be used to assess the magnitude of change over time in participants' outcomes (272, 273). Responsiveness, conceptually and methodologically, is similar to construct validity, and is sometimes described as 'longitudinal validity' (255).

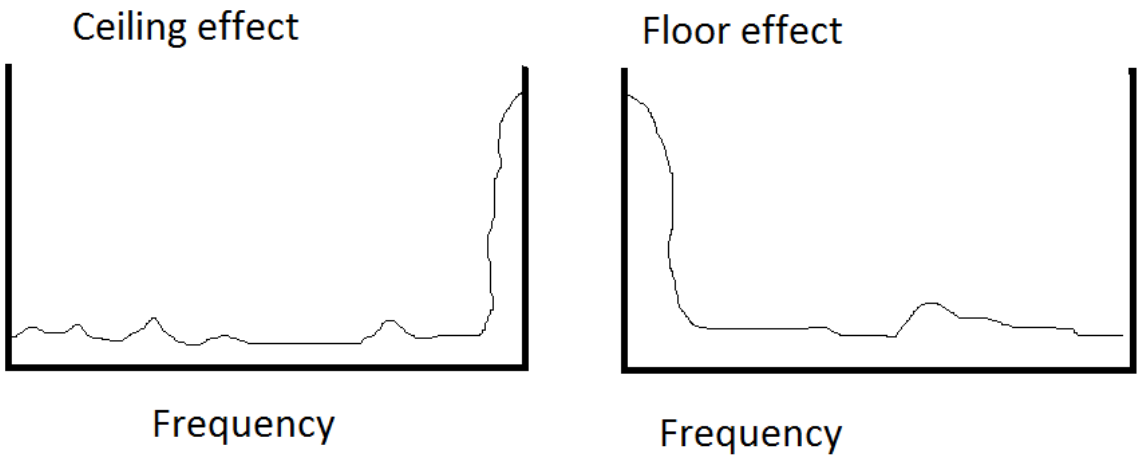
It is important to be aware that there is school of thought that psychometric testing is not useful for health status measures, and it is more important to determine whether these measures accurately reflect individual preferences (274). However, psychometric testing has

been performed to an extensive degree for health status measures, on the back of recommendations by leading scholars (263).

Ceiling and floor effects

Generic health measures are prone to ceiling or floor effects (275). A ceiling effect is where a large proportion of respondents report 'full' or 'perfect' health; a floor effect demonstrates the reverse(275) (Figure 3.4). The existence of a ceiling effect may provide evidence which undermines the validity and responsiveness of an instrument. For example, a large ceiling effect among a sample of individuals may indicate that an instrument is not able to detect health differences for a large segment of the sample (within those who score full health).

Figure 3.4: Graphical demonstration of a ceiling and a floor effect, adapted from Gibbons (2013) (276)



Feasibility

A good measure is not only valid and responsive, but also feasible. The feasibility of a measure can be assessed in part by its completion rate, as a simplistic yet informative way of assessing the quality of an instrument (252). Brazier et al specify that a completion rate of 95% is high for generic health status measures (252). A low completion rate for a measure may reflect the fact the measure is too difficult or takes too much time for a respondent to complete so that it is not fully completed. Qualitative work may be conducted to elicit information on whether respondents were able to easily understand and provide answers to questions and not find the questions too cognitively challenging, for example through the use of the 'think-aloud' technique (277). For example the SF-36 (36 items) may in certain settings be too long or onerous for a participant so that the SF-12 (12 items) is favoured for generating SF-6D utility scores (251). A low completion rate for an instrument may adversely impact analysis by substantially reducing the sample size used for a complete-case analysis in a clinical or cost-effectiveness study.

3.1.3. Existing evidence on the validity of health status measures

The EQ-5D and the SF-6D have been used in a range of studies to measure family member and carer health in different clinical contexts. These studies are mostly cross-sectional in design (5, 13, 278, 279), although there are some pre and post studies and RCTs which have used these measures (12, 231). The systematic review which was carried out for Chapter 2 found that many of the evaluations used the EQ-5D as a measure of health spillovers. However further exploration is required in regards to whether the EQ-5D is an appropriate

measure of health spillovers, or if an alternative health status measure such as the SF-6D may be more suitable.

There is substantial validity literature comparing the EQ-5D (3 level and 5 level versions) with the SF-6D among patient populations, with variable findings reported regarding the validity of the instruments depending on the patient population being assessed (252, 280-282). For instance, existing literature has found that both measures have demonstrated validity for measuring levels of depression severity (252), but less validity for capturing levels of impairment associated with multiple sclerosis (281). However in a literature search only three studies were identified which have assessed the validity of a generic health status measure for measuring health spillovers (243, 244, 279). Two of these studies assessed the convergent validity and known-groups validity of the EQ-5D-3L and SF-6D for measuring health spillovers in carers of children with autism (243) and craniofacial malformations(279). Convergent validity assesses how closely one instrument is related to other instruments that measure the same construct(255). These studies found promising evidence to support the validity of the EQ-5D-5L and SF-6D (and also the HUI:3 instrument) for measuring health spillovers. Another important finding in one of these studies was a smaller Spearman's rho correlation between the carer EQ-5D-3L and the carer SF-6D mental component score (0.39) than the physical component score (0.51) (243). This may have provided an indication that the SF-6D may be more effective in capturing aspects of family members' mental health status that the EQ-5D is not able to. This also tallies with a study which concluded that the EQ-5D-5L may be limited in terms of validity and responsiveness for capturing the mental health effects of providing care for someone with dementia, as the carer EQ-5D-5L was only able to capture weak associations (244).

Only one previous study has investigated instrument responsiveness for family health spillovers, and the study found that the carer EQ-5D-5L was responsive to the Zarit Burden Scale which measures informal care burden, but not responsive to time spent providing care for instrumental activities of daily living over an 18 month period (244).

3.2. Methods

3.2.1. Research aims and justification

Streiner and Norman assert that the (psychometric) properties of a measure need to be reassessed every time the measure is administered in a new context or for a new group of people (255), in this case for measuring health spillover effects in family members. Also, given that the EQ-5D-5L and SF-6D instruments cannot be used interchangeably in many settings to measure an individual's health status (283), particularly as the EQ-5D-5L encompasses a larger range of utility values than the SF-6D, a comparison of the two instruments may be useful.

The purpose of this research is to compare the construct validity, responsiveness, distributional characteristics and feasibility of the EQ-5D-5L and the SF-6D for capturing the health effects of patient illness on carers and 'non-caring' family members. Here, the aim is to understand how well these measures capture the spillover impact on carer and non-carer health, rather than the direct impacts of interventions on the health of the patient. Therefore, a distinct conceptual framework is needed for looking at the validity of health status measures in family members.

This study offers an assessment of the properties of the EQ-5D-5L and the SF-6D by using a previously collected survey dataset of family members of meningitis survivors that covered different aspects of the family member experience of living with and caring for the patient. This enabled a systematic comparison between the EQ-5D-5L and SF-6D in their ability to detect quality of life effects of the experience of living with and caring for an individual with

long-term impairments. The feasibility and the distributional characteristics of the two measures were also assessed. Meningitis and the family impact of meningitis study will be discussed in sections 3.2.2 and 3.2.3 respectively.

This study used an existing dataset for a quantitative analysis of the construct validity and responsiveness of the EQ-5D-5L and SF-6D. The previous literature has only briefly investigated the construct validity of the measures, usually by simply analysing cross-sectional associations between family health status measures and other measures of family member health or wellbeing or patient health status measures. There are no existing studies which have assessed how the health status of specific populations of *non-carers* are affected by changes in the related patients' health status. No previous study has examined whether family health status measures are responsive to patient health status measures. This new study addresses these gaps.

Meningitis illness will now be described. Then the dataset used for analysis and the general approach that was used for analysis will be described and justified, before moving on to describe the specific methods used for analysing construct validity, responsiveness, ceiling effects and feasibility.

3.2.2. Meningitis

Meningitis is inflammation of the covering (or meninges) of the brain and spinal cord. On average there are 3200 cases of meningitis and septicaemia in the UK per year (284). The most common type of meningitis in the UK is meningitis B, caused by the meningococcal B bacterial strain(284).

On average, between 2000 and 2011, there were 1761 cases of meningitis B in the UK per year although the number of cases is declining (284). These cases occur predominantly among babies and young children. Around 50% of cases result in no after-effects, 30% result in minor after-effects, 10% result in major after-effects, and 10% result in death (284). Minor after-effects include psychological disorders and reduced IQ. Major after-effects include amputations, brain damage and vision/hearing loss. These often life-long sequelae in meningitis patients also have a potential impact on family members' health, and especially on parents who are usually the main informal care providers for meningitis patients. Previous studies have found that child meningitis resulted in anxiety and depression in parents up to 2 years after onset of illness (285), and the behavioural sequelae of meningitis imposes a greater health spillover on family members than the physical sequelae (13, 78). A vaccine has recently been developed for meningitis (Bexsero), thus raising the question of Bexsero cost-effectiveness which requires evidence on QALYs. Hence, the study in section 3.2.3 was conducted.

3.2.3. Long term family impact of meningitis: case study dataset

The PhD study reported here is based on a previous longitudinal study which was carried out with postal surveys administered 12 months apart (in 2012 and 2013) to the family members of meningitis survivors for self-completion (13). This study ran a cross-sectional regression model to quantify the spillover effect of patient meningitis on family members' EQ-5D-5L scores. The study also administered a SF-6D questionnaire to family members, and collected contextual information about family members' care provision, their experience of living with

illness, and their proxy assessments of the patient's health status, which provided the data to enable the present validity study (appendix 3.4).

In the family impact of meningitis study, 3417 potentially eligible family members of meningitis survivors were contacted to participate using a database held by the Meningitis Research Foundation (a large UK charity). This resulted in 1587 eligible family members of 1218 survivors (36% of family units) returning the baseline survey in 2012. 1022 (64%) of family members responded to the follow-up questionnaire in 2013. The sampling frame does disproportionately focus on families of people at the more severe end of the illness spectrum. However, this meant that there were a higher number of cases of informal care which increased the power to examine instrument validity in caregiving family members. A specific power calculation was not used for the validity study as the sample size was determined by the requirements of the original family impact study (13). However, the sample size is consistent with other studies measuring validity (247, 252). The sample mostly comprised of family members who were the parents of people who acquired meningitis a long time ago (an average of 12 years prior to being surveyed), and in some cases decades ago. The accumulation of psychological distress and caregiving stress over many years may generate substantial health spillover effects in family members. However, some family members have reported that spillovers attenuated over time as care provision became more efficient and built into the carer's daily routine (17), and also from family members experiencing closer relationships with the patient from them spending more time together and from feelings of compassion being generated (14). 60% of family members were living with the meningitis survivor and 40% were not. Each potential eligible family

member was sent two questionnaires; they were asked to complete the first and to pass on the second questionnaire to an additional person close to the survivor.

This dataset generated from the survey allows us to not only look at family members that provide care, but also family members who describe themselves as non-carers. Non-carers can be defined as family members who do not provide informal care for the patient, but may nevertheless experience health spillover resulting from anxiety and distress from witnessing the illness of a loved one. In the analysis, 'carers' were distinguished from 'non-carers' if they were reported as spending <u>any</u> amount of time 'providing care as the result of meningitis' in the baseline survey. As the survey asked about informal care due to meningitis after-effects, there was a possibility some family members which were classified as non-carers were caring for other individuals or for meningitis patients experiencing other non-meningitis related conditions.

Weekly hours of care provided for the patients was elicited by summing the items from the following question:

"In a typical week, please state roughly how many hours, on average, you spend on the activities below as a result of their meningitis or septicaemia and any after effects.

Assisting the person with daily living ..... _____hours/week

Organisational support for the person affected..... _____hours/week

Extra household activity..... _____hours/week

Other care activity (please state what the activities are below)..... _____hours/week."

A measure of care-related quality of life was also obtained for carers using the Carer Experience Scale (286). The Carer Experience Scale comprises of domains relating to

activities, support, fulfilment, control, and quality of the carer's relationship with the patient (286). Information on the impact of meningitis on aspects of family members' lives was also assessed via a bespoke question enquiring whether "meningitis had no effect, a negative effect or a positive effect" on the family member's life. Domains of life (finances, social life, family life, work, exercise and personal health) were selected based on a focus group discussion with members of the Meningitis Research Foundation (13). Additionally, family members were also asked to complete a section on the patient's health. This involved family members providing a proxy report of the patient's EQ-5D-5L profile (to enable a patient EQ-5D-5L score to be calculated).

3.2.4. Framework and approach for analysis

In order to assess construct validity, we need to know the traits which are associated with health spillovers. This analysis uses Bobinac's conceptual model discussed at length in Chapter 1 (2011). In Bobinac's model, health spillovers of illness on family members were described as the product of two different effects (6). The first effect is the psychological distress from 'caring about' a loved one with an illness. The second effect is the physical and mental strain of providing informal care for a patient (or 'caring for' a patient). This model was developed through an empirical analysis of 751 carers which found that 'caring about' and 'caring for' the patient were separately and independently associated with carers' health (6). The variables used in my analysis were identified as generating health spillovers through one or both of the caring mechanisms set out in Bobinac's model. A model was

developed in Chapter 1 of how health spillover effects occur, predominantly through the mechanisms of caring about and for a patient.

The tests of construct validity and responsiveness carried out in this study are split between the two different mechanisms by which health spillovers are generated; firstly testing associations between participants' health status responses and a range of characteristics that reflect the severity of the patient's condition (and therefore the likely strength of the 'caring about' spillover), and secondly testing associations between participants' (family members') health status responses and characteristics reflecting the burden of caring for the patient.

It was anticipated that the SF-6D would be more valid and responsive than the EQ-5D-5L in detecting health spillovers in family members, by detecting a greater number of statistically significant associations, as well as larger effect sizes and stronger correlation coefficients for the hypothesised associations. This is because the SF-6D contains more items than the EQ-5D-5L related to mental health and social functioning, and these items are expected to be particularly sensitive in detecting health spillovers in family members generated from the psychological and informal care burden of meningitis. The analysis was focused on the validity and performance of the family members' EQ-5D-5L and SF-6D index scores rather than the validity of the response categories of the two measures.

The sample used for the analysis was constrained in two ways. First, the analysis focused on a single close family member for each patient, selected on the basis of the highest degree of social contact; this person could be a carer or non-carer (13). This was done in order to eliminate correlation effects between multiple family members of the same patient. Second, families where the patient had made a complete recovery from meningitis were excluded. This was done to ensure that we only included family members where there was some

degree of potential spillover from the meningitis sequelae or caring role. The sequelae most commonly reported were behavioural or emotional problems (28%), mild or moderate learning difficulties (16%), and scarring or tissue damage (14%) (13).

3.2.5. Construct validity assessment

Assessment of construct validity firstly compared the EQ-5D-5L and the SF-6D for measuring health spillovers generated from 'caring about' the patient, and secondly for spillovers from 'caring for' the patient.

Table 3.1 provides a description of the studies which were reviewed to inform hypothesis generation. The second column of the table describes the factors identified from the studies which were related to the patient's condition and caring situation that have a bearing on the family member's health. The third column of the table marks out the survey variables which were linked to the findings from the study, in order to generate a set of hypotheses that could then be tested with the family member dataset. The studies in general show that negative health spillover on a family member is likely to be produced when the patient's health is worse, when the volume of care provided by the family member is higher, if the family member lives with the patient and is witness to their suffering, and if non-carers and carers feel confined to the house in order to stay with and provide care for the patient, and are consequently inhibited from participation in social and exercise activities.

Table 3.1. Studies which were used to develop hypotheses for the validity analysis

Study	Findings	Survey variables identified to generate family health spillover on the basis of the study findings (direction of effect)
An et al (2011) Health-related quality of life, activities of daily living and parenting stress in children with brain tumors	Carer stress associated with having children with acting-out behaviours and emotional problems.	Caregiving and psychological burden of illness (negative), impact on family and relationships (positive)
Arafa et al (2008) Quality of life among parents of children with heart disease	Longer caregiving hours was associated with worse carer health	Caregiving hours (negative)
Bobinac et al (2010) Caring for and caring about: Disentangling the caregiver effect and the family effect	Carers' happiness was negatively impacted by patient illness: half of this impact was attributed to 'caring about' the patient and half attributed to 'caring for' the patient.	Caregiving burden (negative), psychological burden of illness (negative)
Bobinac et al (2011) Health Effects in Significant Others: Separating Family and Care-Giving Effects	Carers' health was negatively impacted by two effects (at statistically significant levels): from 'caring about' the patient and 'caring for' the patient.	Caregiving burden (negative), psychological burden of illness (negative)
Burton (1997) Preventive health behaviours among spousal caregivers	Being a carer was associated with reduced rest and reduced exercise activities.	Exercise participation (positive), caregiving hours (negative)
Buysse et al (2008) Surviving meningococcal septic shock: health consequences and quality of life in children and their parents up to 2 years after pediatric intensive care unit discharge	Meningitis and sepsis caused symptoms of anxiety and depression in parents	Presence of meningitis sequelae (negative)
Dearden and Becker (2004) Young carers in the UK	Providing intimate care is the type of care work most disliked by young carers	Personal care (negative)
Goldbeck (2006) The impact of newly diagnosed chronic pediatric conditions on parental quality of life	Parents' quality of life decreased as the child's condition progressed/worsened.	Patient health status (positive)
Govina (2013) Effects of patient and personal demographic,	Factors that were associated with higher carer burden were: living with the	Financial situation (positive), sharing

clinical and psychosocial characteristics on the burden of family members caring for patients with advanced cancer in Greece	patient, being unemployed and the cancer patient experiencing depression. Factors that were not significantly associated with carer burden were: having another dependent child at home, and type of relationship with patient (spousal/child/other).	house with patient (negative), psychological burden of illness on family member (negative)
Kespichayawattana (2003) Effects of coresidence and caregiving on health of Thai Patients of Adult Children with AIDS	Living with the patient meant that parents were more likely to provide 'stressful' care such as lifting, bathing, cleaning wounds and applying for welfare benefits. Being the main carer was associated with greater frequency of the carer reporting anxiety, insomnia, and fatigue.	Living with patient, main carer (negative), providing personal care (negative)
Klassen et al (2008) Impact of caring for a child with cancer on parents' health-related quality of life	Carer health was positively associated with better diet, exercise, sleep, younger age, higher income, length of time since diagnosis of patient illness, and patient health	Participation in exercise (positive), caring hours (negative), patient health (positive), financial situation (positive)
Konstantareas and Papageorgiou (2006) Effects of temperament, symptom severity and level of functioning on maternal stress in Greek children and youth with ASD.	Mothers' stress was positively associated with higher levels of caregiving tasks, and worse child autism symptoms.	Caring burden (negative), patient health status (positive)
Lawoko and Soares (2003) Quality of life among parents of children with congenital heart disease, parents of children with other diseases and parents of healthy children	Carer quality of life was negatively associated with patient's disease severity and a worse financial situation	Patient health status (positive), financial situation (positive)
Lin et al (2009) Quality of life in caregivers of children and adolescents with intellectual disabilities: use of WHOQOL-BREF survey	Carer wellbeing was negatively associated with the carer experiencing financial stressors	Financial stressors (negative)
Poley (2011) Assessing health-related quality-of-life changes in informal caregivers: an evaluation in parents of children with major congenital anomalies	Carers were more likely to experience depression if the child's health condition is life-limiting	Patient health status (positive)
Raina (2005) The Health and Well-Being of Caregivers of Children With Cerebral Palsy	Carers' mental health was positively associated with income and better family functioning.	Financial income (positive), positive impact on family and relationships

		[positive)
Schulz et al (2008) Dementia patient suffering and caregiver depression	Patient suffering induces carer depression, independent of care burden	Psychological burden of illness (negative)
Spore (2004) Quality of life of caregivers of children with chronic conditions	Having familial and community support systems were an important coping system for carers. Some carers reported having less free time for themselves, resulting in them being unable to devote consistent time to exercise. The insurance premiums associated with caring were 'often a strain' and 'a financial stress'. Many of the carers reported feeling 'trapped in their own homes' as it was difficult to travel long distances and interact with others in social settings. Over time, carers reported that providing care became routine and thus manageable.	Financial strain (negative), exercise participation (positive), worse social life (negative), caring burden (negative)
Wittenberg (2013) How illness affects family members: a qualitative interview survey	The majority of carers interviewed reported experiencing sadness/depression, stress/anxiety, and financial impacts. Non-carers were impacted in terms of relationships, confinement to house and a heightened attention to self-care.	Financial impact (negative), loss of relationships (negative), exercise participation (positive), loss of social life (negative)
Yamada (2011) Health-related quality of life in parents of children with intermittent exotropia	Longer caregiving hours associated with worse carer health	Caregiving hours (negative)

From the literature review summarized in Table 3.1 which was linked to relevant survey variables from the family impact of meningitis dataset, a set of hypotheses for variables and their predicted relationship with family health spillovers from meningitis were developed for testing in the validity analysis (Table 3.2). For non-carers and carers, hypotheses were developed predicting that better family member health status would be associated with better patient health and less negative experiences of meningitis illness, as observed in previous empirical studies of 'caring about' effects (Table 3.2). Several studies have found

that ‘caring about’ a chronically ill patient negatively impacts the health of family members by causing anxiety and distress (6, 14, 17, 37, 48). In a qualitative interview study of family members of chronically ill patients, Wittenberg et al (2013) observed that both non-carers and carers reported negative impacts to their relationships, social activities and reported feeling confined to the house, which may in turn negatively affect their emotional health, and participation in exercise and other self-care activities (14).

Many of the studies in Table 3.1 identified that the ‘caring about’ the patient was an important determinant of health status among family members. Both caregiving and non-caregiving family members may experience psychological distress from ‘caring about’ the patient.

For carers only, hypotheses were tested predicting that the family member EQ-5D-5L and SF-6D were negatively associated with larger volumes of care provision, greater work and finance related pressures from caregiving and worse carer experiences, as observed in previous studies of ‘caring for’ effects (Table 3.2) (17, 31, 66, 67, 76, 285, 287-295). The amount and intensity of informal care provision was captured through a range of variables including hours of care provided, the need to provide personal care and the need to provide constant supervision for the patient. The variables relating to work and financial pressures were included as they are noted to be among the most salient non-health spillovers experienced by parental carers(17, 296), and these pressures themselves create mental stress or ‘financial stress’ on carers (17), and are associated with a reduced carer health status(17, 67, 288).

In the analysis of construct validity, the EQ-5D-5L and SF-6D were compared using the effect sizes and the statistical significance of the associations tested for (further details are provided in the 'Statistical analysis' section 3.2.7).

Table 3.2: Hypotheses for associations between constructs and family members' health status used in the validity analysis

Survey variable	Predicted effect	Evidence base
'Caring about' variables		
Patient EQ-5D-5L index score Patient Visual Analogue Scale (VAS) score	Positive	Better patient health expected to be associated with lower psychological and care burden in family members thus better health status(6, 37, 48)
Patient EQ-5D-5L item responses	Negative	Higher item response indicates worse patient health which is expected to be associated with worse family member health status (6, 37)
Family members' self-perceived impact of meningitis on areas of life*	Negative	Negative experiences of illness on non-carers and carers in these areas expected to translate to worse family member health status (6, 14, 17, 37)
'Caring for' variables		
Hours of care provided Shares house with patient Daily care for the patient Constant daytime supervision for patient Main carer for patient Provides majority of care	Negative	Greater volumes of informal care provision expected to result in worse carer health (17, 66, 67, 287-289)
Provides personal care/toileting for patient	Negative.	Providing ADLs (assistance with daily living) is associated with high informal care burden and increased chance of carer distress, resulting in impaired carer health. (31, 76, 295)
Carer Experience Scale	Positive.	Higher score indicates better carer experience which is expected to result in better carer health (67, 78, 290)
Family members' self-perceived impact of meningitis on a) work, b) finances.	Negative.	Informal carers frequently experience loss of household income and increased care costs, which can cause stress and impaired mental health. (17, 290, 293, 294)

* Areas of life measured were (1) family and relationships, (2) social life, (3) exercise, and (4) views on personal health

There was an initial list of potentially relevant variables for the validity analysis. Many of these variables were included in the analysis and are described in Table 3.2. The variables which were eventually excluded from analysis are described in Table 3.3, after a discussion within the supervision team over whether they should be included or not. The main reasons for exclusion were that it was ambiguous what the hypothesised direction of effect would be between the variable and the family health status measure (e.g. the variable which assessed how close the family member feels to the patient), the variables were likely to be associated with family member health but not through the causal mechanism of health spillover (e.g. carer age), or there were not enough responses for the variable (e.g. the variable about whether the survivor had contracted meningitis more than once).

Table 3.3. Variables excluded from analysis and reason for exclusion

Variable	Reason for exclusion
If the family member shares a house with the patient, how many people share the house in total?	Ambiguous effect on family member health. The more people that share the house, the more likely the family member provides care for other dependents. On the other hand, the family member may achieve a greater level of emotional and practical support by having other family members around.
Perceived impact of Meningitis on a range of factors; i) stress, ii) depression	This series of questions may have elicited unreliable responses in this study due to misunderstandings in the interpretation of a 'positive or negative effect' on stress and depression. This is because family members who were asked whether meningitis had a positive effect on their stress/depression, could have interpreted a 'positive effect' as either producing an increase or a decrease in their stress/depression symptoms.
How close does FM feel to the patient?	Ambiguous. Feeling close to the patient means that you feel more burdened by their health problems. Alternatively a patient with more severe behavioural problems may cause harm and increase distances in relationships.
How often does the family member see the patient/person affected (PA)?	Ambiguous. The more often the family member sees the patient, the more they witness the patient's suffering. However it also implies a closer relationship with the patient which may be a positive experience.
How long ago did person contract Meningitis?	Ambiguous. The stress of caring may accumulate over a longer period of time. On the other hand the initial emotional shock from the onset of disabling illness may subside in families over time.
Relationship with the patient	Ambiguous effects. Pinquart and Sorensen's meta-analysis in 2007 suggests spousal carers experience fewer adverse physical health impacts, but also experience higher levels of depression compared to non-spousal carers.
Carer gender/age/socioeconomic status	Associations between carer health and carer gender/age/socioeconomic status are not primarily driven by spillover (although demographic characteristics may moderate the experience of caregiving). Also the focus of the validity and responsiveness analysis in this study is on *meaningful* changes which can potentially be brought about by health interventions. Health interventions obviously do not alter carers' gender, age or socioeconomic status, adding additional justification for the exclusion of these variables from analysis.
If the patient has contracted Meningitis more than once?	Not enough data (only 9% of patients in the analysis sample had contracted meningitis more than once).
If more than one person in the family has contracted Meningitis or septicaemia?	Not enough data (only 12% of family members in the analysis sample were related to multiple individuals who had contracted meningitis)

3.2.6. Responsiveness analysis

In the responsiveness analysis, some of the variables that were also tested for in the construct validity analysis were used. Family member EQ-5D-5L and SF-6D were tested for in terms of a longitudinal response to these variables as opposed to a cross-sectional relationship. This was done in order to determine the ability of health status measures to respond to spillover effects generated over a shorter time period akin to the duration of a clinical trial. A much smaller number of variables (constructs) were used in the responsiveness analysis because many of the variables included from the baseline questionnaire were not measured in the follow-up questionnaire.

It was hypothesised that over the course of 12 months, the change in family members' EQ-5D-5L and SF-6D scores would be positively associated with changes in patient EQ-5D-5L scores, and negatively associated with changes in the number of hours family members spent providing informal care.

The responsiveness analysis of the EQ-5D-5L and SF-6D used the baseline data (from 2012) and follow-up data (from 2013) for family members of patients. The analysis was again split to cover the carers and the non-carers separately (as in the construct validity analysis), in order to investigate the performance of the measures in carers and non-carers. Anchor based methods were implemented to assess whether the EQ-5D-5L and SF-6D responded in expected directions to changes in the following anchors over the 12 month period(271):

- Patient EQ-5D-5L score

- Family members' reports on the patient's health change between 2012 and 2013 (improvement/no change/ worsening).
- Number of hours per week spent on caring activities related to meningitis (assistance with daily living/organisational support/extra household activity) (carers only). In calculating weekly hours of care provision, it was assumed that there was no joint production in the different caregiving activities (21) . Also, responses of more than 126 hours of informal care per week (i.e. > 18 hours a day) were truncated at 126 hours, as the carer was assumed to sleep for at least 6 hours a day (297).

Patient health status and informal care hours were selected as anchors based on their conceptual relationship with family members' health status. Two health status measures for patients were available from the dataset (the EQ-5D-5L and a global measure), and both were used for the responsiveness analysis. The anchors were sub-divided into 3 levels to indicate whether the 'anchor' had increased, decreased, or not changed in an important way over time(268). It was predicted that an important improvement in a measurement of patient health or reduction in caring hours would be associated with a statistically significant increase in family members' EQ-5D-5L and SF-6D score from baseline to follow-up assessment, and vice versa. In other words, it was predicted that a positive gradient moving from an improvement to a decline in family health status change would be observed as change in patient health status simultaneously moved from an improvement to a decline. Conversely, a negative gradient moving from a decline to an improvement in family health status change would be observed as change in caring hours simultaneously moved from an increase to a decrease.

An ‘important’ increase/decrease in the patient EQ-5D-5L score was determined by the measurement of a minimal clinically important difference (MCID) in scores between the two periods of at least 0.074, derived from a literature estimate of this difference (298). This estimate was obtained from an EQ-5D-3L study and used as a proxy for the EQ-5D-5L in this study as consistent with other studies(299, 300); as there are only limited empirical estimates of the EQ-5D-5L MCID available (301, 302). The 2013 global rating scale of patient health change explicitly asked family members whether the patient’s health improved, reduced or stayed the same over the preceding 12 months, so these same categories were used in the responsiveness analysis. This global rating question was included as an alternative measure of patient health change to the EQ-5D-5L. It must be acknowledged that there are concerns regarding the reliability of global rating of change measures and it is instead considered preferable to elicit measurements separately at baseline and follow-up and manually calculate change (as was done with the patient EQ-5D-5L) (298). In the absence of an agreed ‘important’ change in caring hours, it was assumed that a change of 5 or more hours / week was important. The grouping of anchors into clinically important change is done in order to assess the ability of the health status measures to respond to changes which actually occur and are clinically important (270). EQ-5D-5L and SF-6D mean changes between 2012 and 2013 were reported in both unstandardised (raw mean score change) and standardised formats (Cohen’s D) (255).

3.2.7. Data preparation and statistical analysis

Only individuals that had a complete set of item responses for a validity test were included in the analysis in order to perform a complete-case analysis. A complete-case analysis produces unbiased results when missing data is random. There was no cause to assume that missing data was non-random for this dataset (13). Participants (family members) were excluded from the study if the meningitis patient had subsequently died, as the health losses experienced by bereaved family members are different to those experienced by the family members of living patients (303), and not the focus of this study. Furthermore, only family members of patients who had not made a complete recovery from meningitis at the time of completing the baseline survey, and the closest surveyed family member to the patient were included in the analysis; the justification for which was provided in section 3.2.4. Participants were *not* excluded on the basis of whether they shared a household, or how they were related to the person with meningitis.

EQ-5D-5L index scores were calculated using the crosswalk algorithm from EuroQol. This algorithm converts EQ-5D-5L responses into EQ-5D index scores using the EQ-5D-3L UK tariff (160). SF-12v2 responses were converted to SF-6D index scores using the UK tariff obtained from the University of Sheffield (159).

Spearman's Rank Correlation coefficents were computed to assess the strength, statistical significance and directions of associations between individuals' health status measure scores, and ordinal independent variables of more than two groups including patient health status variables (EQ-5D-5L scores, EQ-VAS, EQ-5D-5L items (mobility, self-care, usual activity,

anxiety, pain)), hours of care provided and Carer Experience Scale (CES) scores. Spearman's rho is an appropriate test for measuring correlation between a measurement variable (family EQ-5D-5L or SF-6D score), and either another measurement variable such as the CES or ranked variable such as the individual items of the patient EQ-5D-5L (304). The Mann-Whitney test was used to establish any statistically significant differences in health status between two groups within the sample, and the direction of these differences (243). The Spearman's Rank Correlation test and Mann-Whitney test are non-parametric tests that only take into account the existence of a difference between two data points (i.e. how they rank) rather than the magnitude of the difference. This is an appropriate method for handling skewed variables (304). The sizeable presence of a ceiling effect of the family member EQ-5D-5L in this study provided justification for the non-parametric analysis of the two measures. However in the tests of responsiveness, t-tests were used (instead of non-parametric tests) because the changes in EQ-5D-5L and SF-6D scores between 2012 and 2013 were approximately normally distributed (as demonstrated in Chapter 4, section 4.1).

Assessments were also made about the magnitude of associations by calculating effect sizes (Cohen's D) where independent variables consisted of two groups only, and correlation coefficients (Spearman's) where independent variables were ordinal and consisted of more than two groups. Spearman's rank correlation coefficents of between 0.3 and 0.5 are considered small, between 0.5 and 0.7 moderate and > 0.7 large (305). For Cohen's D effect sizes of between 0.2 and 0.5 are considered small, between 0.5 and 0.8 moderate and > 0.8 large (306). Here, Cohen's D effect sizes provide information on the magnitude of the difference in health status scores between one group and another, e.g. between individuals who were the main carers and who were not the main carers of the meningitis survivor.

Spearman's rank correlation coefficients of < 0.3 and Cohen's D effect sizes of <0.2 which are statistically significant, may be considered as 'very small'. The same interpretations apply for negative associations and effect sizes.

The instruments were then compared to find out whether the EQ-5D-5L was associated with larger effect sizes and stronger associations than the SF-6D, or vice versa.

In order to assess ceiling effects, the proportion of family members who reported full health with the EQ-5D-5L and the SF-6D was calculated. In order to assess feasibility, the completion rates of the EQ-5D-5L and the SF-12 instruments and their individual items were calculated at baseline and follow-up.

Analysis was also conducted for the full sample of family members (the present analysis was limited to the closest family members of the patient), and results were broadly similar to the results for the sub-sample. Appendices 3.1 to 3.3 contain the analysis of the construct validity and responsiveness for the full sample of family members.

3.3. Summary

Chapter 3 described the background for assessing the validity of health status measures for capturing spillovers, in the context of the broader literature on the assessment of the psychometric properties of a measure. Subsequently, the methods used to assess validity in the study were described, in terms of a literature review being conducted to inform the generation of hypotheses which could then be statistically tested in the family member dataset. Chapter 4 presents the results and discussion of the study. The general objective of

this study is to explore the potential adoption of widely used measures of patient health in clinical trials for the measurement of family member health spillover effects. In this study, the objective is met through a comparison of the validity of the EQ-5D-5L and SF-6D for measuring health spillovers.

CHAPTER 4: A COMPARISON OF THE VALIDITY AND RESPONSIVENESS OF THE EQ-5D-5L AND SF-6D FOR MEASURING HEALTH SPILLOVERS: A STUDY OF THE FAMILY IMPACT OF MENINGITIS: RESULTS

Chapter 3 described the rationale and methods for the study which aims to understand how valid health status measures are in capturing health spillovers. Chapter 4 presents the results and discussion of the study. This study focuses mainly on the analysis of validity and responsiveness, but also briefly assesses the feasibility and ceiling effects of the two instruments when administered to family members. Section 4.1 presents a descriptive analysis of the survey responses, and assessment of the feasibility and the distributional characteristics of the family member health status measures. Sections 4.2 and 4.3 document the results on construct validity and responsiveness respectively.

4.1. Descriptive analysis

For the present study, 1053 family members (66% of the whole sample) reported being exposed to patient sequelae from meningitis at baseline. 847 of these family members were included in the construct validity analysis as they were the closest surveyed family member to the patient, and within this sub-sample 536 of these family members were included in the responsiveness analysis as they also responded to the follow-up questionnaire (Figure 4.1).

Figure 4.1: Flow chart of participant entry into the validity study

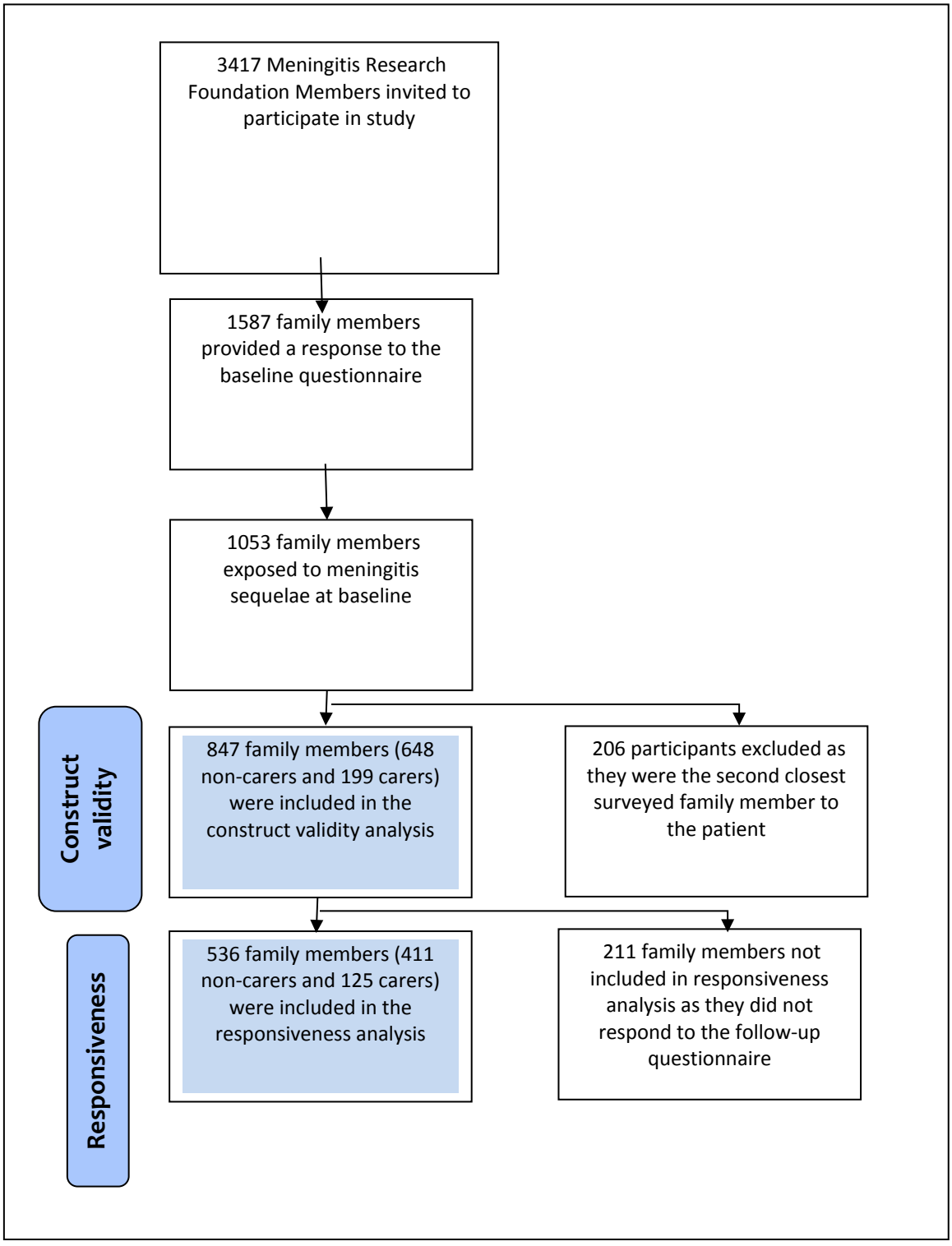


Table 4.1 documents the descriptive statistics in 2012 for the whole family member sample, and the carer and non-carer sub-samples used in the validity analyses. Family member SF-6D scores were much lower than the family member EQ-5D-5L scores at baseline and follow-up. The patients receiving informal care for meningitis sequelae were proxy reported as having a much worse mean EQ-5D-5L health status (0.50) than the patients who did not receive informal care for meningitis (0.87). 86% of patients receiving informal care were reported as having usual activities problems, 74% reported as having anxiety and depression problems and 65% reported as having pain problems.

Carers on average provided 28.8 hours of informal care at baseline, and 21.2 hours of informal care at follow-up. 79% of carers provided informal care daily. Higher proportions of carers reported negative impacts of meningitis on various aspects of their lives (work, finances, exercise, family life, social life) compared with non-carers.

Table 4.1: Descriptive statistics for full sample, non-carer sample and carer sample

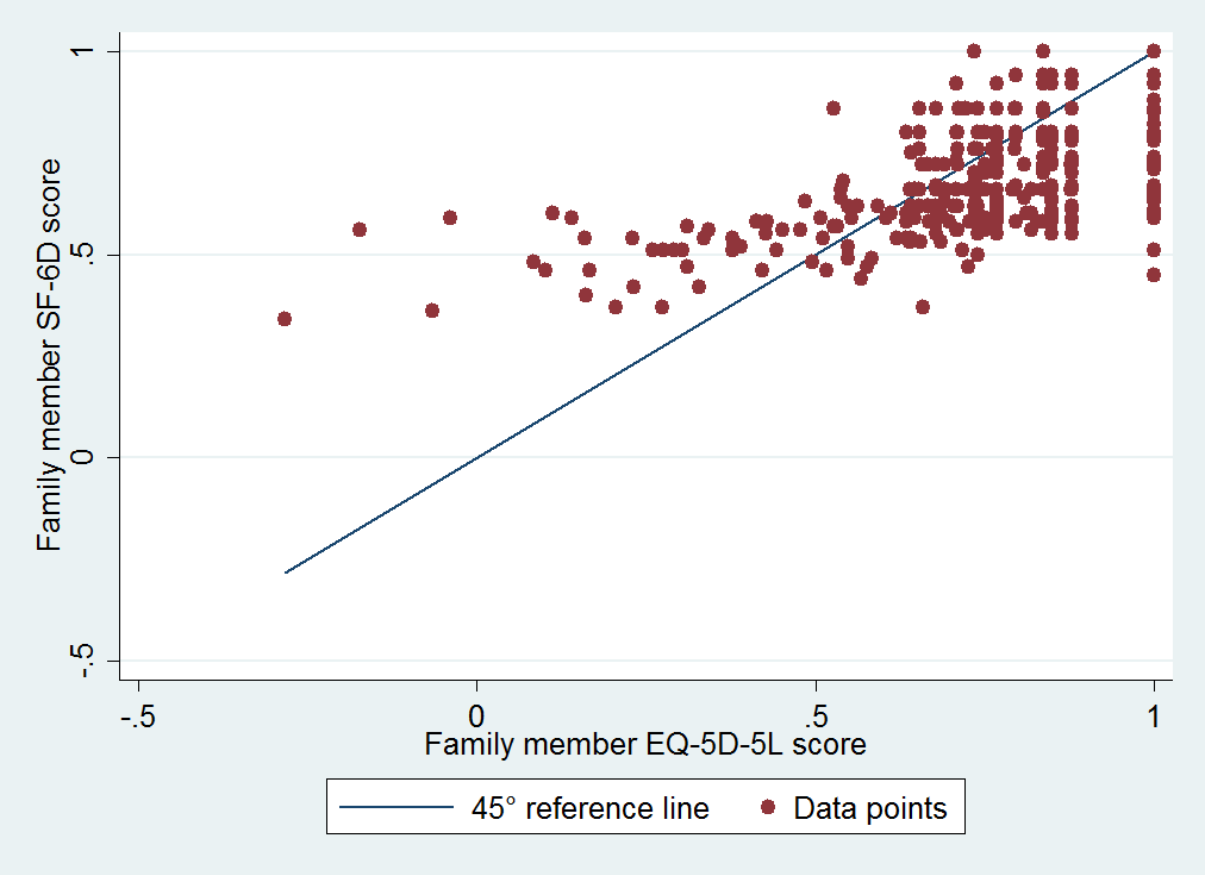
Characteristic	Full sample (n=1587)	Non-carer sample (n=648)	Carer sample (n=199)
Family member			
Female (n, %)	1152 (72)	556 (86)	166 (83.8)
Age (years, mean (SD))	51.1 (12.8)	51.2 (12.1)	45.9 (11.9)
EQ-5D-5L in 2012 (mean (SD))	0.88 (0.16)	0.87 (0.18)	0.83 (0.17)
EQ-5D-5L in 2013 (mean (SD))	0.86 (0.18)	0.85 (0.19)	0.80 (0.20)
SF-6D in 2012 (mean (SD))	0.79 (0.13)	0.78 (0.13)	0.71 (0.12)
SF-6D in 2013 (mean (SD))	0.77 (0.14)	0.77 (0.14)	0.68 (0.13)
Survivor (patient)			
Female (n, %)	732 (46)	292 (45.2)	100 (50.3)
Age (years, mean (SD))	23.3 (16.1)	24.1 (16.2)	24.1 (20.3)
Time since infection (years, mean (SD))	12.0 (7.3)	12.3 (7.3)	10.4 (8.7)
Health in 2012 (EQ-5D-5L, mean (SD))	0.84 (0.26)	0.87 (0.19)	0.50 (0.35)
Health in 2013 (EQ-5D-5L, mean (SD))	0.83 (0.25)	0.85 (0.20)	0.52 (0.36)
Mobility problems (n, %)	257 (16)	83 (13)	115 (59)
Self-care problems (n, %)	207 (13)	51 (8)	113 (58)
Usual activities problems (n, %)	396 (25)	133 (20)	169 (86)
Anxiety/depression problems (n, %)	519 (33)	240 (39)	139 (74)
Pain problems (n, %)	414 (27)	175 (28)	126 (65)
Informal care provision			
Provides care for patient (n, %)	n/a	n/a	199 (100)
Caring hours/week in 2012 (hours, mean (SD))	n/a	n/a	28.8 (31.7)
Caring hours/week in 2013 (hours, mean (SD))	n/a	n/a	21.2 (27.5)
Daily carer (n, %)	n/a	n/a	139 (79)
Main carer (n, %)	n/a	n/a	137 (79)
Provides majority of care (n, %)	n/a	n/a	103 (60)
Provides personal care (n, %)	n/a	n/a	102 (51)
Provides constant supervision (n, %)	n/a	n/a	94 (54)
Carer Experience Scale (mean (SD))	n/a	n/a	68.5 (16.5)
Family member spillovers and context			
Negative impact on family (n, %)	346 (23)	133 (22)	106 (56)
Negative impact on social life (n, %)	289 (20)	98 (17)	118 (61)
Negative impact on exercise (n, %)	161 (11)	52 (8)	70 (38)
Negative impact on work	284 (19)	105 (18)	110 (59)
Negative impact on finances	277 (19)	104 (18)	120 (64)
Positive impact on personal health view (n, %)	591 (38)	242 (38)	82 (42)
Relationship to patient (parent, n (%))	1193 (75)	510 (79)	147 (74)
Lives with patient (n, %)	964 (60)	390 (60.5)	166 (83)

Note: Total carer and non-carer sample statistics presented here are only for the family members used in the validity analysis (that is, family members exposed to meningitis sequelae and assessed as the closest family member to the patient)

Figures 4.2 and 4.3 illustrate substantial differences in family member health status measured with the EQ-5D-5L and SF-6D. This shows both measures cannot be used interchangeably, and justifies a validity comparison of the two instruments (the focus of this study).

A scatter plot of family members' SF-6D scores and family members' EQ-5D-5L scores was generated (Figure 4.2). The plot uses 2012 data of the family members exposed to meningitis sequelae. A 45° reference line was superimposed on the plot to represent equality in EQ-5D-5L and SF-6D scores.

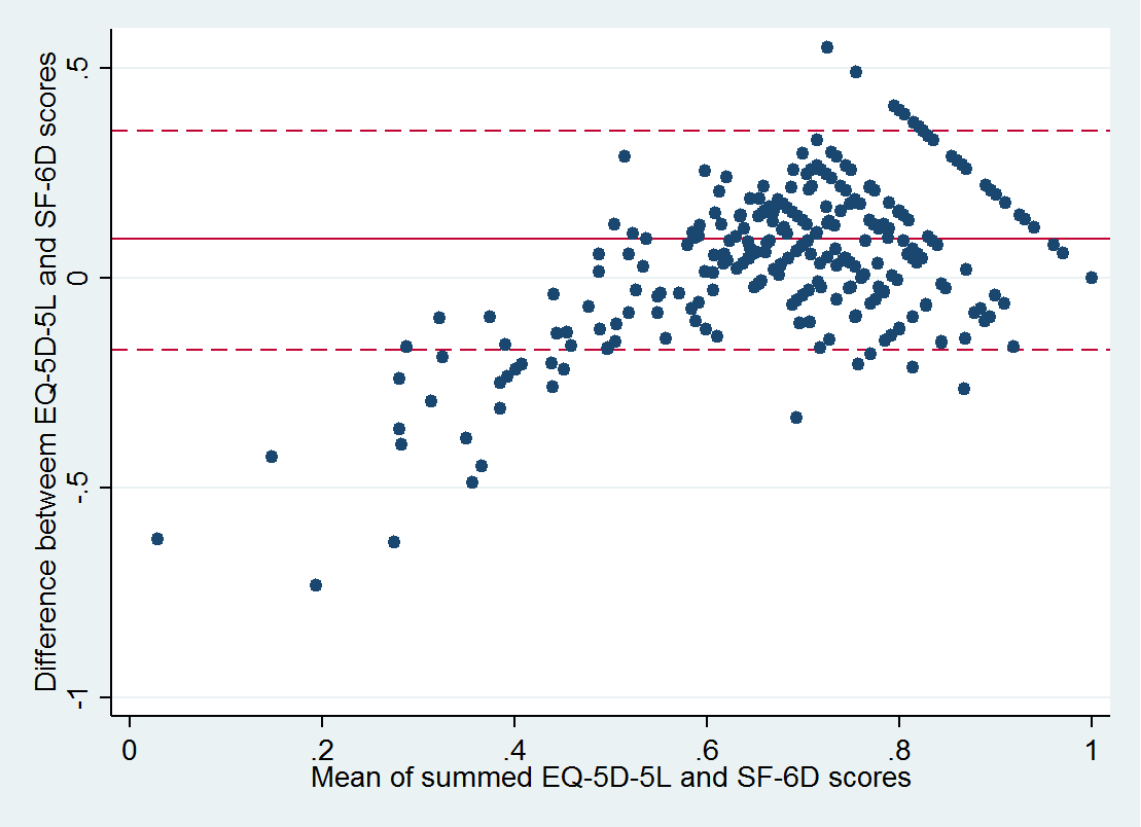
Figure 4.2: Scatter plot of family members' EQ-5D-5L and SF-6D scores in 2012 (n=1053) and 45 degree reference line



In figure 4.2, there is considerable divergence of data points away from the 45 degree reference line. This is particularly observable at low utility scores.

Figure 4.3 depicts the Bland Altman plot for family members' EQ-5D-5L and SF-6D scores in 2012. The Y axis plots the difference between the EQ-5D-5L and the SF-6D score. The X axis plots the average of the two scores summed together.

Figure 4.3: Bland Altman plot of family members' EQ-5D-5L and SF-6D scores in 2012 (n=1053)



In figure 4.3, larger differences between the EQ-5D-5L and the SF-6D are observed at low utility scores. Furthermore these differences at low utility scores are negative, showing much lower EQ-5D-5L scores compared to SF-6D scores at this low range of scores (which is also illustrated in Figure 4.2).

The changes in family member EQ-5D-5L and SF-6D scores between 2012 and 2013 were normally distributed, of similar width and centred around zero, although the distribution of the EQ-5D-5L was slightly flatter (Figures 4.4 and 4.5).

Figure 4.4. Histogram of family member EQ-5D-5L change scores (n=518)

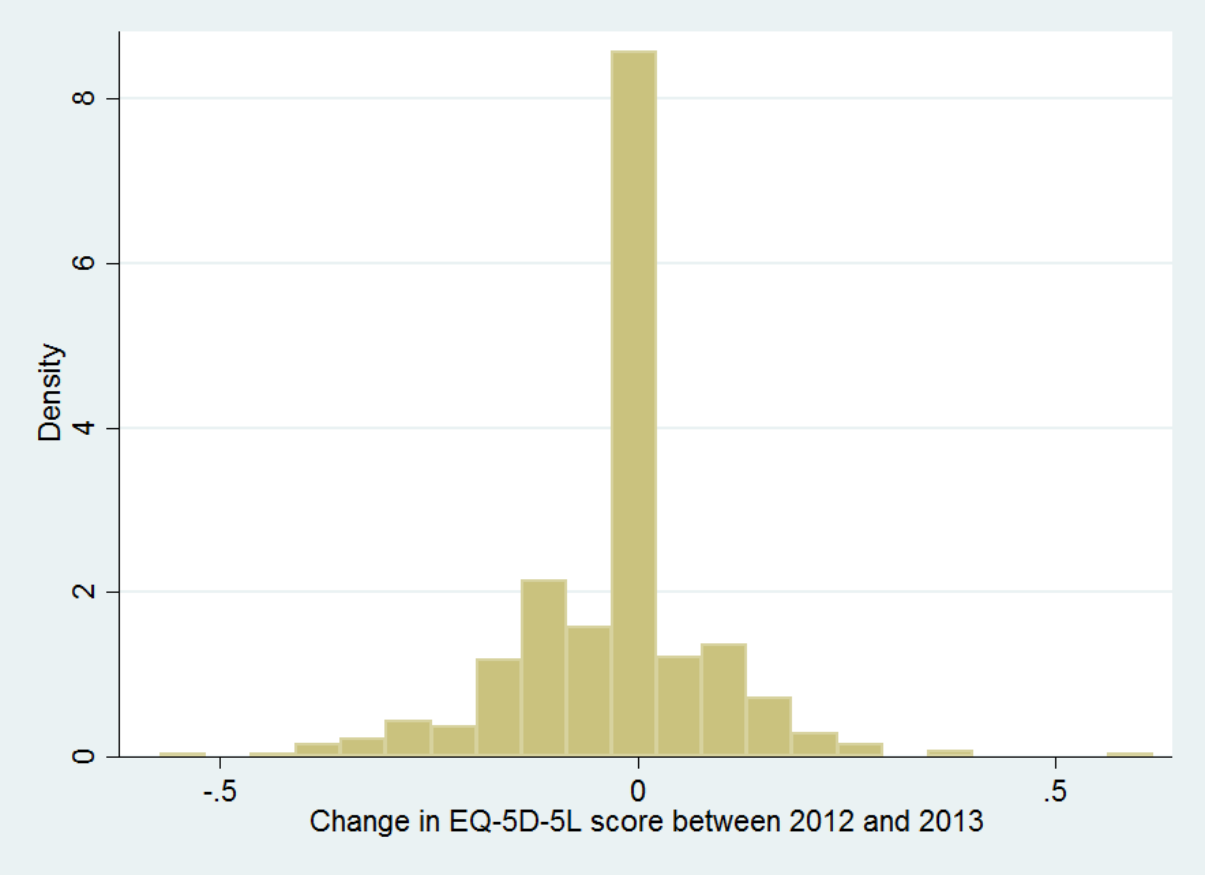
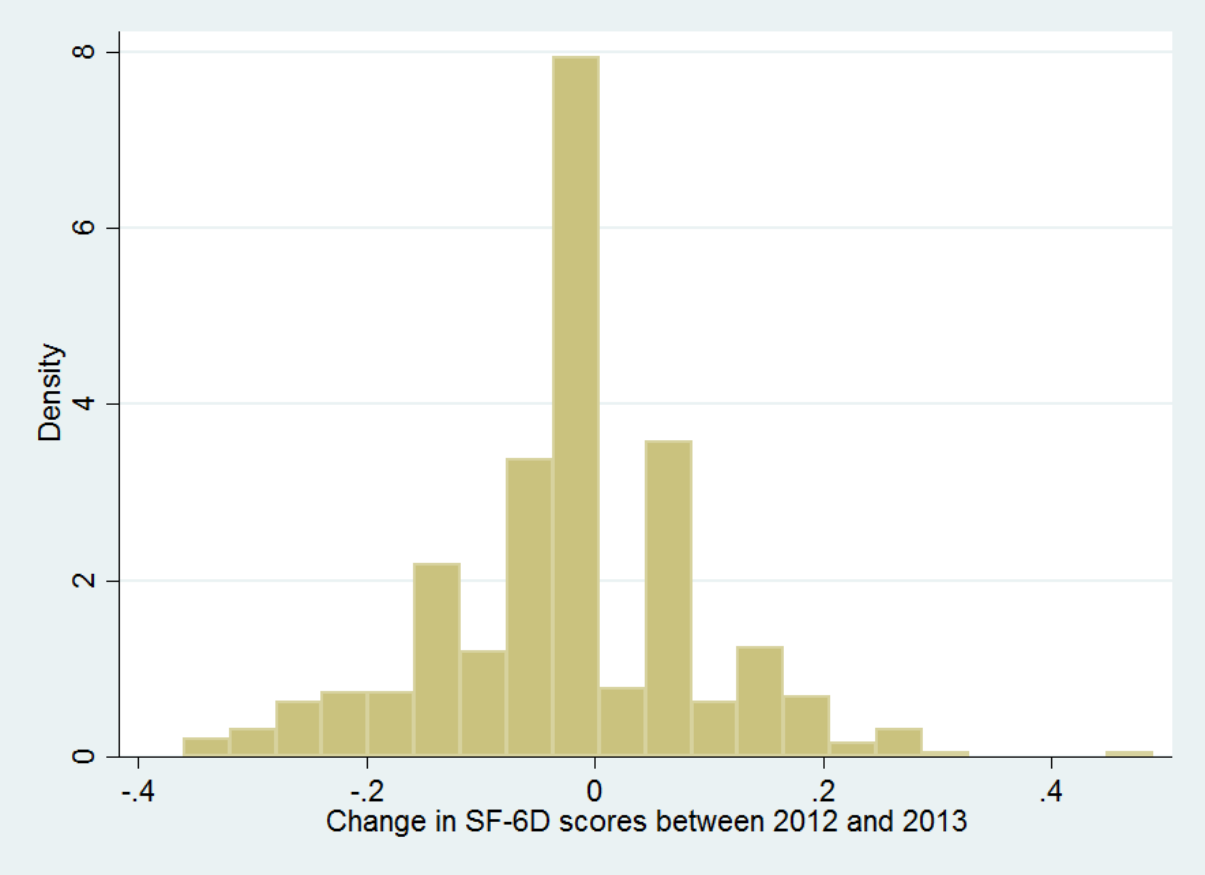


Figure 4.5. Histogram of family member SF-6D change scores (n=477)



4.1.1. Completion rates (feasibility)

For the present study, 1546 (97%) family members completed the EQ-5D-5L at baseline (96% at follow-up), and 1485 (94%) family members completed the SF-6D (92% at follow-up). For the EQ-5D-5L at baseline, the usual activities item achieved the highest completion rate (99%) and the anxiety and depression item the lowest (98%). For the SF-6D at baseline, the general health item achieved the highest response (98%), and the items equally obtaining the lowest response rates were related to accomplishing less a result of emotional difficulties, being less careful in activities due to emotional difficulties, pain impacting work activities, and ability to climb stairs (96%).

4.1.2. Distributions and ceiling effects

An assessment of the distributional characteristics of the two instruments was made (Figures 4.6 and 4.7). The family members' EQ-5D-5L scores illustrated a clear 'ceiling effect', with 43% of the family members included in the validity analysis reporting full health at baseline (37% at follow-up). The SF-6D distribution did not exhibit a ceiling effect with just 3% of family members reporting full health at baseline (5% at follow-up). The distribution of the SF-6D did not form a smooth curve with five large spikes observed between utility scores of 0.6 and 1.0.

Figure 4.6: Histogram of family EQ-5D-5L scores at baseline (n=828)

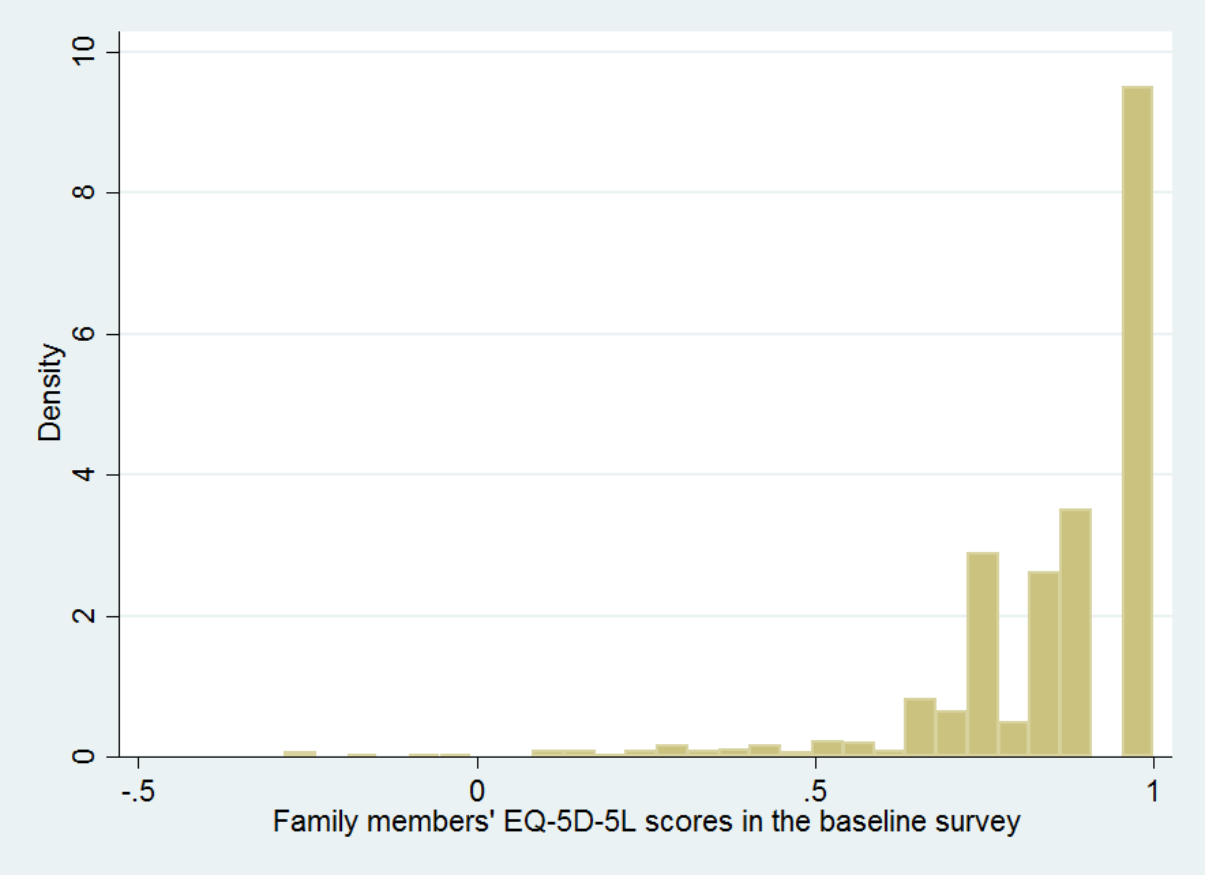
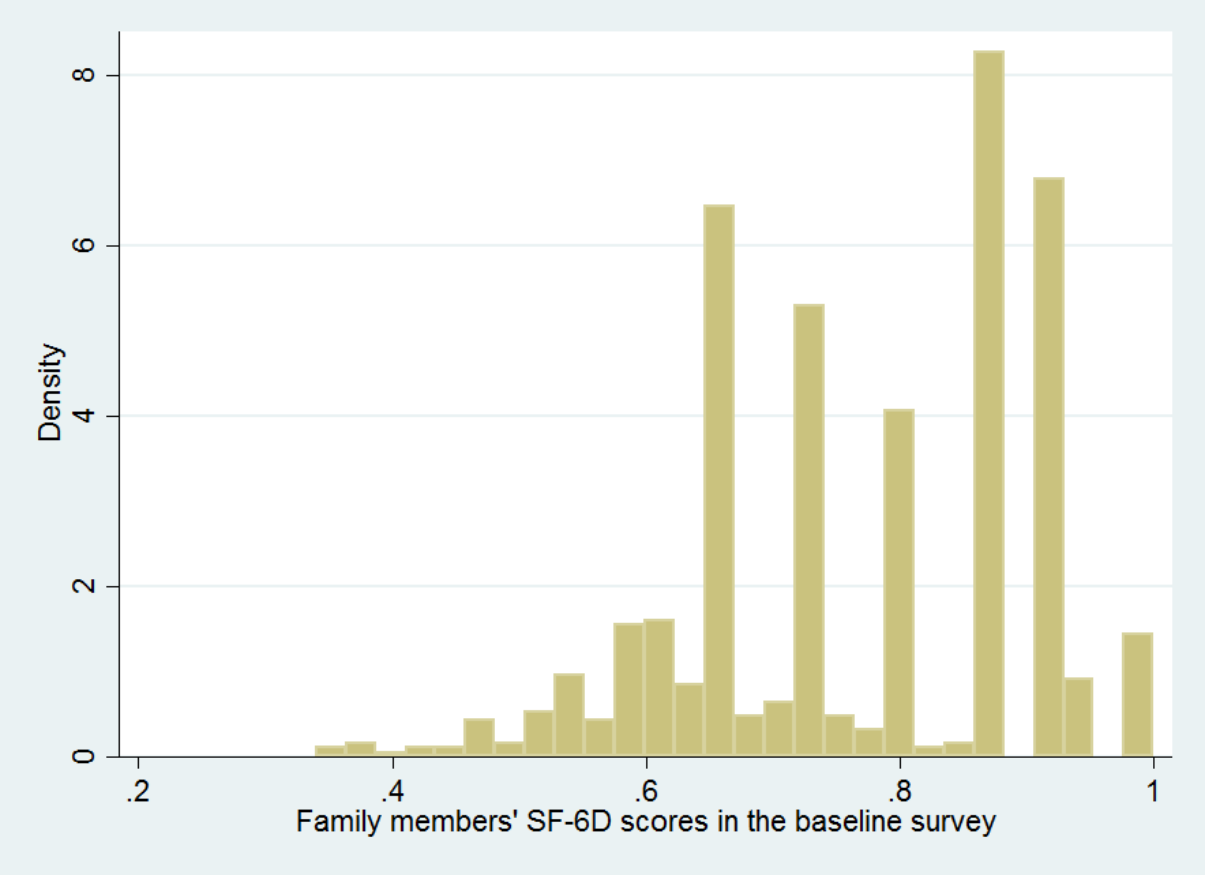


Figure 4.7: Histogram of family SF-6D scores at baseline (n=795)



4.2. Construct validity

Tables 4.2 to 4.4 detail the results for the tests of construct validity. Table 4.2 reports the tests of the construct validity of the instruments for measuring spillovers among non-carers generated from 'caring about' the patient. Table 4.3 reports the tests of the hypotheses among carers which either relate to 'caring about' or 'caring for' the patient. Table 4.4 reports the tests of the construct validity of the instruments for measuring spillovers attributed to 'caring for' the patient among carers. Each table set of results will be discussed separately in the following subsections.

4.2.1. Non-carer sample

In the 'caring about' tests for the non-carers in Table 4.2, both the EQ-5D-5L and SF-6D each detected statistically significant associations with ten out of the eleven constructs, with all of these associations falling in the expected directions that were hypothesised prior to testing. Statistically significant associations were reported for patient health variables (the patient VAS, and EQ-5D-5L items and composite score), and these associations were below the threshold for a small effect. Moderate-to-large effect sizes were reported for constructs relating to the negative impact of meningitis on family members' social life, family life, exercise and how they view their personal health.

Table 4.2. Effect sizes for tests of construct validity of the EQ-5D-5L and SF-6D for measuring non-carer health spillovers generated from caring about the patient (n=648)

Constructs associated with family member health spillover	**EFFECTS ON NON-CARER HEALTH STATUS INDEX SCORES**	
	EQ-5D-5L (95% CI)	**SF-6D (95% CI)**
Patient EQ-5D-5L	0.22*** (0.14 to 0.29)	0.19*** (0.11 to 0.26)
Patient VAS	0.19*** (0.11 to 0.26)	0.24*** (0.17 to 0.32)
Patient Mobility	-0.09* (-0.16 to -0.01)	-0.04 (-0.12 to 0.04)
Patient Self-Care	-0.14***(-0.22 to -0.06)	-0.13** (-0.21 to -0.05)
Patient Usual activity	-0.07 (-0.15 to 0.00)	-0.09* (-0.17 to -0.01)
Patient Anxiety	-0.23***(-0.30 to -0.15)	-0.20*** (-0.28 to -0.12)
Patient Pain	-0.18***(-0.26 to -0.10)	-0.15*** (-0.23 to -0.07)
Family life †	-0.28* (-0.48 to -0.09)	-0.45*** (-0.66 to -0.26)
Social life †	-0.52***(-0.74 to -0.31)	-0.56*** (-0.79 to -0.34)
Exercise †	-0.82** (-1.11 to -0.53)	-0.59*** (-0.89 to -0.30)
Personal health †	-0.95***(-1.31 to -0.59)	-0.83*** (-1.29 to -0.46)

*p<0.05, **p<0.01, ***p<0.001

† Measure of the perceived impact of meningitis on area of the family member's life

§VAS- visual analogue scale

§Spearman's rho effect sizes of between 0.3 and 0.5 are considered weak, between 0.5 and 0.7 moderate, > 0.7 strong. For Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large. The same interpretations apply for negative correlation coefficients and effect sizes.

§ Spearman's rho reported for all constructs which are continuous variables (patient EQ-5D-5L, VAS, mobility, self-care, usual activity, anxiety, pain). Cohen's D reported for all other variables.

§ Note: Higher score of patient EQ-5D-5L and VAS indicates better patient health, whereas higher score of the individual items of patient EQ-5D-5L indicates poorer patient health.

4.2.2. Carer sample

In the tests for carers either relating to 'caring about' or 'caring for' the patient (Table 4.3), the EQ-5D-5L generally detected larger Cohen's D effect sizes and stronger Spearman's rho associations than the SF-6D, and more statistically significant associations (nine out of eleven) than the SF-6D (4/11). The family member EQ-5D-5L was able to capture a range of associations that were absent with the SF-6D. Specifically, these associated variables were patient mobility, self-care, usual activity, family life, view on personal health and the overall patient EQ-5D-5L composite score. The family member SF-6D was able to detect a statistically significant association between the patient anxiety variable ($p<0.05$) unlike the EQ-5D-5L.

Table 4.3. Effect sizes for tests of construct validity of the EQ-5D-5L and SF-6D for measuring spillovers among carers either relating to 'caring about' or 'for' the patient (n=199)

Constructs associated with family member health spillover	**EFFECTS ON CARER HEALTH STATUS INDEX SCORES**	
	EQ-5D-5L (95% CI)	**SF-6D (95% CI)**
Patient EQ-5D-5L	0.26*** (0.12 to 0.39)	0.09 (-0.05 to 0.24)
Patient VAS	0.24*** (0.10 to 0.37)	0.15* (0.01 to 0.29)
Patient mobility	-0.19** (-0.32 to -0.05)	-0.06 (-0.21 to 0.08)
Patient self-care	-0.18** (-0.32 to -0.05)	-0.08 (-0.22 to 0.06)
Patient usual activity	-0.24***(-0.38 to -0.11)	-0.05 (-0.20 to 0.09)
Patient anxiety	-0.14 (-0.27 to 0.01)	-0.17* (-0.31 to -0.03)
Patient pain	-0.07 (-0.21 to 0.07)	-0.03 (-0.17 to 0.11)
Family life †	-0.30* (-0.59 to -0.01)	-0.09 (-0.38 to 0.21)
Social life †	-0.45** (-0.74 to -0.15)	-0.34* (-0.64 to -0.05)
Exercise †	-0.55***(-0.85 to -0.24)	-0.48***(-0.79 to -0.18)
Personal health †	-0.88** (-1.33 to -0.44)	-0.44 (-0.88 to 0.01)

*p<0.05, **p<0.01, ***p<0.001

† Measure of the perceived impact of meningitis on area of the family member's life

§VAS- visual analogue scale

§Spearman's rho effect sizes of between 0.3 and 0.5 are considered weak, 0.5 and 0.7 moderate, > 0.7 strong. For Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large. The same interpretations apply for negative correlation coefficients and effect sizes.

§ Spearman's rho reported for all constructs which are continuous variables (patient EQ-5D-5L, VAS, mobility, self-care, usual activity, anxiety, pain, hours of care provided, Carer Experience Scale). Cohen's D reported for all other variables.

§ Note: Higher score of patient EQ-5D-5L and VAS indicates better patient health, whereas higher score of the individual items of patient EQ-5D-5L indicates poorer patient health.

§ Note: Higher score on the Carer Experience Scale indicates a better experience, hence a positive association with family member index scores.

In the tests of carers solely related to 'caring for' the patient (Table 4.4), the SF-6D detected statistically significant effect sizes or associations five out of ten times, and the EQ-5D-5L two out of ten times. These effect sizes were either small or below the conventional threshold of a small effect size (0.20). The SF-6D was able to pick up statistically significant effect sizes at the 5% level for variables relating to the impact of meningitis on work activities and daily/main carer status. These associations were however absent with the EQ-5D-5L. Furthermore the SF-6D detected a moderate negative statistically significant effect size for the main carer variable, whereas the effect size detected using the EQ-5D-5L was in the opposite direction (i.e. contrary to study hypothesis) and non-significant. For the variable 'hours of care provided', statistically significant associations ($p<0.01$) were detected using both the EQ-5D-5L and SF-6D, and both associations were considerably lower than the conventional threshold of a small effect.

Table 4.4. Effect sizes for tests of construct validity of the EQ-5D-5L and SF-6D for measuring spillovers among carers solely related to 'caring for' the patient (n=199)

Constructs associated with family member health spillover	**EFFECTS ON CARER HEALTH STATUS INDEX SCORES**	
	EQ-5D-5L (95% CI)	**SF-6D (95% CI)**
Hours of care provided	-0.21** (-0.34 to -0.07)	-0.21** (-0.34 to -0.06)
Carer Experience Scale	0.34***(0.19 to 0.47)	0.23** (0.08 to 0.38)
Shares house	-0.21 (-0.58 to 0.17)	-0.06 (-0.45 to 0.32)
Daily care	-0.04 (-0.39 to 0.32)	-0.43* (-0.80 to -0.06)
Main carer	0.07 (-0.29 to 0.43)	-0.50* (-0.87 to -0.12)
Provides majority of care	-0.08 (-0.37 to 0.23)	0.12 (-0.19 to 0.42)
Provides personal care	0.11 (-0.17 to 0.39)	0.14 (-0.13 to 0.42)
Impact of meningitis on work	-0.24 (-0.53 to 0.05)	-0.35* (-0.65 to -0.05)
Impact of meningitis on finances	-0.13 (-0.42 to 0.18)	-0.04 (-0.34 to 0.26)
Provides constant supervision	-0.10 (-0.40 to 0.20)	-0.20 (-0.51 to 0.10)

*p<0.05, **p<0.01, ***p<0.001

§Spearman's rho of between 0.3 and 0.5 are considered weak, 0.5 and 0.7 moderate, > 0.7 strong. For Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate, and > 0.8 large. The same interpretations apply for negative effect sizes and correlation coefficients.

§ Spearman's rho reported for constructs which are continuous variables (hours of care provided, Carer Experience Scale). Cohen's D reported for all other variables

§ Note: Higher score on the Carer Experience Scale indicates a better experience, hence a positive association with family member index scores.

It was found that the SF-6D detected a moderate negative effect on health from being a carer (average score of 0.71) relative to not being a carer (average score of 0.78) (difference in scores= 0.07, Cohen's D effect size = 0.55), and the EQ-5D-5L detected a small negative effect on health from being a carer relative to being a non-carer (0.83 vs 0.87 respectively) (difference in scores= 0.05, Cohen's D effect size= 0.25).

It was also observed that the SF-6D detected a larger negative effect on the health of family members from being exposed to meningitis sequelae compared to non-exposed family

members (difference in scores=0.07, Cohen's D effect size= 0.52) than the EQ-5D-5L (difference in scores=0.05, Cohen's D effect size= 0.30). A further investigation was carried out for determining which items of the family member EQ-5D-5L and SF-6D were capturing spillovers. This offered a comparison of the EQ-5D-5L and SF-6D in terms of how many of the individual item responses of the two instruments were scored more negatively as a result of exposure to meningitis sequelae. In this further investigation, a higher proportion of the items of the SF-12 detected statistically significantly worse outcomes for the exposure group relative to the non-exposure group (all 12 of the items), compared to the EQ-5D-5L (3 out of 5 items) (Tables 4.5 and 4.6).

Table 4.5: EQ-5D-5L item responses for the groups exposed and not exposed to meningitis sequelae

EQ-5D-5L items and levels		FMs exposed to sequelae (%)	FMs not exposed to sequelae (%)	Chi-squared test of statistical significance
Mobility	No problems	85	87	P=0.23
	Slight problems	9	10	
	Moderate problems	4	2	
	Severe problems	2	1	
	Unable to walk	0	0	
Self-care	No problems	96	98	P=0.10
	Slight problems	2	2	
	Moderate problems	1	0	
	Severe problems	1	0	
	Unable to dress	0	0	
Usual Activities	No problems	85	90	P=0.01**
	Slight problems	9	7	
	Moderate problems	4	2	
	Severe problems	1	1	
	Unable to do them	1	0	
Pain/ Discomfort	No problems	66	73	P=0.003**
	Slight problems	21	21	
	Moderate problems	9	5	
	Severe problems	3	1	
	Extreme pain	0	0	
Anxiety/ Depression	No problems	57	77	P<0.001***
	Slight problems	30	19	
	Moderate problems	10	3	
	Severe problems	1	1	
	Extreme anxiety	1	0	

*p<0.05, **p<0.01, ***p<0.001

The pain/discomfort, anxiety/depression, and usual activities domains were statistically significantly worse for the family members exposed to sequelae. A much higher proportion of exposed family members compared with unexposed family members reported problems of anxiety and depression.

Table 4.6: SF-12 item responses for the groups exposed and not exposed to after-effects (2012 data)

SF-12 items and levels		FMs exposed to sequelae (%)	FMs not exposed to sequelae (%)	Chi-squared test of statistical significance
General health	Excellent	19	25	P<0.001***
	Very good	43	45	
	Good	28	24	
	Fair	8	7	
	Poor	3	0	
Moderate activities	Limited a lot	5	3	P<0.001***
	Limited a little	15	10	
	Not limited at all	80	87	
Climbing stairs	Limited a lot	7	4	P=0.02*
	Limited a little	19	16	
	Not limited at all	74	79	
Problems with physical accomplishments	All of the time	3	1	P<0.001***
	Most of the time	5	3	
	Some of the time	13	6	
	A little of the time	18	17	
	None of the time	61	73	
Problems with kind of work/activity	All of the time	3	1	P<0.001***
	Most of the time	4	2	
	Some of the time	10	6	
	A little of the time	14	15	
	None of the time	68	76	
Problems with emotional accomplishments	All of the time	2	0	P<0.001***
	Most of the time	4	2	
	Some of the time	15	7	
	A little of the time	20	13	
	None of the time	60	79	
Problems with doing careful work	All of the time	2	0	P<0.001***
	Most of the time	3	2	
	Some of the time	10	4	
	A little of the time	21	13	
	None of the time	64	81	
Pain	Not at all	65	72	P=0.002**
	A little bit	22	20	
	Moderately	6	4	
	Quite a bit	6	3	
	Extremely	2	1	

Calm and peaceful	All of the time	8	13	P<0.001***
	Most of the time	47	59	
	Some of the time	28	20	
	A little of the time	13	7	
	None of the time	4	1	
Energy levels	All of the time	7	12	P<0.001***
	Most of the time	44	53	
	Some of the time	29	25	
	A little of the time	13	9	
	None of the time	7	1	
Downhearted and low	All of the time	3	1	P<0.001***
	Most of the time	7	2	
	Some of the time	28	18	
	A little of the time	36	34	
	None of the time	26	45	
Interference with social activities	All of the time	2	0	P<0.001***
	Most of the time	5	1	
	Some of the time	16	6	
	A little of the time	18	13	
	None of the time	60	79	

*p<0.05, **p<0.01, ***p<0.001

In Table 4.6, it was found that all items of the SF-12 scored statistically significantly better health for the group of family members not exposed to meningitis sequelae. A higher proportion of unexposed family members compared with exposed family members, reported excellent general health, and no problems for the other 11 items. This was particularly noticeable for the items related to feeling downhearted and low, emotional problems impacting work and activities, and emotional problems impacting accomplishments over the past 4 weeks. For these items, a substantially higher proportion of unexposed family members reported 'no problems' in these areas compared with exposed family members.

4.3. Responsiveness

This section details the results of the tests of responsiveness of the family member EQ-5D-5L and SF-6D to clinically relevant external changes between 2012 and 2013, tested among the non-carers and carers separately.

In table 4.7, there are no clearly observed 'gradients' of effect in the non-carers' EQ-5D-5L or SF-6D moving between an improvement through to a decline in the subgroups of patient health change. This is the result of there being few significant changes in the expected direction in non-carers' health status when the patients' health improved/did not change importantly/worsened.

Table 4.7: Tests of responsiveness of the non-carer EQ-5D-5L and SF-6D

	Non-carer EQ-5D-5L 2012 baseline (mean)	Non-carer EQ-5D-5L 2013 follow-up (mean)	Difference between follow-up and baseline EQ-5D-5L (95% CI)	Effect size (Cohen's D)	n
Patient EQ-5D-5L					
Improved	0.83	0.84	0.01 (-0.02, 0.04)	0.01	46
No MCID	0.91	0.88	-0.03*** (-0.04, -0.01)	-0.19	234
Worsened	0.84	0.81	-0.03** (-0.06, -0.01)	-0.14	115
Patient health change					
Improved	0.89	0.85	-0.04* (-0.07, -0.01)	-0.23	60
No MCID	0.88	0.86	-0.02* (-0.03, -0.01)	-0.10	304
Worsened	0.85	0.77	-0.07* (-0.13, -0.01)	-0.34	26

	Non-carer SF-6D 2012 baseline (mean)	Non-carer SF-6D 2013 follow-up (mean)	Difference between follow-up and baseline SF-6D (95% CI)	Effect size (Cohen's D)	n
Patient EQ-5D-5L					
Improved	0.76	0.76	0.00 (-0.03, 0.03)	0.00	43
No MCID	0.81	0.79	-0.02** (-0.03, -0.01)	-0.17	210
Worsened	0.76	0.75	-0.01 (-0.03, 0.01)	-0.05	104
Patient health change					
Improved	0.80	0.77	-0.03* (-0.06, -0.00)	-0.24	52
No MCID	0.79	0.78	-0.01* (-0.03, -0.00)	-0.11	278
Worsened	0.72	0.72	0.00 (-0.03, 0.04)	0.02	23

*p<0.05, **p<0.01, ***p<0.001

§ Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large.

§ No MCID = no minimal clinically important difference, i.e. the patient's EQ-5D-5L score did not improve or worsen by more than 0.074 between 2012 and 2013; family members directly reported that the patient's health did not change between 2012 and 2013 with the global patient health change measure

In Table 4.8, the carer EQ-5D-5L scores detected a gradient of effect in the expected direction when moving from the subgroup of patients whose EQ-5D-5L scores improved to the subgroup of patients whose EQ-5D-5L score worsened. This gradient of effect was evidenced by the carer EQ-5D-5L score improving by 0.04 between 2012 and 2013 as the patients' EQ-5D-5L improved, not changing when patients' health did not change in a clinically important way, and declining by 0.06 (which equated to a small standardised Cohen's D effect size) as patients' health worsened. That is, a gradient from positive change through to negative change in carer EQ-5D-5L scores was observed, in line with patient EQ-5D-5L change score degradation. In table 4.9, the carer SF-6D did not detect such an effect. Both the carer EQ-5D-5L and SF-6D detected a gradient of effect (and the SF-6D a larger gradient) with the variable which asked family members to explicitly state whether the patient's health had improved, declined or not changed from baseline to follow-up (the global rating of patient health change measures). Neither the carer EQ-5D-5L or the SF-6D detected a gradient of effect as caring hours moves from an increase to a decrease.

Table 4.8: Tests of responsiveness of the carer EQ-5D-5L

	Carer EQ-5D-5L 2012 baseline (mean)	Carer EQ-5D-5L 2013 follow-up (mean)	Difference between follow-up and baseline EQ-5D-5L (95% CI)	Effect size (Cohen's D)	n
Patient EQ-5D-5L					
Improved	0.79	0.83	0.04 (-0.04, 0.13)	0.19	22
No MID	0.84	0.83	0.00 (-0.03, 0.02)	-0.02	60
Worsened	0.80	0.73	-0.06** (-0.11, -0.02)	-0.27	41
Global rating of patient health change					
Improved	0.86	0.88	0.02 (-0.02, 0.05)	0.12	16
No MID	0.83	0.82	-0.01 (-0.04, 0.01)	-0.08	68
Worsened	0.77	0.74	-0.03 (-0.09, 0.03)	-0.11	36
Hours of care provided					
Less care	0.80	0.77	-0.03 (-0.08, 0.01)	-0.16	29
No MID	0.81	0.82	0.01 (-0.04, 0.06)	0.05	30
More care	0.84	0.79	-0.05* (-0.10, 0.00)	-0.31	23

*p<0.05, **p<0.01, ***p<0.001

§ Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large.

§ No MID = no minimal important difference, i.e. the patient's EQ-5D-5L score did not improve or worsen by more than 0.074 between 2012 and 2013; family members directly reported that the patient's health did not change between 2012 and 2013 with the global patient health change measure; informal care hours provided did not increase or decrease by more than 5 hours between 2012 and 2013

Table 4.9: Tests of responsiveness of the carer SF-6D

	Carer SF-6D 2012 baseline (mean)	Carer SF-6D 2013 follow-up (mean)	Difference between follow-up and baseline SF-6D (95% CI)	Effect size (Cohen's D)	n
Patient EQ-5D-5L					
Improved	0.71	0.70	-0.01 (-0.07, 0.06)	-0.04	22
No MID	0.71	0.70	-0.01 (-0.04, 0.01)	-0.12	59
Worsened	0.69	0.65	-0.05* (-0.08, -0.01)	-0.36	39
Global rating of patient health change					
Improved	0.71	0.74	0.03 (-0.02, 0.08)	0.27	16
No MID	0.72	0.70	-0.02 (-0.05, 0.01)	-0.15	67
Worsened	0.68	0.63	-0.05* (-0.08 ,-0.01)	-0.36	33
Hours of care provided for patient					
Less care	0.68	0.66	-0.02 (-0.06, 0.03)	-0.12	27
No MID	0.71	0.71	0.00 (-0.04, 0.04)	-0.02	31
More care	0.72	0.67	-0.05* (-0.10, -0.01)	-0.51	21

*p<0.05, **p<0.01, ***p<0.001

§ Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large.

§ No MID = no minimal important difference, i.e. the patient's EQ-5D-5L score did not improve or worsen by more than 0.074 between 2012 and 2013; family members directly reported that the patient's health did not change between 2012 and 2013 with the global patient health change measure; informal care hours provided did not increase or decrease by more than 5 hours between 2012 and 2013

4.4. Discussion

4.4.1. Discussion of results

Key findings

This is the first study to systematically explore whether two commonly used health status measures are valid and responsive measures of health effects (spillovers) amongst carers and non-carers in patients' family networks. The findings from the results suggest that the EQ-5D-5L and SF-6D both exhibit some degree of validity in measuring health spillovers on family members. This is because in terms of construct validity, the scores of both instruments were statistically associated with many of the variables that were hypothesised to generate spillovers on family members' health (particularly in the tests of construct validity among the larger non-carer sub-sample), and all of the statistically significant relationships were found to be in the predicted directions that were hypothesised prior to analysis.

Some small gradients were observed in the responsiveness analysis. A gradient was observed for carers for whom a small and statistically significant health status improvement was observed where patients' health was reported to have improved, and a small decline was observed in carers' health where reported patients' health also declined. Apart from this case, neither the EQ-5D-5L nor the SF-6D exhibited clear responsiveness to changes over the course of a year in patient health or the caring situation with lack of gradient of effect.

Also found in the construct validity analysis was that the family member SF-6D detected larger effect sizes (unstandardised and standardised) than the EQ-5D-5L in relation to carer status and exposure to meningitis sequelae. This suggests that it is unlikely that the two instruments can be used interchangeably in trials as the SF-6D is likely to detect a larger effect.

Relationship to other studies

These findings complement existing validity literature which indicates that the EQ-5D-5L and the SF-6D (including the 12 item measure) adequately cover relevant domains related to depression experienced among carers (279) as well as for other populations (252). However, one systematic review described mixed results with using the EQ-5D and the SF-6D for measuring anxiety (252). The ability of the instruments to detect the presence and severity of anxiety symptoms among family members may therefore merit further attention and research. The findings from this study also add to previous studies which support the convergent validity of the EQ-5D-3L and SF-6D in measuring the health status of carers of ill children (243, 279). These studies showed that the EQ-5D-3L was significantly correlated with the SF-6D(243), and the SF-6D was strongly correlated with the HUI:3 instrument (which is another generic preference-based health measure) (279).

Explanation for results

Comparing the relative validity of the two instruments was made more complex by contrasting findings. In the carer sub-sample, the EQ-5D-5L exhibited greater construct

validity by detecting stronger associations than the SF-6D for spillovers resulting from poor patient health, and also detecting an anticipated gradient in the responsiveness analysis as patients' EQ-5D-5L scores declined over time. However the SF-6D detected more statistically significant associations than the EQ-5D-5L for spillovers resulting from caring burden, and larger effect sizes from carer status and from exposure to meningitis sequelae. It was expected that an instrument that is more socially-oriented such as the SF-6D would be better at picking up associations relating to aspects of the caring situation. What was unexpected was that the EQ-5D-5L would be better than the SF-6D at detecting spillovers relating to patient health among the carers, particularly in terms of construct validity. One factor that may partially explain this result is that the EQ-5D-5L was used to measure patient health status. As a result, there may some degree of greater alignment in scores obtained from the same instrument administered to both patients and family members, than if different instruments are administered. This would also explain why in the tests of carer responsiveness, the carer EQ-5D-5L was more responsive than the SF-6D to changes in the patient EQ-5D-5L scores as the EQ-5D-5L was used to assess both the health of the carer and the patient, but the carer SF-6D was more responsive than the EQ-5D-5L to family members' global ratings in which family members stated whether the patients' health improved, did not change, or worsened over the survey administration period.

The findings from the responsiveness analysis were mostly null, suggesting a need to use a longer time period (>12 months) for future studies in this area, as was used for a recent study of dementia carers (18 months) which found that the carer EQ-5D-5L was responsive to the Zarit Burden Scale (a measure of caregiver burden) but not responsive to the time spent providing assistance with daily living for the patient(244). Furthermore, as the spillover

effect (on the average family member) is likely to be a small proportion of the direct effect (12), it may be too small to be detected even when the changes in patient health exceeded the threshold for a clinically important difference. This was also evidenced in this study by the small effect sizes that were reported in the construct validity analysis. It is important to note in the responsiveness analysis that there was a general worsening in the health of family members between 2012 and 2013 that had a sizeable downward effect on all of the mean differences in family member health status between follow-up and baseline assessment. This may also explain why there was little evidence of positive change for family health when the patient's health improved; more generally effect sizes and clinically important differences from the responsiveness analysis need to be interpreted with this in mind.

The positive associations between patient health status and family member health status in this study may not be completely attributed to spillover from the patient to the family member. However, the previous study of the family impact of meningitis demonstrated that the positive association between patient health status and family member health status remains when controlling for a wide range of potentially confounding factors related to the characteristics of the two individuals and the shared environment (13).

Study implications

Even though in this study the SF-6D exhibited greater validity in detecting associations solely related to 'caring for' the patient, the EQ-5D-5L may yet be chosen for measuring family member health status if the EQ-5D-5L is a preferred measure for patient health. This is

because it may be considered inappropriate to use different health status measures to elicit patient QALYs and family member QALYs for subsequent aggregation in an economic evaluation (307). For instance, this may be the case for economic evaluations conducted in England and Wales for NICE which recommend using the EQ-5D-5L for measuring the health of patients (158).

One disadvantage of the SF-6D instrument from this study was that it was more prone to missing data than the EQ-5D-5L. In this study, the EQ-5D-5L exceeded Brazier's threshold of a high completion rate for a health status measure of 95% (252), but the SF-6D did not. Although at baseline the first item of the SF-12 (general health) achieved a high completion rate of 98%, four of the subsequent items of the SF-12 were only completed by 96% of respondents, resulting in an overall completion rate of 94%. This may exacerbate the problem of missing data on family health spillovers within the context of health intervention trials, where the focus is more likely to be on achieving high response rates from the patients themselves. It is important to be aware that the position where the health status measures were presented in the questionnaire may have also influenced the completion rates of the two measures. The family member EQ-5D-5L was presented first, and the family member SF-6D presented after, which may have led to lower completion of the SF-6D. This is because family members may have felt more fatigued when answering the second set of health-related quality of life questions (assuming that they completed the survey questions in consecutive order).

4.4.2. Strengths and limitations

There are a number of strengths of this study. The study used a large sample of family members, and data completion of the surveys was generally high. Few alternative datasets exist for looking at health-related quality of life spillovers in carers and family members. This study is a novel investigation of the responsiveness of generic instruments for measuring health spillovers, investigates the validity of the EQ-5D-5L (rather than the 3 level instrument) and is the first study to assess instrument validity specifically in non-carers. An extensive number of tests were performed in the construct validity analysis.

Some limitations of the study are also acknowledged. There was a relatively small sub-sample of informal carers (n=199) compared with non-carers (n=648) used in analysis. Also, some non-carers may have provided some informal care for the meningitis patient in the past (i.e. prior to completing the survey), so not all of the non-carer spillover in the construct validity analysis at baseline can be attributed to 'caring about' the patient. The analysis only related to long-term effects on health of meningitis. Although meningitis is a condition which creates a wide range of symptoms among young individuals, and therefore a range of caring situations, the findings of this study may not be generalisable to other health conditions, especially where patients are older and care is mostly provided by spouses. Another limitation is that validity and responsiveness were not assessed in relation to a healthcare intervention. Further research addressing some of these limitations could be informative.

Reliability was not investigated in this study although a future study may do this. Perhaps the consistency of health status measures when repeatedly administered to carers or family members is unlikely to differ much to when these measures are administered in general

populations or patient populations. Content validity was not assessed in this study, although again there may be scope to do this in a future study. Also, content validation may only be required for examining whether health status measures cover the essential domains of health rather than to assess whether they capture the nuances of family health spillovers (308). Furthermore, if attempting to assess content validity in family members, it may be difficult for family members being interviewed to pinpoint the areas of their health which have been impacted indirectly through lifestyle changes and stress. Criterion validity was not assessed in this study as there is no gold-standard measure for an abstract variable such as health-related quality of life to compare the EQ-5D-5L or SF-6D against, so there is no scope for a future study to assess this (256).

4.4.3. Conclusion

In conclusion, both the EQ-5D-5L and SF-6D appear to be satisfactory instruments for measuring family members' health status in an economic evaluation. This is because both instruments exhibit construct validity in capturing family member health spillovers. However further research is required to assess the validity and responsiveness of the instruments in capturing health spillovers generated from other illnesses and from health interventions. The next two chapters describe a study of the household spillovers arising from a COPD telephone coaching intervention.

CHAPTER 5: INVESTIGATING THE IMPACTS OF A COPD TELECOACHING INTERVENTION ON THE HEALTH AND HEALTH BEHAVIOURS OF HOUSEHOLD MEMBERS: METHODS

The previous chapter described the results and discussion for the first empirical study of the PhD. This chapter presents the methods for the second empirical study for the PhD. This study investigates the impacts of a telephone health coaching intervention to support self-management of COPD (Chronic Obstructive Pulmonary Disease), on the health and health behaviours of household members. The rationale for undertaking this work is to explore the feasibility of prospectively collecting data on health spillovers alongside an RCT; and to estimate the magnitude of health spillovers which are generated. For the rest of this thesis, the intervention will be referred to as a telecoaching intervention. The terms 'FIS' and 'PSM-COPD' will be used to refer to the 'Family Impact Sub-study' (this study) and the 'Patient Self-Management of COPD' (main trial) respectively.

The methods for collecting and analysing the data for this study will be reported. First, a description of the existing literature on the impact of COPD on family members and details of the main PSM-COPD trial will be provided. This will be followed by a description of the objectives and the data collection methods for the family impact study (FIS). The FIS was an additional study that I conducted alongside the existing PSM-COPD trial. A description of the FIS questionnaire design and methods for analysing the elicited data will be described in the latter sections of this chapter.

5.1. Background

5.1. Chronic Obstructive Pulmonary Disease (COPD)

COPD (Chronic Obstructive Pulmonary Disease) is a progressive and irreversible respiratory disease which usually occurs in an older population, and encompasses conditions such as chronic bronchitis and emphysema (309). Most people get COPD because they are smokers or ex-smokers. Another major risk factor for COPD is from continued occupational exposure to dust, gas and fumes. A relatively rare cause of COPD is genetic (Alpha-1 Antitripsin deficiency). It is estimated that 3.9% of men and 2.4% of women in the UK have COPD (310). COPD is a disease that is the third leading cause of death worldwide, after heart disease and strokes(311).

COPD impacts quality of life, and typical symptoms include frequent coughing, increasing breathlessness when active and frequent chest infections (312). Nevertheless its progression can be slowed, primarily by the patient changing their behaviours. The most effective way to slow COPD progression is for the patient to reduce their smoking or completely stop smoking(312). Increased physical activity is another way for the patient to enable a slower progression of symptoms (312).

5.2. Health spillovers of COPD

A review of the literature on the family impact of COPD shows that research in this area is scarce, with no studies having investigated the effects of a COPD patient intervention on family members. This highlights the importance of this study which aims to quantitatively

measure the effects of a COPD telecoaching intervention on the health of family members. This section discusses the limited evidence on the health outcomes of COPD family members, and why an effective intervention that reduces the symptoms of COPD may also alleviate the stress and caring burden on family members.

In a previously published integrative review of the qualitative and quantitative literature on the family impact of COPD, it was found that there was a dearth of research in this area compared with other chronic diseases, with mostly studies with small sample sizes, and no intervention or longitudinal studies(313). However, existing evidence does go some way to establishing the spillovers imposed on family members, particularly the spouse (usually wife) of the patient, and these spillovers include attending health care appointments with the patient, and family members having to compensate for household tasks (e.g. gardening, housework and shopping) that the patient is restricted from doing by their condition (314). Worrying about the COPD patient is generally reported as being the most significant spillover that family members experience (314, 315).

More recently, larger cross-sectional studies on the family impact of COPD have been carried out (88, 316, 317).Two of these studies show COPD carers experience a heightened risk of depression particularly if the patient's condition is moderate or severe (88, 317). One key factor that may result in this heightened risk of depression is that as the patient's condition becomes more severe, the patient may become dependent on oxygen therapy and therefore less able to leave the house. Family members therefore feel obligated to stay at home with the patient and also become confined to the house (318, 319).

A high prevalence of anxiety symptoms has also been noted in the quantitative and qualitative literature on COPD family impact (317, 319), with 62% of mild COPD carers reporting anxiety in one study (317). COPD family members experience anxiety and distress particularly when patients experience exacerbations of breathlessness, because the occurrence of these exacerbations are unpredictable and may lead to hospitalisation and death of a patient(318). Family members may also experience anxiety from financial worries because many COPD patients have to take early retirement due to their illness, and in countries without free health care families may also have to buy expensive medications for patients (318). Studies have reported that female partners of COPD patients are statistically significantly more likely than male partners to report anxiety symptoms despite having the same care burden, suggesting the two groups use different coping mechanisms (98, 99). Despite the negative experiences of many COPD family members, some COPD spouses have reported experiencing positive feelings from being able to spend more time with their partner and help ease their suffering (315, 320).

The percentage of COPD informal carers who reported a deterioration in their health was 35% in one large study; a rate which was comparable with the rates for carers of mental illness, cancer and heart attacks, but less than the rate for stroke carers (45%) (88). It is unclear from existing evidence whether the physical health of COPD carers is impacted from providing care. One study reported a negative association between the severity of COPD, and the physical health of a family carer, although this association was not clear from the figures reported in the table of summary statistics, in which the median physical health scores of early and advanced COPD family members were reported to be the same (318). In a qualitative study one COPD carer reported being ‘physically worn out’ from the combined

demands of providing care and having to work to ‘put food on the table’ (p.616) (315). These heightened demands and strains on carers and family members may last and intensify over several years as the COPD gradually worsens (100). COPD carers may also experience disrupted sleep; in a qualitative study one carer notes that despite her partner’s noisy breathing, she would still sleep with her partner due to the fear that he may stop breathing(315).

No full quantitative investigation of the impact of a COPD intervention on family members has been conducted until this study (316).

5.3. PSM-COPD trial

PSM-COPD (Patient self-management of COPD trial) is a two-arm randomised controlled trial (RCT) of a telephone health coaching intervention to support self-management compared with usual care (321). In a RCT, participants are randomly allocated to groups, thus eliminating allocation bias at baseline, and the person recruiting the participants does not know which is the next allocation, thus allocation is concealed (275). An RCT is seen as the 'gold standard' study design for measuring the effect of an intervention on relevant individuals (including those beyond the patient who are affected) (275, 322).

The patients enrolled in the PSM-COPD trial were individuals diagnosed with mild symptoms of their COPD. The multi-centre trial was administered at 4 different centres: Birmingham, Oxford, Keele and Manchester, and recruitment of patients for the trial took place between February 2014 and January 2015, overlapping in part with the data collection for the FIS.

Patients were identified as eligible for the trial if they were on the general practice COPD register, aged 18 or over, and reported only mild breathlessness after spirometry assessment (further details are provided in the trial protocol) (321).

The telephone coaching intervention covered 4 different elements distinct from usual care. The elements were the provision of advice for patients on smoking cessation, becoming physically active, using the correct inhaler technique, and managing their medication correctly including action planning for an exacerbation. These components were delivered by telephone coaching sessions between the nurse and the patient, and through postal information leaflets. The whole intervention was delivered over a 6 month period. Participants in the usual care group received a 13 page standard information booklet about self-management of COPD (321).

The planned telephone consultations comprised of a 35-60 minute consultation at week 1, and three 20 minute consultations at weeks 3, 7 and 11. During these consultations, goals were set with the patient to induce their behaviour change. After the consultation, the patient would then receive by post an individually tailored information sheet summarising the goals (an additional goal setting sheet was also sent to the patients at week 16). Along with these goal setting sheets, patients would also receive by post advice leaflets on physical activity, access to smoking cessation services and inhaler technique, at weeks 1, 3 and 24. In the telephone coaching sessions and advice leaflets, patients were encouraged to seek support from family and friends to quit smoking, and also to participate in physical activity (such as walking) with family and friends; such components to stimulate family member participation were absent from usual care.

The primary outcome measure for patients was the St Georges Respiratory Questionnaire (SGRQ), a respiratory specific health-related quality of life measure that is currently used in COPD research and has shown sensitivity to change in people with mild COPD (323). The secondary outcome measures for patients included self-reported health measured using the EQ-5D-5L, anxiety and depression, health behaviours including physical activity measured using the IPAQ-short, and smoking behaviour (321). These outcomes were assessed at baseline and follow-up at 6 and 12 months. A within-trial economic evaluation (cost-utility analysis) was also designed alongside the trial.

5.4. Methods

5.4.1. Study aims

The overall aim of this study is to investigate the degree to which a 'behavioural' intervention has health spillovers in the patient's household network that may be relevant to economic evaluation. As documented in Chapter 1, there are various mechanisms by which health spillovers could potentially be created by patient-centred health interventions. These mechanisms broadly fit into 3 categories. Two of these categories are the health spillovers generated from providing informal care, and from caring about a patient's wellbeing(37). The third category only relates to behavioural (or self-management) health interventions such as a telecoaching intervention. This mechanism concerns the concordance of patient health behaviour changes with surrounding individuals; with family and household members being the individuals most likely to be affected by this type of health spillover (12, 22, 121).

This study investigated whether the telecoaching intervention for COPD patients generates health spillovers in household members that may be relevant for economic evaluation. The focus of the analysis is on household members' EQ-5D-5L scores, because this is relevant to economic evaluation. Other household member outcomes were also collected because they may be indicative of health and wellbeing spillovers that are important but not picked up by the EQ-5D-5L.

This was done by answering two research questions. The primary research question is:

a) Is telephone health coaching for patients with COPD associated with positive effects on EQ-5D-5L scores for patients' household members?

The secondary research question is:

b) Is telephone health coaching for patients with COPD associated with improved health behaviours (physical activity, smoking), less stress and more happiness in patients' household members?

This is a novel study exploring the health spillover generated from a telephone coaching health intervention; none of the studies from the systematic review in Chapter 2 were focused on the health spillovers generated from a behavioural intervention. Another novel aspect of this study is that it prospectively measures health spillovers in a trial setting, which has rarely been done before (322).

The research questions were addressed using a postal survey administered to the adult household members of patients participating in the PSM-COPD trial. Through the postal survey, the family members self-complete the questionnaire, which is likely to be more reliable than the alternative approach of obtaining a proxy report of the family members' outcomes through the patient (324). The survey data collection methods are described in the following section.

5.5. Study design

5.5.1. Data collection

The process for collecting data for this study is documented in this section. Household members (≥ 18 years) were recruited at baseline between August 2014 and January 2015. A

household perspective may be a reasonable approximation for the individuals who are most negatively affected by health spillovers (5, 80). Previous randomised controlled trials have only measured health spillovers for the primary carer of the patient (209, 221, 223), although other household members may experience health spillovers which are important to capture (245). A household perspective may be limited in the sense that non-household members may also be affected, and are sometimes the most affected, by health spillovers (112).

At the baseline clinic assessment, patients were assessed for their eligibility into the main PSM-COPD trial. Once confirmed eligible, patients were provided with a patient information sheet for the family impact sub-study (FIS). The information sheet outlined the objective of the study, the patient's potential role as a gateway to their household member/s and invited the patient to participate in the study.

The patients that subsequently (and provisionally) consented to participate in the FIS were then provided with questionnaire packs according to the number of adult household members the patients lived with, using information provided by the patients (the questionnaire is described in section 5.6). Patients kept the patient information sheet to enable them to read it after the appointment, before they made a final action to pass on questionnaire packs to the household members; and thereby fully opt into the study. Patients who were accompanied by a household member to the appointment were also given the option to pass on a questionnaire to the household member to fill in and return it directly back to the nurse during the appointment, while the patient was being assessed.

The nurses that passed on the questionnaire packs to patients were guided through the process using a SOP (Standard Operating Procedure). The SOP ensured nurses did not miss out key procedural steps, such as writing the patient ID numbers on the front of the questionnaires to enable household member data to be linked to patient data, and also reminding the nurses to record in an online form whether a patient opted into the sub-study.

Each questionnaire pack for the household member contained a questionnaire, cover letter, information sheet and pre-paid envelope. In the cover letter, household members were asked to either opt into the study by completing and returning the questionnaire ideally within a four week period, or alternatively to return a blank questionnaire to formally indicate that they were opting out of the study. Household members were encouraged to opt into the study even if they felt that the patient's mild lung disease had not impacted them, in order to ensure a representative sample of household members of COPD patients, including those who are less affected by the patient's illness.

A single reminder letter was sent to patients who consented to the FIS but where no reply had been received from their household member/s after four weeks (13). This letter reminded patients what the family sub-study was about and encouraged patients to help the study by passing on questionnaires to their household members. If household members did not return the questionnaire following the reminder letter, it was assumed that the patient or their household member did not want to participate in the study. An option of calling up household members to encourage them to return questionnaires was considered but

ultimately not actioned, in order to not make household members feel pressured to participate in the study.

At 12 months follow-up, questionnaires and reminder letters were again sent out, but this time directly to the household members using data they had provided at baseline. Questionnaires were sent out in batches every fortnight, to ensure that household members received them approximately 12 months after they received the baseline questionnaire, over the period August 2015-January 2016. The timing of the follow-up data collection was also aligned with the collection of patient data at 12 months follow-up which enabled patient and household member outcomes to be analysed in conjunction with each other (321). However, it is important to be aware that a 12 month follow-up period may not capture 'lagged' health spillover effects by which family members may only experience health spillovers from a patient's health change a long time after the change has occurred. This is exemplified in one study which found that physical health effects in carers only emerged two years after they started caregiving (325). However, more generally it may be considered infeasible to extend trial data collection for family members beyond the time horizon of the collection of the patient data in order to capture these physical health spillover effects. This is because extending the data collection period may cause a considerable delay in completing the economic evaluation component of a health technology assessment. Records of the numbers of blank questionnaires received, reminder letters sent out, and exclusions of participants were kept.

The returned questionnaires were stored in a locked filing cabinet. Data from the questionnaires for the analysis was entered and saved in a password protected Microsoft

Excel file, before being subsequently transferred to a Stata file for the analysis. Sensitive data on household members (names and addresses) were entered and stored separately in a different password protected Microsoft Excel file, and transferred to Microsoft Access to send out cover letters for the follow-up questionnaires by using an automated mailing list.

5.5.2. Inclusion and exclusion criteria

All adult household members who returned baseline questionnaires were included in the baseline analysis, apart from the household members excluded according to the criteria in section 5.5.3. Included in the analysis were multiple household members related to the same patient, as the aim of the analysis was to estimate the average spillover effect of telephone coaching of COPD patients across all household members.

Household members were excluded from the family impact study and all data analysis, if they met one or more of the following exclusion criteria:

- Household member was related to a patient withdrawn from the PSM-COPD trial.
- Household member qualitatively mentioned in the baseline questionnaire that they were living temporarily with patient (for less than 6 months).
- Household member returned the baseline questionnaire over 4 months after the questionnaire was originally sent.

5.5.3. Ethical approval

The submission of the ethics application for the family impact study was approved in July 2014 by the National Research Ethics Service (Solihull, West Midlands) as a substantial amendment to the main trial protocol. The study presented a limited number of ethical concerns that concerned data protection of survey data, and did not involve the collection of any highly sensitive information. It was important in this study to gain consent from patients to allow family members to be contacted to participate in data collection associated with the PSM-COPD trial. Delays in obtaining ethical approval due to lack of clarity about whether a full ethics application or an amendment was required, meant that the process of acquiring ethical approval for the study took longer than anticipated, and prevented the full sample of patients being invited to participate in the family sub-study, as the main PSM-COPD trial began recruiting in February 2014.

5.6. Questionnaire design

The baseline and follow-up questionnaires were designed to capture information to measure health-related quality of life spillovers and related variables, to give insights into mechanisms by which health spillovers are generated by self-management interventions. Information on household members' age, sex, relationship to the patient, previous diagnosed health conditions and primary care utilisation was elicited. The components of the questionnaire are described in more detail below.

5.6.1. Health-related quality of life (EQ-5D-5L)

The EQ-5D-5L is an instrument used for measuring the health of respondents; further details about the EQ-5D-5L are provided in section 3.1.1 (248). The EQ-5D-5L is the recommended instrument for measuring health in NICE economic evaluations (158). The EQ-5D-5L exhibits better measurement properties than the EQ-5D-3L (3 levels) with reduced ceiling effect, improved discriminatory power, and confirmed construct validity in patients (247). Furthermore the first empirical study for the PhD in Chapters 3 and 4 produced favourable evidence for the validity of the EQ-5D-5L for capturing health spillovers in affected family members. It was hypothesised that if patients' mean EQ-5D-5L scores increased from the telephone coaching intervention, household members' mean EQ-5D-5L scores would also increase from health spillovers, albeit at a smaller magnitude than the patient EQ-5D-5L score improvement (12). This is because patient health improvement may be the result of health behaviour improvements which may also be generated in some of the patient's

household members through peer effects, and also the alleviated anxiety (317), distress and care burden in household members resulting from the patient's health improving.

5.6.2. Lifestyle (physical activity and smoking)

The IPAQ-short is a widely used measure that was used to measure the physical activity of the household members at baseline and follow-up (326). The short version of the IPAQ was used to make it less time-consuming and easier for respondents to complete, and was also the same version used to measure the physical activity of patients. The long IPAQ was tested in the feasibility study with patients, but was dropped in favour of the short IPAQ because participants found the long IPAQ too onerous to complete. The IPAQ-short estimates the weekly activities of respondents across 4 domains: time spent doing vigorous activities, moderate activities, walking and sitting down.

It was hypothesised that if patients increased their physical activity from the telecoaching intervention, some of their household members would also increase their physical activity as a result. This is because intervention patients were encouraged to recruit their family members to do physical activities together (321). Goal setting interventions may produce lasting behavioural changes by focusing on changing situations in which the behaviour manifests including within social settings and relationships (327). Previous literature of successful exercise interventions have found no evidence of a peer effect of physical activity improvement on the wife or the family member of the participant especially compared with dietary intervention trials (328-330), unless the intervention involves getting participants to

actively recruit family members to support them in their increased physical activity (146). Household members who increase their physical activity from intervention spillover, may as a result experience better health and well-being (for example in terms of improved fitness, weight control and circulation, sleep and mental health) (331, 332).

The estimates across three of IPAQ domains (vigorous activities, moderate activities and walking) were used to calculate MET (metabolic equivalent) minutes per week. One MET minute is equivalent to the metabolic expenditure when sitting quietly for one minute (333). The full process by which these MET minutes were calculated is documented in the IPAQ scoring manual (334). These MET minutes provided a continuous measure of the physical activity of household members.

Household members' smoking behaviours were measured at baseline and follow-up, in terms of how many cigarettes/cigars they smoked per day, whether they presently wanted to give up smoking and whether they had attempted to give up smoking over the preceding 12 months. Household members who reduce their smoking as a result of intervention spillover, may reduce the risk of them contracting lung diseases, such as lung cancer and COPD. A high prevalence of smokers among COPD partners (33%) has been documented in a previous study from the Netherlands (335). It was expected that if patients reduced their smoking due to the telecoaching intervention, some of their household members who are smokers would also reduce their smoking as a result. This is due to the positive peer effects associated with smoking cessation which have been observed in the empirical literature, particularly in spousal relationships (119, 121).

5.6.3. Stress/happiness

The perceived stress scale (PSS) is a 4-item scale used to measure the stress of respondents (336). The telecoaching intervention may improve patients' health and consequently alleviate the stress of household members, leading to improvements in household members' physical and mental health over time (30, 42). Each of these 4 items is measured using a Likert scale. These Likert scales measure how often respondents felt 'in control', 'confident', 'things were going well' and 'in difficulty' over the past month. In employing the Likert technique, the PSS changes the polarity of the middle two questions (Q2 and Q3) of the 4-item scale. This means that a response of '1' for questions 1 and 4 indicates no stress, and a response of 1 for questions 2 and 3 conversely indicates the highest levels of stress. This method of changing polarities of questions is designed to minimise pattern answering (337). However respondents who do not notice this change in the direction of questioning may respond in the opposite way to the attitude they really feel (338). Nevertheless the overall reliability and validity of the 4-item PSS for measuring stress of people experiencing adverse health is established (336, 339). It was predicted that some household members would experience less stress from being alleviated of emotional and care burden, if patients' health improved from the telecoaching intervention (6, 14).

A single-item happiness scale was used to measure 'how happy one feels at the moment'. The happiness scale that was used was taken as one segment of the CarerQoL instrument (340). The measure is a Likert scale measuring happiness from 1 to 10. The happiness scale provides a broader measure beyond health of an individual's wellbeing, and may be sensitive to various health and non-health spillovers that household members experience (340). It was

hypothesised that household members' happiness would increase if the patient's health improved due to the telecoaching intervention as spillovers are generally experienced as negative emotionally (14). However, one study observed that individuals who provided low levels of informal care were on average happier than matched non-carers, which may be applicable to some household members in the family impact study (341). Furthermore some authors have proposed that a happiness scale could be used as a measure of 'experienced utility', alternative to a health utility measure in economic evaluations (342).

5.6.4. Costs

Participants were asked about their health care use over the past 3 months in terms of GP, nurse and pharmacist visits. This was done in order to capture changes in household members' health care usage as a result of the telecoaching intervention, for inclusion in the cost-utility analysis of Chapter 7. Changes in health care use of household members resulting from intervention spillover, are accountable on the cost side of an economic evaluation (158). Household members whose health improves as a result of spillover of the intervention may require fewer health care visits. However, patients and household members whose learning about their health improves from the telecoaching intervention, may become more proactive in making visits to their health care practitioners (321).

5.6.5. Qualitative free text question

In addition to the outcome measures, two qualitative free text questions were used. In the baseline questionnaire household members were asked what the 'biggest impact the patient's COPD has had on your life'. In the follow-up questionnaire, household members were asked 'how the patient's health care for COPD has affected your life'. Only the latter question may capture the impact of the intervention (or usual care) on household members.

O'Cathain et al classify the rationales for using qualitative free text responses in surveys into 4 types: extension, expansion, general and substitution (343). Extension refers to the "other, please specify" option of a question to ensure that all categories are covered. Expansion involves asking respondents to elaborate on their response to a closed ended question, for example respondents may be asked: "if yes, why?". General involves asking respondents to describe their experience in relation to the overall topic of the survey. Substitution refers to using a free-text question as a substitute for a closed-ended question.

The purpose of the qualitative questions here were both used a 'general' elicitation of the household members' experiences of COPD and the telephone coaching intervention, as well as a 'substitution' to a closed-ended question. This substitution of a closed-ended to an open-ended question was preferred because an open-ended question may produce more in-depth and rich responses to the questions. For example, a closed-ended approach may ask household members to tick a box if physical activity was the biggest impact of COPD/COPD health care, whereas an open-ended approach may produce a more detailed and rich response on what types of physical activity were affected, and whether their physical activity decreased or increased.

The qualitative responses also serve another purpose in putting findings into context. From the responses, it can be assessed whether the spillovers experienced by household members from COPD and the COPD self-management intervention are primarily health related, or relate to other areas of a household member's life. In a literature search, no existing qualitative investigations were found that look specifically at the family impact of mild symptoms of COPD, although previous studies have looked at the family impact of severe COPD, or COPD more generally (313, 314).

5.7. Data processing

Data were entered onto an Excel spreadsheet and checked for typographical errors by assessing frequency tables. Issues related to data coding are detailed below.

5.7.1. Data coding

IPAQ

As well as the calculation of MET minutes (continuous scale), IPAQ responses were converted to a reduced number of discrete values, to establish whether a respondent was reporting low levels, moderate levels or high levels of weekly physical activity. This involved using information on the frequency and amounts of vigorous, moderate and walking activities that respondents undertook over a week using the process taken directly from the IPAQ scoring manual (334), described as follows:

Respondents were classed as 'highly' physically active if they accumulated at least 3000 MET minutes from more than 6 sessions per week of any physical activity, or if they undertook vigorous activity for at least 3 days and accumulated at least 1500 MET-minutes per week. Respondents were classed as 'moderately' physically active if they were not 'highly' physically active and either did in a week: i) at least 3 days of vigorous activity of at least 20 minutes per day, ii) at least 5 days of moderate/walking activities of at least 30 minutes per day, or iii) at least 5 days of any physical activities and accumulated at least 600 MET minutes in a week from these activities. Finally, respondents were classed as 'low' in their level of physical activity if they did not meet the criteria for being either 'moderately' or 'highly' physically active.

The IPAQ-short manual provides recommendations for truncating implausible answers, and these were adhered to in this analysis (334). Respondents who stated that they participated on average in more than 3 hours of either vigorous, moderate, or walking activity per day, were capped at a maximum of 3 hours of that activity. Also, responses of participation in an activity for more than 7 days a week, or sitting down for more than 16 hours a day, were considered implausible and therefore truncated at these limits.

EQ-5D-5L

EQ-5D-5L scores were calculated using the UK value sets that were published in January 2016, based on a hybrid model combining time trade-off and discrete choice experiment elicitations obtained from interviews with 996 members of the English general public (249).

This generates a range of health-related quality of life scores ranging from 1 (full health on all domains) down to -0.281 (worst health score on all domains).

5.7.2. Missing data

A complete case analysis was used for the analysis. Assumptions were made for the question on resource use (GP, pharmacist and nurse visits), in order to deal with missing data. If respondents declared that they had visited a nurse, GP or pharmacist but left blank responses to the other providers, it was assumed they had not visited the other providers at all. Also, if respondents left blank responses to all three providers but provided responses to subsequent questions in the survey about their general health, it was assumed they had read the question, but had no information to record, and had therefore made zero visits to all three providers. All other blank responses to the question on resource use were recorded as missing data.

5.8. Analysis plan

The main analysis carried out to evaluate outcomes of household members in the PSM-COPD trial were between-groups analyses using the intention-to-treat principle to measure causal effects of the telecoaching intervention. These analyses compare outcomes at follow-up adjusted for baseline between the intervention and control groups. A full specification of

the quantitative and qualitative investigations carried out for the family impact study is described in this section, and summarised in Table 5.1.

Table 5.1. Summary of the methods used to assess the health spillovers of the COPD telephone coaching intervention

Method	Objective
Descriptive analysis	To analyse the baseline characteristics of the household members and their relatives with COPD
Between groups analysis	The core analysis that was used for the study, for evaluating household members' primary and secondary outcomes from the COPD telephone coaching intervention.
Cross-sectional analysis	Used to provide a 'second-best' estimate of the health spillover effect, using household members' and patients' EQ-5D-5L scores at baseline only.
Longitudinal analysis	Used to assess concordance between patients and household members in their smoking and physical activity change
Qualitative analysis	Used to assess how the household members perceived COPD and the telephone coaching intervention had affected them

5.8.1. Descriptive analysis

Descriptive analyses were carried out to summarize demographic, clinical and health behaviour characteristics of household members (and for context the patients). Means and standard deviations were reported for continuous variables, or medians and interquartile ranges if the variable was highly positively or negatively skewed. Frequency distributions were reported for categorical variables.

First, baseline data were summarised to compare clinical, demographic and health behaviour characteristics between the intervention and the control groups for the household members participating in the family impact study, and their related patients. This provides a way of subjectively (but not statistically) assessing whether baseline

characteristics were balanced between trial arms. Statistical comparisons of these differences are discouraged in CONSORT guidelines for the reporting of randomised trials due to problems of multiple hypothesis testing producing type 1 and type 2 errors (344).

Second, patient baseline clinical, demographic and health behaviour characteristics were assessed for the patients who had at least one of their adult household members participating in the Family Impact Study (FIS), the patients who lived alone, and the patients reporting the presence of adult household members that did not participate in the FIS. This was done to subjectively assess potential selection bias into the FIS. For example, one potential source of selection bias is that patients with poorer health may have been less likely to enrol their household members into the FIS.

Third, baseline demographic, clinical and health behaviour characteristics for household members who responded to the baseline questionnaire were subjectively compared with the subset of household members who also responded to the follow-up questionnaire, in compliance with guidelines for reporting attrition in randomised trials (345). This was done to assess whether the household members who were included in the between-groups analysis described in section 5.8.2 (as they were not lost to follow-up), were similar in demographic and clinical characteristics to the overall sample of household members obtained at baseline but some of whom were lost to follow-up. Assessed differences in these characteristics may suggest that household member loss to follow-up may be non-random (e.g. household members who are more ill at baseline may be less likely to respond at follow-up).

5.8.2. Between-groups analysis

Between-groups analyses were carried out using the intention-to-treat principle to assess the relative impact of telecoaching intervention compared with usual care on household member primary outcome (EQ-5D-5L scores) and secondary outcomes (stress, happiness, smoking and physical activity). Intention-to-treat analysis means that household members were analysed strictly according to the randomisation group assigned to the related patient at baseline, even if the patient did not subsequently receive the intervention they were initially randomised to get (346). These analyses directly address the two research questions for this study, and the methodology used to estimate treatment effect is the 'gold standard' procedure used for assessing outcomes in randomised controlled trials (275), including in assessing health spillover outcomes (221, 229).

Analysis of covariance (ANCOVA) was used to assess the impact of the telephone coaching on household members' outcomes (347). In the unadjusted and adjusted between-groups analyses each follow-up outcome score was regressed using OLS against the baseline outcome score and a binary variable denoting whether the household member was in the telecoaching or the usual care group. The coefficient of the binary variable denotes the treatment effect, and the corresponding p value measures the degree to which this could be a chance finding. In the adjusted analyses, household member age and gender were also included as pre-specified covariates in the linear regression and CONSORT guidelines recommend the pre-specification of covariates (344). Normality of the residuals is an assumption that needs to be satisfied for linear regression models (348), and was checked for all the models that were run. If the assumption was not satisfied, a transformation of the

dependent variable in the model was made only if it substantially improved the normality of the residuals; otherwise no transformation was made. A range of different transformations of the dependent variable were considered using the 'ladder' command in Stata.

A sensitivity analysis was performed where outliers were identified for baseline and follow-up outcomes (values that were more than 1.5 interquartile ranges above the upper quartile or below the lower quartile for the outcome) (304), and the outlier was subjectively considered to be implausible, by removal of the outliers before re-running the specified regression from the base-case analysis.

Mean changes in primary and secondary outcome scores (and in percentage of individuals reporting problems for each of the individual items of the multi-attribute outcomes) between baseline and follow-up were also presented for the intervention and usual care groups. The statistical significance of treatment effects in analysis was assessed in the reporting of p values and 95% confidence intervals. Results for household member outcomes were assessed in the context of the main trial analysis of patient outcomes in the PSM-COPD trial (including patient health status, quality of life, behaviours and mental health). For example, a significant change in a patient primary or secondary outcome in the main trial may explain an observed spillover effect on household members.

For the secondary outcome of smoking behaviours, if the number of household members who were smokers in the sample was too small (less than 25), a regression-based between-groups analysis was not used due to insufficient power. Instead, the mean change in the number of cigarettes consumed from baseline to follow-up was compared between the smokers in the intervention and control groups.

Sensitivity analysis was carried out on between-groups analyses for the spouses of patients only for the primary outcome (EQ-5D-5L), to assess the health spillover effect on the subset of household members who were considered to be the most likely primary carers of the patients (314). This is also consistent with previous approaches for estimating and including health spillovers in trial-based economic evaluations, which only include one family member/carer of the patient in analysis (221, 223). Including health spillovers of one household member only may be the most feasible way of enabling a generalised approach for incorporating health spillovers into economic evaluation, so that only a single adjustment to the decision threshold is needed (78, 116).

5.8.3. Cross-sectional analysis (using household member baseline data)

An alternative approach to a between-groups analysis to estimate health spillovers on household members was also explored as a 'second-best' approach, to address research question 1. This approach was based on a regression model using cross-sectional data developed by Al-Janabi et al (13), and previously used to inform two economic evaluations (20, 226). Specifically, univariate and multivariate linear regressions were run to regress baseline household member EQ-5D-5L score against baseline patient EQ-5D-5L score. The coefficient of the patient EQ-5D-5L represents the health spillover effect per unit change in the patient's EQ-5D-5L score. This coefficient can be multiplied by the estimated change in patient EQ-5D-5L score from the telecoaching intervention in the main trial analysis of patient data, to calculate an estimate of the health spillover on the family member EQ-5D-5L score resulting from the change in patients' health.

As with the between-groups analysis, the same procedure was used to identify and test a transformed dependent variable (household member EQ-5D-5L score), to assess whether the transformed regression substantially improved the normality of residuals compared with the untransformed regression; if so then the transformed regression model was used in analysis. In the multivariate regression, control variables were added for household member sex and age, patient sex and age, index of multiple deprivation for household according to the postcode, whether other adults were sharing the house, and whether children were sharing the house. These variables could 'confound' the true causal impact of patient health on family member health if the variables were not included in the regression (13). This is because these variables may determine the household members' EQ-5D-5L scores, and also be associated with the patients' EQ-5D-5L scores.

The disadvantage of this cross-sectional approach compared with the between-groups analysis using the intention-to-treat principle is that it does not use household member follow-up data from the RCT to estimate the spillover effect of the intervention. Another disadvantage from this approach is that there may be a degree of reverse causality in which the household members' own health conditions produce a spillover on the patient's health, particularly if the health of the family members is on average similar to (or worse) than the health of the related patient. The substantial presence of reverse causality would mean that much of the estimated effect is attributable to the family members' health impairment producing a health spillover on the patients rather than attributable to the patient's COPD. Christakis and Fowler (2013) recommend addressing reverse causality to isolate causal health spillover effects, but the approach that the authors specify for doing this require multiple follow-up health measurements that are not available in this study (349).

However if spillover data has not been collected prospectively, or there is a substantial loss to follow-up in household member data, such an approach using household member cross-sectional data at baseline only may be the only option. Another advantage of the cross-sectional regression analysis over the between-groups analysis is that it may better capture the 'lag period' over which health spillovers are generated from COPD prior to the commencement of the trial, whereas the between-groups analysis over a limited 12 month period may fail to capture this 'lag' in which patient health changes take time in generating health spillovers on household members (325). Therefore, the cross-sectional analysis for estimating health spillovers was used in this study as a sensitivity analysis.

5.8.4. Longitudinal analysis of concordant health behaviour changes

Observational analyses were conducted for the pooled intervention and control samples. This was done by running a linear regression of change in household members' physical activity and smoking over the trial period (in terms of self-reported MET minutes and number of cigarettes consumed), against patients' change in the corresponding health behaviour. Scatter plots were produced of household members' and patients' health behaviour change scores with linear regression lines superimposed onto the graphs to visually assess for trend. The objective was to assess the extent to which there was concordance in health behaviour change between patients and their household members.

A comparison of the frequency and proportion of household members who improved their health behaviours over the trial period (by increasing their physical activity or reducing their smoking) was also made. This was done by comparing the 'improved' household members of

patients who also improved the same health behaviour, with the 'improved' household members of patients who did not change or worsened the same health behaviour over the trial period. The Chi-squared test was carried out to assess whether the proportions of household members being compared were statistically different. Changes in amounts of cigarette consumption were assessed qualitatively (rather than by calculating summary statistics) if there were fewer than 10 household member-patient dyads where both individuals were smokers. Outliers for baseline and follow-up outcomes identified according to the ±1.5 interquartile range rule (304), that were also considered as implausible values, were removed prior to all longitudinal analyses that were carried out.

One of the main mechanisms for the telecoaching intervention generating health spillovers hypothesised prior to analysis was through the concordance of patient physical activity change with other household members. In the telephone consultations and advice leaflets, patients were encouraged to recruit other household members to participate in physical activities together in order to motivate the patient (321). Therefore, analysis was rerun to explore physical activity concordance in the intervention group only.

5.8.5. Qualitative analysis

A simple thematic analysis of the free text responses at the end of the questionnaire was performed. In the question, participants were asked to specify 'the single biggest way' in which their lives have been impacted by COPD. The process for analysis was based on guidance from the literature for the descriptive thematic analysis of qualitative free text

responses, in which important dimensions are detected, responses are categorised under each dimension and the dimensions are classified into higher levels (343, 350).

The approach to analysis was as follows. All the responses were read, and the themes that emerged on the main impacts of COPD and the causes of these impacts were mapped out in a theme-based framework. Single or multiple themes were assigned to all qualitative responses. Some impacts were only mentioned by a small number of respondents, so they were grouped into the category of 'other impacts' as they were not a prominent feature of the data. Responses were reorganised in a table according to the themes they fell under. A frequency table for how many responses were categorised under each theme was then produced. Responses were reread under each theme and an account of each theme was then produced (350), using the theme-based framework to structure the account.

5.9. Summary

Chapter 5 described the methods for data collection and analysis in a study investigating how a COPD telecoaching intervention impacts household members. This study aimed to estimate the effect of the intervention on household members' health status, mental health and health behaviours. The outcomes of household members of COPD patients in both trial arms were elicited at baseline and 12 months via a questionnaire. Chapter 6 presents the results and discussion of the quantitative and qualitative components of the study.

CHAPTER 6: AN INVESTIGATION OF THE IMPACTS OF A COPD TELECOACHING INTERVENTION ON THE HEALTH AND HEALTH BEHAVIOURS OF HOUSEHOLD MEMBERS: RESULTS

Chapter 5 described the methods of an investigation into how a COPD telecoaching intervention impacts household members' outcomes. Chapter 6 presents the results of the study. First, a descriptive analysis is presented, followed by the main analysis for the study comparing changes in household member outcomes between groups. Subsequently, the cross-sectional, longitudinal and qualitative analyses are presented, followed by a study discussion.

6.1. Summary of outcomes of PSM-COPD trial

Compared to usual care, the telephone coaching intervention was associated with non-significant improvements in patients' COPD quality of life (primary outcome), EQ-5D-5L scores and physical activity. Intervention patients were associated with improved EQ-5D-5L scores of 0.01 at 12 months, although this improvement was not statistically significant (p=0.4). There was a non-significant reduction in smoking cessation behaviour over 12 months in the intervention group.

6.2. Participant characteristics

Overall 577 patients were enrolled in the RCT, with 289 patients allocated to the intervention group, and 288 patients allocated to the usual care group. By the time ethical approval had been granted for the Family Impact Study (FIS), 129 patients had already been recruited into the PSM-COPD trial. These 129 patients were therefore not invited to participate in the FIS.

Out of the remaining 448 patients, 210 of the patients opted into the FIS at the baseline clinic assessment by agreeing to pass on questionnaires to 222 household members. 199 patients agreed to pass on questionnaires to one household member, ten patients to two household members, and one patient to three household members. 149 patients lived alone or without another adult household member, and 89 patients either did not consent to participate in FIS or were not asked by the study nurse to participate.

Household members' entry into the family impact study is summarized in Figure 6.1:

Figure 6.1: Flow chart of household members' participation in the family impact study

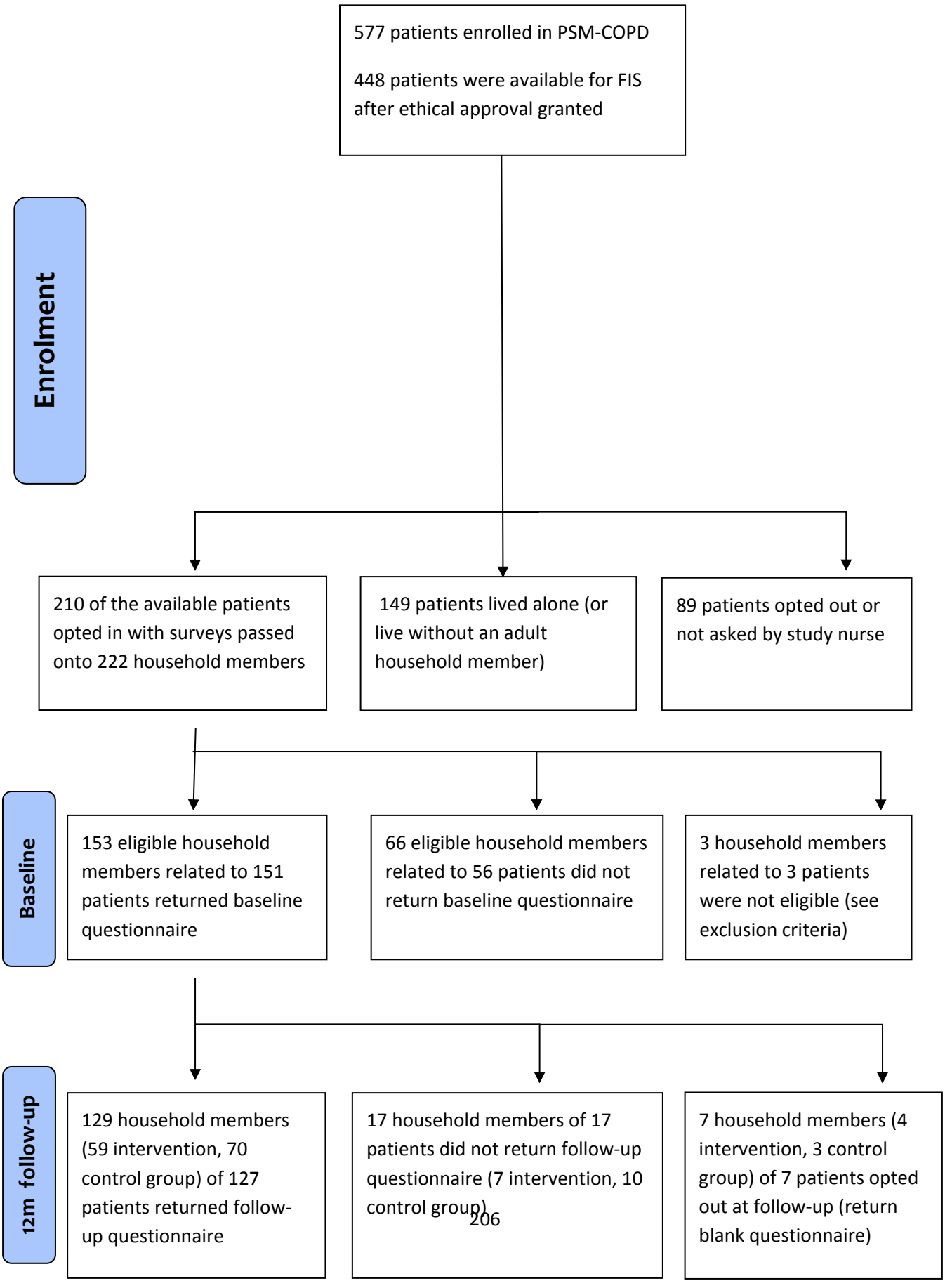


Table 6.1 reports baseline characteristics for household members and their related patients in the intervention and control groups. It can be seen that household members' mean EQ-5D-5L scores were slightly worse than the patients' mean EQ-5D-5L scores, although on average both patient and household member EQ-5D-5L scores were high. The average age of household members was 65.7 years, 73% of household members were female, 93% of household members were the spouse of the patient and their average IMD score was 18.0 (which is in third quintile group of deprivation in the population). Household members in the control group exhibited poorer health behaviours (smoking and exercise) than the intervention group.

The most common health conditions reported by household members in the study as having previous or ongoing experiences of were high blood pressure (44%), osteoarthritis (18%) and depression (18%). The most common comorbid health conditions reported in the overall COPD patient sample were high blood pressure (44%), asthma (34%), osteoarthritis (17%) and depression (17%).

Table 6.1: Descriptive statistics for intervention and control samples in FIS (baseline data)

Characteristic	Intervention	Control
Household member (n=153)	**(N=70)**	**(N=83)**
Female (n, %)	52 (74.2)	58 (70.7)
Age (years, mean (SD))	67.6 (9.63)	64.2 (11.9)
Relationship to patient (spouse, n (%))	66 (94.3)	76 (92.7)
IMD (mean (SD))	17.1 (12.1)	19.0 (15.5)
EQ-5D-5L, (mean (SD))	0.85 (0.22)	0.85 (0.18)
Happiness (mean (SD))	7.5 (1.9)	7.9 (1.5)
Perceived Stress Scale (mean (SD))	4.5 (3.1)	4.7 (3.0)
Household size (two-person, n (%))	59 (85.5)	66 (84.6)
Patient (n=151)		
Female (n, %)	20 (28.9)	28 (34.2)
Age (years, mean (SD))	71.3 (6.9)	69.3 (8.28)
SGRQ-C score (mean (SD))	26.6 (13.6)	30.6 (16.1)
EQ-5D-5L (mean (SD))	0.90 (0.13)	0.91 (0.10)
MRC Scale 1 n (%)	22 (31.9)	19 (23.5)
2 n (%)	47 (68.1)	59 (72.8)
Household member health behaviours		
Smokers (n (%))	5 (7.3)	16 (19.1)
Physical activity- Low (n (%))	16 (29.6)	19 (31.1)
Moderate (n (%))	15 (27.8)	25 (40.1)
High (n (%))	23 (42.6)	17 (27.9)

*SGRQ-C is a 0 to 100 disease-specific measure of COPD quality of life. Score of 0 indicates full COPD QoL

*MRC Scale is a measure of patients' level of breathlessness (1 indicates the patient only gets breathless with strenuous exercise; 2 indicates the patient gets short of breath when hurrying on level ground or walking up a slight hill

*IMD is the index of multiple deprivation for a postcode. Score of <9 indicates the postcode is within the least deprived quintile in the UK, score of >34 indicates it is within the most deprived quintile.

Table 6.2 reports baseline characteristics for all COPD PSM participants, i.e. including those who did not participate in the family impact study, and who lived alone. In table 6.2, it can be seen that demographic and clinical characteristics are broadly similar across the three groups of patients. However it was observed that a greater proportion of the patients who lived alone were female and reported worse EQ-5D-5L scores. Patients who lived alone on average reported lower physical activity of 462 MET minutes/week compared to the patients who did not live alone, and were almost twice as likely to smoke compared to patients in the FIS. The risk of pathology in terms of anxiety and depression for participating and non-participating patients in the FIS, as measured with the HADS was low. On the MRC dyspnoea scale, 28% of patients reported a score of 1 to indicate that they were untroubled by breathlessness apart from when undertaking strenuous exercise.

Table 6.2: Descriptive statistics at baseline for patients enrolled in the PSM-COPD trial

Baseline data	Patients in FIS (n=151)	Patients not in FIS but live with other adults (n=252)	Patients who live alone (n=149)
Demographic characteristics			
Sex (female), n (%)	48 (31.8)	83 (32.9)	66 (44.3)
Age (years, mean (SD))	70.2 (7.71)	69.7 (8.67)	72.4 (8.27)
IMD	18.0 (13.8)	20.1 (14.1)	22.2 (14.9)
Ethnicity (white) n (%)	141 (93.4)	243 (96.4)	137 (92.0)
Currently married/civil partnership n (%)	139 (92.1)	217 (86.1)	4 (2.7)
Household size (two-person, n (%))	124 (85.6)	193 (78.8)	0 (0.0)
Clinical characteristics			
MET minutes per week (median, interquartile range)	2205.5 (819 to 4536)	2445 (742 to 4782)	1893 (594 to 4158)
HADS Anxiety score	3.95 (3.36)	4.09 (3.57)	4.04 (4.05)
Depression score (mean (SD))	3.13 (2.53)	2.73 (2.42)	3.11 (3.30)
EQ-5D-5L (mean (SD))	0.90 (0.12)	0.91 (0.11)	0.87 (0.15)
MRC Scale 1 n (%)	41 (27.3)	64 (29.2)	38 (27.9)
2 n (%)	106 (70.1)	153 (69.8)	93 (68.4)
SGRQ-C (mean (SD))	28.8 (15.1)	27.9 (13.6)	29.3 (15.4)
Current smokers n (%)	24 (15.9)	54 (21.4)	44 (29.5)

*HADS is the Hospital Anxiety and Depression Scale ranging from 0 to 21 (higher score indicates greater symptoms of anxiety or depression)

*MET minutes is a measure of participants' metabolic equivalents (i.e. their energy expenditure)

*IMD is the index of multiple deprivation for a postcode. Score of <9 indicates the postcode is within the least deprived quintile in the UK, score of >34 indicates the most deprived quintile.

Table 6.3 reports household member characteristics for the full sample of household members recruited at baseline into the family impact study, the sub-sample of household members who responded to the survey at follow-up, and the sub-sample of household members who did not respond to the survey at follow-up. The statistics in table 6.3 suggest the characteristics of the household members who were lost to follow-up are broadly similar compared with those who weren't. However there is some indication that household members lost to follow-up reported worse EQ-5D-5L scores at baseline.

Table 6.3: Baseline characteristics for full household member sample, sub-sample of household members who responded at follow-up and sub-sample lost to follow-up

Household member characteristic	Full sample at baseline	Sub-sample at follow-up	Lost to follow-up
Demographic characteristics	**(n=153)**	**(n=129)**	**(n=24)**
Female (n, %)	110 (72.4)	94 (72.9)	16 (69.5)
Age (years, mean (SD))	65.7 (11.0)	66 (10.1)	64.2 (15.5)
IMD	17.9 (13.7)	17.6 (13.1)	19.6 (16.8)
Relationship to patient (spouse, n (%))	142 (93.4)	122 (94.6)	20 (87.0)
EQ-5D-5L, (n, mean (SD))	0.85 (0.20)	0.86 (0.19)	0.80 (0.22)
Household size (two-person, n (%))	125 (85.0)	106 (84.8)	19 (86.1)
Health behaviours			
Smoker (n, (%))	20 (13.3)	16 (12.6)	4 (17.4)
Physical activity- Low (n (%))	35 (30.5)	29 (30.5)	6 (30.0)
- Moderate (n (%))	40 (34.8)	32 (33.7)	8 (40.0)
- High (n (%))	40 (34.8)	34 (35.8)	6 (30.0)

*IMD is the index of multiple deprivation for a postcode. Score of <9 indicates the postcode is within the least deprived quintile in the UK, score of >34 indicates the most deprived quintile.

6.3. Between groups analysis

6.3.1. Primary outcome (EQ-5D-5L)

The primary aim of the study is addressed in this section, which is to measure the impact of a patient health intervention on household members' health status scores. Here, it is addressed whether the telephone coaching intervention produces health spillovers (i.e. an increase) in household members' EQ-5D-5L scores. Table 6.4 reports the estimate of the health spillover effect of the telecoaching intervention on household members. Mean household members' EQ-5D-5L scores decreased by 0.02 in the control group, and by 0.03 in the intervention group. The household members' EQ-5D-5L follow-up score adjusted for baseline score, age and gender was slightly lower (-0.007) in the intervention group, although this difference was not statistically significant.

Table 6.4. Comparison of change in EQ-5D-5L scores between intervention and control for all household members and spousal household members from baseline to 12 months

	Mean EQ-5D-5L change (sd)		**Between-groups analysis (95% CI)**	
	Control n=58	Intervention n=56	Unadjusted* n=114	Adjusted* n=114
All household members EQ-5D-5L n=114	-0.019 (0.14)	-0.029 (0.10)	-0.009 (-0.05 to 0.04) p=0.69	-0.007 (-0.05 to 0.04) p=0.75
Household members who are spouses EQ-5D-5L n=107	-0.019 (0.14)	-0.029 (0.10)	-0.007 (-0.05 to 0.04) p=0.75	-0.005 (-0.05 to 0.04) p=0.82

* Unadjusted analysis assesses the intervention effect on follow-up EQ-5D-5L, adjusted for baseline EQ-5D-5L. Adjusted analysis additionally adjusts for age and gender.

Table 6.5 details the percentage of household members reporting problems for individual items of the EQ-5D-5L, for the household members who completed the EQ-5D-5L at baseline and 12 months. The biggest difference between groups in changes in problems reported for EQ-5D-5L items were for the items 'usual activities' and 'pain/discomfort'. There was a large increase in the percentage of household members in the intervention group reporting problems for usual activities (10.7%) and pain/discomfort (14.3%), whereas there was little change for these items in the control group.

Table 6.5: Percentage of household members reporting problems for EQ-5D-5L domains at baseline and 12 months

Household member	Control (n=58)			Intervention (n=56)		
EQ-5D-5L domains	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference
Anxiety problems (%)	36.2	44.8	8.6	28.6	41.1	12.5
Self-care problems (%)	10.4	10.3	-0.1	16.1	12.5	-3.6
Usual activities problems (%)	29.3	27.6	-1.7	21.4	32.1	10.7
Mobility problems (%)	32.8	36.2	3.4	35.7	41.1	5.4
Pain/discomfort problems (%)	63.8	67.3	3.5	55.4	69.7	14.3

*Item response scores of 2,3,4 or 5 indicated the presence of a problem

6.3.2. Physical activity

Table 6.6 reports the analysis of the impact of the telephone coaching intervention on the physical activity outcome of household members of people with COPD. Intervention household members reported on average becoming more sedentary with 21 fewer MET minutes per day and 34 more minutes per day sitting down (after outliers were removed). Even after outliers were removed, large standard deviations were reported for mean changes in physical activity over time. Follow-up MET minutes were not statistically significantly different between the control and intervention groups in the unadjusted and adjusted analysis.

Table 6.6. Comparison of change in physical activity between intervention and control for household members from baseline to 12 months

	Mean change (sd)		**Between-groups analysis (95% CI)**	
	Control n=44	Intervention n=38	Unadjusted* n=82	Adjusted* n=82
Physical activity MET minutes per week	457.3 (2024.3)	-418.7 (2389.8)	-289.9 (-1187.6 to 607.6) p=0.52	-331.9 (-1234.5 to 570.7) p=0.46
Physical activity (outliers removed) MET minutes per week	267.0 (1601.3)	50.7 (1632.2)	-118.1 (-824.3 to 588.1) p=0.74	-144.4 (-860.8 to 571.9) p=0.69
Sitting time (hours per day)	-0.30 (1.61)	0.008 (2.83)	0.56 (-0.31 to 1.42) p=0.21	0.57 (-0.31 to 1.46) p=0.199

* Unadjusted analysis assesses the intervention effect on follow-up METs, adjusted for baseline METs. Adjusted analysis additionally adjusts for age and gender

In the main trial analysis of *patients*, the intervention patients were associated with increased physical activity measured using the IPAQ questionnaire (an improvement of 410 METs), although this increase was not statistically significant (p=0.2).

6.3.3. Stress

Table 6.7 details the estimate of the spillover effect of the telecoaching intervention on household members' stress. Stress on average reduced very slightly for household members in the control group but increased in the intervention group. The PSS follow-up score was not statistically significantly different between the control and intervention groups in the unadjusted and adjusted analysis.

Table 6.7. Comparison of change in stress between intervention and control for all household members from baseline to 12 months

	Mean change (sd)		**Between-groups analysis (95% CI)**	
	Control n=68	Intervention n=57	Unadjusted n=125	Adjusted* n=125
All household members PSS	-0.19 (3.06)	0.51 (2.78)	0.73 (-0.16 to 1.62) p=0.11	0.69 (-0.19 to 1.57) p=0.12

*Assessment of intervention effect on follow-up PSS, adjusted for baseline PSS, age and gender

For the household members who completed the perceived stress scale (PSS) at baseline and 12 months, table 6.8 reports the percentage of household members who reported problems for each of the PSS items. Table 6.8 reports that the biggest difference between groups in changes in problems reported for perceived stress scale items, was for the item about 'whether things were going one's way'. For this item, there was a large reduction in the percentage of household members reporting problems for the control group but little change in the intervention group.

Table 6.8: Percentage of household members reporting problems for PSS domains at baseline and 12 months

Household member	**Control (n=68)**			**Intervention (n=57)**		
PSS domains	**Baseline**	**Follow-up**	**Difference**	**Baseline**	**Follow-up**	**Difference**
Problems in controlling important things in life (%)	63.2	57.4	-5.8	65.9	64.9	-1.0
Problems in feeling confident to handle life (%)	66.2	66.2	0	61.4	64.9	3.5
Problems in feeling that things were going own way (%)	82.3	75.0	-7.3	82.5	80.7	-1.8
Problems with difficulties piling up (%)	45.6	47.1	1.5	59.7	57.1	-2.6

*Item scores of 1,2,3,4 for the control and difficulty items, and item scores of 0,1,2,3 for the confidence and things going own way items, were used to define a 'problem'.

6.3.4. Happiness

Table 6.9 reports the estimate of the impact of the telephone coaching intervention on household members' happiness scores. There was a small average decline in happiness in the control group and a small average increase in the intervention group. In both the unadjusted and adjusted analyses, there was a non-significant increase in happiness of 0.22 associated with the intervention.

Table 6.9. Comparison of change in happiness between intervention and control for all household members from baseline to 12 months

	Mean change (sd)		**Between-groups analysis (95% CI)**	
	Control n=66	Intervention n=57	Unadjusted n=123	Adjusted* n=123
All household members happiness	-0.11 (1.24)	0.22 (1.41)	0.22 (-0.23 to 0.67) p=0.34	0.22 (-0.23 to 0.67) p=0.34

*Assessment of intervention effect on follow-up happiness, adjusted for baseline happiness, age and gender

**Happiness was measured on a Likert scale ranging from 1 to 10

6.3.5. Smoking

A descriptive assessment of household members' smoking behaviours was made rather than a between-groups analysis, due to fewer than 25 household members of people with COPD in the sample reported as being a smoker (n=21) (Table 6.10). There was negligible change in the average cigarette consumption during the trial period for the control group, but there was a decrease by an average of 2.6 cigarettes for the 5 smokers in the intervention group (table 6.10).

Table 6.10. Changes in household member smokers' cigarette consumption between baseline and 12 months in control and intervention arms

	Mean change (sd)	
	Control n=12	Intervention n=5
All household members cigarette consumption per day*	0.33 (6.78)	-2.60 (2.97)

*Four household members who smoked at baseline were lost to follow-up and were therefore not included in the analysis in Table 6.A

Table 6.11 reports household member smokers' quitting attempts during the study. Table 6.11 reports that 3 out of the 5 household member smokers in the intervention group tried unsuccessfully to quit smoking during the trial period. Also three low-level smokers at baseline in the control group successfully quit smoking during the trial period.

Table 6.11. Household member smokers' quitting attempts during PSM-COPD trial

Household member smoking behaviour	Smokers in control group (n=16)	Smokers in intervention group (n=5)
Loss to follow-up	4	0
Quit smoking during trial	3	0
Tried unsuccessfully to quit smoking during trial	2	3
Did not quit or try to quit smoking during trial	7	2

*3 household members (in control group) reported quitting smoking at 12 months follow-up, and all 3 of these household members had a low cigarette consumption rate at baseline (smoked fewer than 5 cigarettes a day).

In the main trial analysis of *patients*, 13% of smokers in the intervention group reported quitting smoking over the trial period, and 25% of smokers in the usual care group reported quitting. This difference was not statistically significant (p=0.1).

6.4. Cross-sectional analysis

Table 6.12 reports the results of the analyses that regress household members' baseline EQ-5D-5L scores (dependent variable) against patient baseline EQ-5D-5L scores. Both the univariable and multivariable analyses regressed the household member EQ-5D-5L scores against the patient EQ-5D-5L scores. The multivariable analysis adjusted for a range of control variables. In table 6.12, there is a small and positive association that is not statistically significant between patient EQ-5D-5L score and family member EQ-5D-5L score, in both the univariable and multivariable analyses. The control variables suggested that

household members who were from a less deprived area were statistically significantly more likely to report better health.

Table 6.12: Linear regression coefficients for household members' health status (n=139)

Independent variables	Univariable coefficients (p value)	Multivariable coefficients (p value)
Patient EQ-5D-5L score	0.06 (0.71)	0.04 (0.79)
IMD	-	-0.003* (0.04)
Adults sharing house	-	0.12 (0.22)
Children sharing house	-	-0.12 (0.41)
Household member age	-	-0.0002 (0.91)
Household member sex	-	0.11 (0.24)
Patient age	-	-0.0009 (0.77)
Patient sex	-	0.12 (0.17)
	R^2 = 0.001	R^2 = 0.07

*p<0.05, **p<0.01, ***p<0.001
IMD: index of multiple deprivation

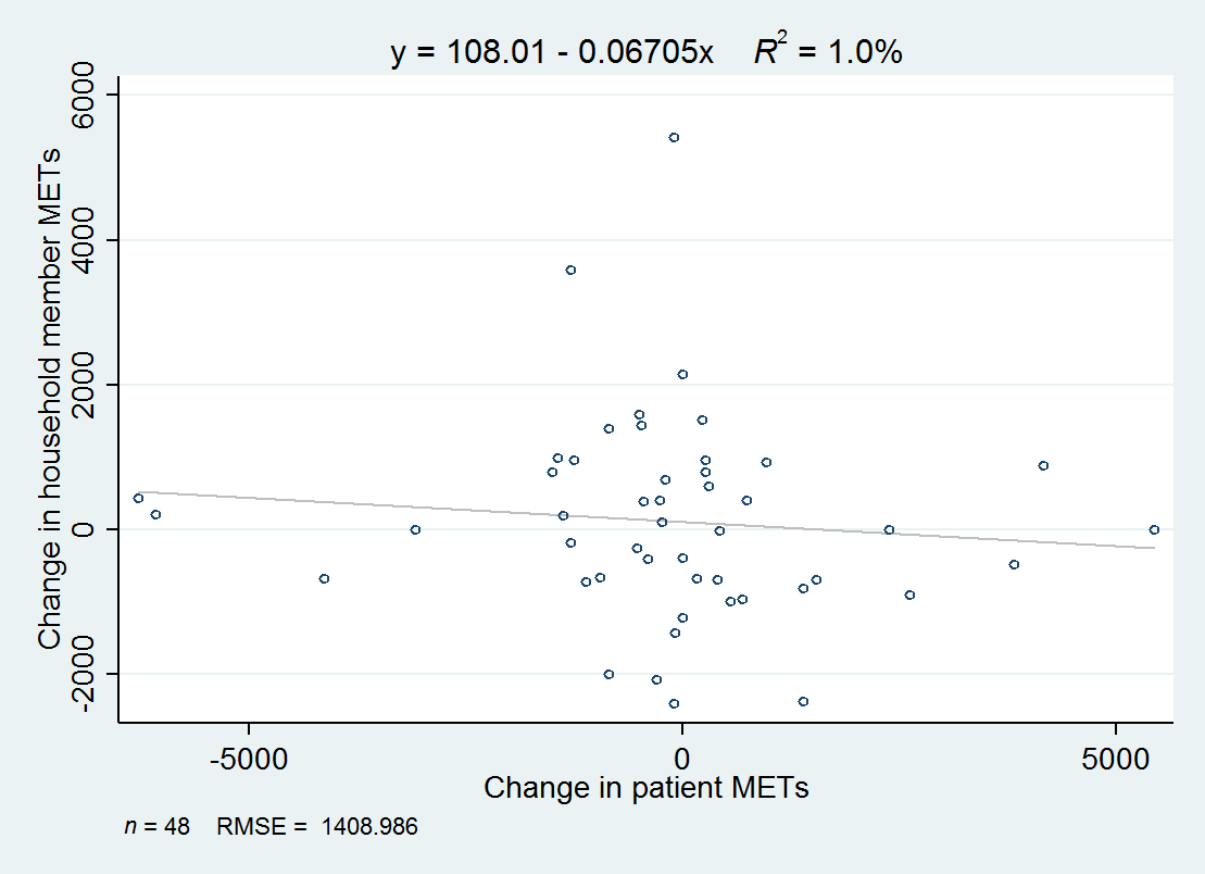
6.5. Longitudinal analysis

The objective of the longitudinal analysis was to assess whether there was concordance between patients and their household members in terms of physical activity and smoking change over the course of the trial.

6.5.1. Physical activity

There was complete physical activity data from 48 patient-household member dyads at baseline and 12 months, for which analysis was undertaken to explore concordance in MET minute changes between patients enrolled in the trial and their related household members. Figure 6.2 depicts a scatter diagram and a line of best fit (linear regression) to assess a relationship between the change in patients' physical activity and related household members' physical activity.

Figure 6.2: Change in physical activity of trial patients and change in related household members' physical activity over 12 months with a linear regression plot



The scattering of values does not visibly trend in either a positive or negative direction, although the linear regression line is slightly negative. The coefficient of the linear regression line (-0.067) is non-significant (p=0.50).

47% (9/19) of household members of patients who increased their physical activity also did so, and 59% (17/29) of household members of patients who did not increase their physical activity reported increasing their physical activity. The difference between these two proportions obtained using the Chi-squared test was not statistically significant (p=0.44). In the intervention group only, 45% (5/11) of household members of patients who increased their physical activity also did so, and 38% (5/13) of household members of patients who did

not increase their physical activity reported increasing their physical activity, which again was a non-significant difference (p=0.73).

6.5.2. Smoking

Only five household member smokers were related to patients who were also smokers at baseline, and with both members of the dyad providing complete data on smoking consumption at baseline and 12 months follow-up. Three of these household members reported reducing their smoking at 12 months follow-up; these household members were all related to patients whose smoking consumption stayed the same at 12 months. Two household members smoking consumption did not decrease at 12 months, and were both related to patients whose cigarette consumption decreased at 12 months.

6.6. Thematic analysis of qualitative free text responses

Household members were asked in the baseline questionnaire to provide a text answer on the 'single biggest way in which their lives had been impacted by COPD'. This analysis was carried out to provide a novel investigation of how mild COPD impacts household members. As documented in section 5.2, previous qualitative studies have found that severe COPD or COPD more generally, produces a variety of spillovers on family members. Quantitative studies have also documented a substantial informal care burden (100) and a high prevalence of anxiety (317) among COPD family members. Mild COPD is likely to produce less of an emotional or care burden on family members compared with moderate or severe

COPD. The variety of spillovers that mild COPD produces has yet to be explored in the qualitative literature until this study. 144 out of 153 household members provided a qualitative response to the question, and a simple thematic analysis was performed on these responses. The themes that emerged either directly related to an impact of COPD in an area of life, or related to a specific cause of the impact. The frequency of the themes that were mentioned are summarized in the table below:

Themes on COPD family impact	**Frequency**
No or little impact on household member	49
Potentially restricts walking or physical activity/leisure activity	50
Negative impact on emotional health	49
Impact on sleep	7
Impact of coughing	13
Other impacts	9

This thematic analysis is presented below with themes as headings and text and key quotes to illustrate the range of answers.

6.6.1. Impact on activities

Impact on leisure activities

Many household members mentioned that joint activities with their partner had been restricted by the patient's COPD; a range of activities were mentioned:

> *'Due to his inability to sleep comfortably r.e. breathing difficulties a general tiredness affects some usual household and social activities.'* (wife, 75 yrs)

> *'We go rock and roll dancing most weekends. It has affected our dancing because xxx gets breathless easily so rarely dances anymore.'* (wife, 63 yrs)

'Limiting type of holidays able to take and going out for the whole day.' (wife, 72 yrs)

'We do less socially, we do not have holidays etc.' (husband, 63 yrs)

'We do not have sex as he gets out of breath.' (wife, 59 yrs)

The slowness of general daily activities as a result of the patient's COPD may (or may not) restrict household members' usual activities.

'Often slows everything down and prevents me doing certain things' (husband, 64 yrs)

'Walking, shopping, sightseeing together is now slower and somewhat curtailed.' (husband, 68 yrs)

'I do not find the COPD stops us from doing many things - they might take longer but they usually get done.' (wife, 71 yrs)

Walking was frequently cited as an affected joint activity with COPD patient, which may (or may not) affect the household member's overall level of physical activity:

'We are unable to go on long walks together with the dog'. (wife, 62 yrs)

'We used to go for long walks in the countryside but my husband's condition now prevents us from doing this anymore (wife, 66 yrs)

'When we go out walking in the countryside my wife walks much slower than I do. This means I cannot walk at my natural speed and this is frustrating as I don't feel that I am getting the most benefit from the exercise.' (husband, 68 yrs)

Impact on care activities

Some household members mentioned that they had to take over household tasks that the patient could no longer do (which may have also affected their physical activity levels).

'One third of free time taken in support such as cooking, cleaning, house maintenance etc. above what would expect to share as a partner.' (husband, 63 yrs)

'Having to do more manual work, e.g. gardening, decorating, shopping, driving.' (wife, 71 yrs)

In one situation, the wife of the COPD patient finds taking over domestic activities to be physically straining rather than beneficial to her physical health. This is because the wife is experiencing health problems and mobility issues of her own:

'As my husband has difficulty walking distances I have to do the shopping on my own most of the time. I do have to use a mobility scooter and can walk short distances (around shops) with the aid of a walking stick. This causes me some considerable pain and cannot do this 2 days running.' (wife, 56 yrs)

When patients had exacerbations, care provision on household members may have intensified, as described by one respondent:

'A cold will start weeks of problems, from being unable to breath to panic attacks and generally not able to look after herself' (daughter, 58 yrs)

Some household members mentioned doing active care tasks for the patients:

'Having to make lots of trips to the GP'. (wife, 66 yrs)

'Reminding X (the patient) to take his tablets and sprays'. (wife, 71 yrs)

6.6.2. Impacts on emotional health

Emotional impact of lifestyle change

As described in the previous section, many household members reported lifestyle changes from the patients' COPD. Some household members explicitly mentioned the resulting emotional impact of these lifestyle changes.

'We used to go on 5 mile walks at least once a week but husband is now unable to do this and is very slow at walking. I really miss this.' (wife, 70 yrs)

'It is now not really feasible to think of going away on holiday expect in limited conditions and involving minimal activity, which is quite restrictive for me.' (husband, 52 yrs)

'In general everything is done at a slow pace which can sometimes be very frustrating.' (wife, 68 yrs)

Worry and concern for patient

Negative impacts to the household members' emotional health- namely worry, concern, anxiety and fear- were identified as the main impact by many of the household members. The reason provided for these effects varied; one household member describes a range of causes:

'Fear ! Being frightened that xxxx would suddenly become very unwell. Worried that xxx is frightened about his medical issues. Afraid to leave xxx alone for any length of time.' (wife, 62 yrs)

For some household members of patients with milder COPD, it appeared their worry/concern stemmed from their fears that the patient's COPD will get worse in the future leading to a deterioration of health and early death, as described by one household member:

'…concerned about the incurable nature of the condition and the potential for deterioration over time'. (wife, 68 yrs)

'concern that his lifespan might be affected although he has not had too many problems lately'. (wife, 74 yrs)

'My mother had severe COPD and was on oxygen and in a wheelchair. She passed away at the age of 60. I am very scared that my partner will also end up this way'. (wife, 37 yrs)

For several household members of the patients with more moderate symptoms of the disease, these fears were already being realised, resulting in anxiety from bad coughs:

'Dismay at the discomfort she suffers when she has a bout of coughing'. (husband, 65 yrs)

'I become anxious and distressed when my husband is coughing up large quantities of phlegm'. (wife, 63 yrs)

'I have found his coughing is really loud, and it really upsets me'. (wife, 58 yrs)

Household member anxiety was also mentioned as being caused by chest infections resulting from cold and flu virus especially likely to occur during winter, causing potentially weeks of patient suffering:

'It's a constant worry especially in the winter with colds and flu about' (wife, 64 yrs)

'I am concerned about his difficulty when he has a cold' (wife, 62 yrs)

'A cold will start weeks of problems' (daughter, 58 yrs)

Some household members mentioned that leaving the patient alone (or letting them go out by themselves) caused anxiety. This could also affect household members' usual activities resulting in further emotional impacts:

'I feel I need to be with him (COPD patient) all the time to help as much as I can which has made me feel anxious and depressed'. (wife, 67 yrs)

'My husband's lung condition means he cannot go out when it is very cold, or walk too far. I worry when he goes out on his own' (wife, 55 yrs)

The patient's ability to self-manage their COPD effectively may leave household members feeling either reassured or concerned, as described by the contrasting experiences of two household members:

'In the eight years since first having COPD my husband manages it very well now. Having lost lots of weight'. (wife, 66 yrs)

'I am concerned that she has been advised to quit smoking but seems to be smoking more than ever.' (son, 27 yrs)

Other emotional effects

Other emotional effects mentioned occasionally by household members were feeling helpless at not being able to do more to help the patient:

'Feel that as he is in GP care, I can't do much more to help him & I would like to' (wife, 83 yrs)

'I am disabled with arthritis, so my husband has had to take over most of the chores, it has become more difficult for him because of his lung condition with makes me feel guilty about not being able to do more to help him' (wife, 76 yrs)

Some household members mentioned COPD in the context of the patient's other health conditions and lifestyle changes resulting in impacts to emotional health and shared activities:

'I worry about my partner's breathing more so in the mornings, i.e. coughing and wheezing. I think he suffers with anxiety. When he is like this, he drinks which causes me stress and I am unsure how to handle this problem.' (wife, 68 yrs)

'I worry that Mum drinks a bottle of wine every day? To cope with life/breathing and that this makes her fragile. Mum is basically housebound due to her chest, bowel condition'. (daughter, 45 yrs)

'My husband was a quiet confident man when I met him 31 years ago but due to retirement, change of lifestyle and a serious cancer illness, his personality is very different now ! I find his personality difficult to deal with and at times makes me very unhappy.' (wife, 56 yrs)

'My husband's heart and lung conditions have severely restricted our activities that can do together' (wife, 61 yrs)

Other emotional effects mentioned by individual household members were annoyance, potential embarrassment, and hope:

'Annoys me as I consider it self-inflicted due to his previous heavy smoking' (son, 47yrs)

'I worry if we are going somewhere which requires us to be quiet, e.g. weddings, cinema, funerals'. (wife, 62 yrs)

'She has good and bad days- hope though from the program her health will improve daily' (sister, 74 yrs)

6.6.3. No or little impact on household member

A third of household members mentioned that the patient's COPD had had very little or no impact on them personally. These responses were expressed along the lines of: '(COPD has) not affected me in any way' or '(I am) not really affected (by the condition)'.

The reason why household members may have stated “not feeling impacted by COPD” is because some patients with mild COPD were not impaired very much in terms of their health. For example one household member describes that the patient ‘has no restrictions due to his condition’ (wife, 65 yrs). Other household members perhaps did not think to mention that the patient’s suffering was a shared psychological experience, for example the household member who said:

> *‘Personally I don’t think it has affected my life, but I’m sure he (COPD patient) would like to do certain things without getting out of breath.’* (daughter, 24 yrs)

6.6.4. Occasionally mentioned impacts of COPD

Several household members indicated that their sleep had been disturbed as a result of the patient’s coughing, sleeplessness and noisy breathing at night.

‘My partner wakes during the night - coughing etc. which obviously disturbs me’. (wife, 71 yrs)

‘(My partner) snores with a rumbling chest sound (not all nights)’. (wife, 51 yrs)

In contrast, one household member describes that her sleep was not affected by her partner’s COPD:

> *‘My partner’s breathing worries me in the mornings, i.e. coughing and wheezing. This does not affect my sleep’.* (wife, 68 yrs)

Some household members were experiencing health problems of their own, and were predominantly recipients of care from the COPD patient, rather than being the providers of

care. The patient's COPD may (or may not) impact the patient's ability to provide informal care for the household member:

> *'My wife's COPD has not really affected me. I have had a stroke so my wife assists me'.* (husband, 75 yrs)

> *'I am disabled with arthritis, so my husband has had to take over most of the chores, it has become more difficult for him to help because of his lung condition'.* (wife, 76 yrs)

Some household members alluded to the potential financial implications of COPD on the household:

> *'We do less socially (e.g. holidays), although it is impossible to say whether this is caused by COPD or other health problems or the change in financial circumstances.'* (husband, 63 yrs)

> *'We still manage to get out and go on holidays abroad. Although the insurance is rather high but that is the same for both of us being in our seventies'.* (husband, 75 yrs)

Potential positive spillovers were described by some household members pertaining to the closening of the bond between the household member and COPD patient:

> *'We make the most of our precious time together'.* (wife, 62 yrs)

> *'Before my wife's lung condition, she spent two days walking with friends each week. These days we now spend together'.* (husband, 77 yrs)

6.6.5. Impact of telecoaching intervention

Household members were asked in the follow-up questionnaire to describe qualitatively 'how the patient's health care for COPD has affected your life'. In many of the responses, household members did not answer the specified question and instead described how COPD, rather than how COPD health care, had affected the household member's life. Only two household members provided a response that could be definitively be considered to answer the question that was being asked. These responses are provided below:

> *'X (patient) really enjoyed the projects you put before him and was much improved by this and I felt really happy for us to do this together'* (wife, 68 yrs, intervention group)

> *'There has been no effect directly attributable to family member's health care'* (wife, 75 yrs, control group)

6.7. Discussion

6.7.1. Quantitative analysis

Summary of findings

Household members' EQ-5D-5L scores were analysed over the course of 12 months, and it was found that there was negligible change resulting from the telecoaching intervention, with a 0.007 decrease reported in the intervention group (p=0.75). The analysis of spillover outcomes for household members EQ-5D-5L, happiness, physical activity and stress, in this trial, found no statistically significant changes from the telecoaching intervention over the 12 month period. Furthermore little inference could be drawn on the directions of change in the outcomes given the absence of statistical significance.

Comparison with other studies

Only 3 trial-based economic evaluations that have assessed health spillovers alongside patient health were identified in the systematic review in Chapter 2. None of these trials illustrated a statistically significant improvement in either patient health status or in family member health spillover from intervention (221, 223, 351). Even when patient health status improves at a statistically significant level over the course of a trial, health spillovers may not do so, as health spillovers are generally much smaller in magnitude than direct patient health changes and the precision of health spillover estimates is likely to be resultantly weaker (5).

The spread of physical activity and smoking behaviours across the social network of an individual have been documented in large empirical studies (22, 133, 352), but less so in intervention studies that change these behaviours. A series of weight-loss trials that successfully changed dietary and physical activity behaviours in participants, found that the spouses of participants experienced very little change in their physical activity behaviour, although their diets did change as a result of adjustment in shared household food habits (328-330). However a different observational study of an exercise intervention by Rossini et al of 230 family members, found that when participants were actively encouraged to recruit family members in their physical activities as part of the intervention, there was an increase in motivation in both participants and family members to take part in physical activity (146).

The analysis of baseline data explored the interdependence of family member and patient EQ-5D-5L scores, and found that there was a positive non-significant association between the two variables. Previous studies that have regressed family member EQ-5D scores against patient EQ-5D scores, found a larger, positive and statistically significant association between the two variables (6, 13). However the way health spillover is generated between patients and household members is likely to be different across these studies, in terms of being moderated by factors such as the type of illness, relationship to patient, family member age, duration of illness and the direction of spillover. In this study, the COPD patients in this study on average reported remarkably high average EQ-5D scores at baseline (0.90) which were slightly higher than their related household members (0.85). This suggests that that health-related quality of life spillover effects were unlikely to be generated by the people with COPD on the household members (nor the other way round).

Explanation of findings

Absence of statistical significant results for household member outcomes may in part be explained by the fact that the telecoaching intervention did not produce a statistically significant effect on patient outcomes, although there was a trend towards improved physical activity, health-related and COPD-related quality of life for patients in the intervention group. This meant that the possibility that patients' health and health behaviours were not impacted by the intervention could not be rejected, thus leading to no spillover. Another factor is that the relatively small sample of household members that were recruited to the study, may have resulted in insufficient statistical power to detect differences between trial arms.

COPD patients reported high EQ-5D-5L scores at baseline. Also, household members, particularly those in the intervention group, were already exhibiting positive health behaviours at baseline, with only 7% of the group reporting being smokers, and 43% of the group reporting participating in high levels of physical activity. These factors may explain a potential lack of scope for the intervention improving the health of patients, and also outcomes in household members.

In the longitudinal analyses, there was little evidence of concordance in physical activity and smoking behaviour changes between household members and patients over the course of the trial. Furthermore the potential lack of responsiveness of the IPAQ questionnaire used in this study (353) may have been an inhibiting factor in detecting peer effects of physical activity change between participants and their family members, should they have existed.

Implications of quantitative findings

Estimations of health spillovers from randomised trials are likely to be more uncertain than estimates of patient health changes due to their smaller magnitude (12), which may undermine the case for including health spillovers in a clinical or cost-effectiveness analysis. In clinical effectiveness studies, it may be more useful to assess spillover effects in household members by using instruments specifically aimed at being sensitive in detecting these effects with more certainty, for example by using a care-related quality of life instrument. However measurement of care-related quality of life is irrelevant in economic evaluations aiming to maximise health-related quality of life (21). Sample size calculations in randomised controlled trials aim to detect statistically significant changes in the primary outcome for patients (275), but are unlikely to be relevant to a household member spillover outcome, which may be an area for further research.

6.7.2. Qualitative analysis

The qualitative analysis provides novel data of the impact of mild COPD on family members. Household members provided free-text responses at baseline on how COPD (rather than the intervention) had impacted them. Thirty four percent of household members reported the patient's COPD had little or no impact on them. Thirty five percent of household members reported being impacted by patient COPD in terms of limitations to their general activities, especially joint walking activities or other leisure activities. Thirty four percent of household members reported that the patient's COPD had a negative impact on their emotional health,

especially from worrying or concern for the patient's suffering and potential deterioration. Household members occasionally mentioned that their sleep was being disturbed from the patient's coughing and noisy breathing. These findings suggest that within the duration of a trial, a successful COPD telecoaching intervention may generate spillovers by alleviating the burden on household members from 'caring about' the patient, and allowing COPD spouses and other family members to participate in more leisure and physical activities with the patient. In the long-run, a successful COPD telecoaching intervention may prevent the patient's COPD progressing to the severe stages where the patient becomes housebound, and where the health spillover generated is largely caused from providing informal care for the patient (100, 354).

The fact that a third of household members reported no or very little impact of COPD on their lives may perhaps reflect participants not understanding the nature of the question and how it was aimed to elicit both emotional impacts and not just tangible impacts. Alternatively, it may indeed reflect a genuine absence of worry and concern among these spouses in regards to the patient. Approximately 30% of the patients in the trial scored 1 on the MRC dyspnoea scale and thus had almost no symptoms of shortness of breath, which may also have accounted for the lack of impact on their family members. Furthermore, given that many household members in this study had experienced high blood pressure, osteoarthritis or depression, perhaps household members were more concerned about their own health than the health of the COPD patient.

Only a small proportion of household members qualitatively reported providing informal care for the patient. However, we cannot conclude these household members did not

provide informal care, but can only infer that providing informal care was not the 'single biggest impact' of the COPD. Furthermore, we also cannot infer that for the informal carers, that providing informal care produced a net disutility to the carer unless the household member made an explicit reference of it having done so. This is because the process utility of being a low or moderate burden carer has been often been shown to outweigh health spillover disutility (68, 143).

Previous qualitative studies on the family impact of COPD have focused on people with the more severe symptoms of COPD (313, 314, 355-358). This survey of the family impact of mild/moderate COPD shows that even a milder range of symptoms of COPD impose a recognisable impact on the emotional health and general activities of household members.

6.7.3. Strengths and limitations

Household members in the intervention and control arms of the trial were balanced in most baseline characteristics. The sample of household members in this study is a similar sample size to other studies that have collected health spillover data from carers to inform a trial-based economic evaluation (221, 223, 351). The loss to follow-up of household members (24 out of 153 household members) was also not substantial, and therefore unlikely to have resulted in substantial bias. A large range of outcomes of household members were assessed in the between-groups analysis, including variables that might be associated with undetected future health spillovers. A qualitative free-text box in the baseline questionnaire

elicited useful responses describing how the sample of household members was impacted by the patient's COPD, in terms of both health and non-health spillovers.

There were several limitations in this study. A major limitation was that although the sample size of household members was large enough to result in balanced demographic and clinical characteristics for patients and household members between treatment arms at baseline (n=153), the sample size was nonetheless much smaller than the sample size of patients (n=577). This meant a lack of statistical power in the analysis of household member outcomes. One factor explaining this was that 26% of the patients lived alone. Also late ethical approval for the FIS study meant that some patients who had already been recruited were not asked to participate. A further factor may have been that the nurses occasionally overlooked inviting patients to participate in the FIS study, due to a greater focus on the patient's eligibility for the main study during the baseline clinic appointment. Future studies should attempt to invite all patients to participate in household member data collection by obtaining ethical approval and having invitation information in the standard operating procedures before the start of the trial. Even though reminder letters were sent to patients at baseline to participate in the FIS study, there was nevertheless substantial attrition during this phase of FIS study recruitment, with 66 out of 222 household members either deciding not to participate in the FIS study, or the patient deciding not to pass on the questionnaire to the household member. This may be an unavoidable problem in studies such as this one where household members or carers do not have face-to-face contact with the trial administrators (229). Data collection in this study depended entirely on the generosity of household members to complete questionnaires for free. The absence of an incentive may be one factor in explaining the limited recruitment of household members into the study.

Furthermore the household members and patients had to opt into the FIS study, so were therefore not fully randomised. There may have been analytical problems resulting from this. There could be selection bias if recruitment of family members was affected by whether PSM participants were assigned to intervention or usual care. Also, some patients may have felt uncomfortable involving their household members in the trial and therefore not participated, reducing the sample size of household members. Additionally household members with closest relationships and most concern about the person with COPD were potentially more likely to be involved in the FIS, than the household members who were not very close to the patient. This could potentially have led to overestimates of health spillovers.

It was necessary to restrict data collection to individuals who are adults, in order to ensure that family members have the necessary comprehension abilities to participate in a postal survey and may appropriately provide a response to the EQ-5D-5L measure which is designed for adult respondents. However, this approach risked neglecting in accounting for young children and young carers who may be substantially impacted by health spillovers (94). It is important to be aware of this risk for future trials where the patients are more likely to have young dependents.

A limitation of the physical activity measure used in this study for both patients and their household members (IPAQ short-form questionnaire) was that it was a self-report measure. Similar to other studies that have used this measure (359, 360), there was quite a lot of missing data (due to many participants ticking the ‘don’t know/not sure’ box for the time

spent doing a specific physical activity), and there were also several outlier responses for physical activity that were implausible. Furthermore it has yet to be established whether the IPAQ measure is responsive, i.e. able to detect changes in a person's physical activity over time (353, 361). However alternative self-report measures of physical activity may also be limited in terms of their validity and feasibility (362), and the FIS study lacked the resources to use objective measures of physical activity for household members as were used for participants in the main trial (accelerometers).

For the qualitative free text question in the follow-up questionnaire for how 'COPD health care' affected household members' lives, many household members did not interpret the question correctly and instead described how COPD (illness) had affected them. Future qualitative research investigating impacts and perceptions of health intervention trials in household members may wish to either pilot test the survey questionnaire to ensure that the wording is understood, or alternatively use more robust qualitative methodologies such as interviews with household members.

6.7.4. Conclusion

This study found that a COPD telecoaching intervention aimed at improving the health of patients did not generate health spillover effects on household members over the course of 12 months. These findings appeared plausible given that the intervention appeared to lack effectiveness in improving patients' health (and health behaviours), resulting in an absence of health spillover. Although the null hypothesis that the intervention is not effective for

both patients and household members cannot be rejected, it is nonetheless possible that with a larger sample size, the intervention would have demonstrated effectiveness for patients and their household members. Furthermore, it has been argued that in order to maximise population health, the decision to approve a health technology should be informed by the cost-effectiveness result which is built on QALYs rather than the clinical effectiveness result which is based on the primary outcome of the trial. Therefore, a cost-utility analysis of the intervention may be justified from either a patient or household-level perspective. Also, it is useful to think through the methods by which health spillovers would be incorporated in a cost-utility analysis regardless of the size of the impact in this specific example. The next chapter will explore the various ways in which the average estimate of health spillover effects in household members derived from this study may be included in the economic evaluation of the COPD telecoaching intervention.

CHAPTER 7: INCLUDING HEALTH SPILLOVERS IN THE ECONOMIC EVALUATION OF A COPD TELEPHONE COACHING INTERVENTION

This chapter presents the third empirical study which is a re-analysis of the cost-effectiveness analysis of the COPD telecoaching intervention incorporating household member costs and QALYs. This follows on from Chapter 6 which assessed the spillover effects of the same intervention on 153 household members. Analyses within Chapter 7 were mostly restricted to the 'main' household members of patients; that is the 151 household members who were assessed to be the closest surveyed household member to the patient.

The background and objective of the study will now be described (section 7.1), followed by a description of the primary economic evaluation of the COPD telephone coaching intervention (section 7.2). The methods, results and discussion of the secondary analysis of the economic evaluation are presented in sections 7.3 to 7.5 respectively.

7.1. Background

Economic evaluations of health interventions typically only include patient QALYs. However health interventions may also generate health spillovers, captured in household member QALYs. Including household member QALYs in economic evaluations may enable the

maximisation of QALYs across patients' household networks rather than just across patients. This involves matching the definition of health in economic evaluations to focus on a household perspective rather than a patient perspective.

A randomised controlled trial (RCT) is usually the most appropriate study design for estimating effectiveness and outcomes of health interventions – either for patients or household members. This is because an RCT is the best study design for assessing causal effects of health interventions (275), as it is the only study design which minimises the risk of confounding from the imbalance of unknown prognostic factors at baseline. As a result, the internal validity of estimated treatment and quality-of-life effects from RCTs is strong (363). Such estimates of effects can then be appropriately included in a trial-based economic evaluation or to parametrise an economic decision-analytic model. In Chapter 6, the health spillover (QALY) effect generated in household members in the RCT of a COPD telecoaching intervention was estimated. This has been rarely done for health interventions; there is a dearth of studies which have used randomised trials to estimate QALYs in family members generated through spillover (322). In fact, the majority of applied studies in health spillover research are observational and/or measure health spillovers from illness rather than from interventions (5, 12, 13, 140, 278, 364, 365).

7.1.1. Methodological issues in the inclusion of QALYs/costs in this context

A range of existing approaches have been used in the applied literature for including health spillovers in a cost-utility analysis, which were described in the systematic review in Chapter 2. These include a base-case analysis that only included carer QALYs (225), deterministic sensitivity analyses that aggregate average QALYs for patient and carer samples (208, 216), and deterministic and probabilistic analyses that analyse costs and QALYs across patient-carer dyads (221, 223).

The impact of including health spillovers on intervention cost-effectiveness may be best illustrated through point estimates of the ICER in a deterministic sensitivity analysis where averages of patient and household member QALYs are summed (176, 307). A number of methodological challenges need addressing to provide a way forward for systematic inclusion of health spillovers in economic evaluation. Some of these challenges were discussed in Chapter 2. Areas of uncertainty include how to address the missing data generated from family members and what decision threshold should be used in economic evaluations that include health spillovers. Another area of uncertainty lies in which family members should be included in economic evaluations and how many (78, 366). A specific consideration here relates to whether only the primary carer of the patient or all of the patient's household members should be incorporated into the economic evaluation. Including more than one family member per patient in the analysis will have the potential to reduce an intervention ICER even further, and therefore implies that the cost-effectiveness threshold also needs to be reduced further. These areas of uncertainty are explored through a case study in this chapter.

The purpose of this research is to extend a trial-based economic evaluation of the COPD telecoaching intervention versus usual care to incorporate health spillover effects and costs on the wider household. This study serves as a methodological proof-of-principle study for how researchers might incorporate health spillover effects and costs into an economic evaluation in the future.

7.2. Primary economic evaluation of the COPD telecoaching intervention

This study builds on a recently conducted economic evaluation of the aforementioned telecoaching intervention to support self-management of COPD. The primary economic analysis of the intervention was conducted from a standard NHS perspective as part of a funded study (321). In the primary economic analysis, a trial-based economic evaluation was carried out to estimate cost-effectiveness of the telecoaching intervention compared with usual care including only patient-level costs and patient QALYs. A trial-based economic evaluation only incorporates effects measured within the trial, with no extrapolation of effects beyond the time horizon of the trial(367).

In the primary analysis, costs and QALYs were presented in a disaggregated form in a cost-consequence analysis. Subsequently, costs and QALYs were combined in a cost-utility analysis to calculate an incremental cost-effectiveness ratio (ICER).

Health care costs that were included in the analysis were intervention and usual care costs, including practice nurse time, telephone calls, website support, written materials, staff

training workshops, and health care utilisation costs relating to COPD, such as emergency admissions for exacerbations, medication costs, and GP, nurse and pharmacist visits. Unit costs were obtained from standard sources including NHS and PSSRU reference costs for 2015.

EQ-5D-5L scores were calculated using the UK tariffs published in January 2016 (249). Using the 'area under the curve' method, QALYs were calculated using mortality data and patient EQ-5D-5L scores at baseline, 6 and 12 months, with a regression-based adjustment for baseline imbalance in patient EQ-5D scores between trial arms (368).

Multiple imputation (predictive mean matching) was used to impute missing data for costs and QALYs (369). Bootstrapping was used to enable a probabilistic sensitivity analysis to explore uncertainty with 1000 paired cost and QALY differences generated, and a cost effectiveness acceptability curve produced.

It was estimated that the telecoaching intervention generated £26.23 higher costs and 0.007 higher QALYs relative to usual care, resulting in an ICER of £3659 per QALY. In the probabilistic sensitivity analysis, the telephone coaching intervention was estimated to have an 82% probability of being cost-effective using a threshold of £20,000 per QALY.

This study subsequently carried out a series of scenario analyses that involved including household member costs and QALYs alongside patient costs and QALYs in the cost-utility analysis. The methods for this study will now be described.

7.3. Methods

7.3.1. Calculation of costs and QALYs

QALYs accrued over the intervention period for each household member were calculated using the commonly used 'area under the curve' approach (or trapezium rule) (368). This was done by multiplying the sum of EQ-5D-5L scores at baseline and at 12 months follow-up by 0.5 for each household member. QALYs were then regressed against baseline household member EQ-5D-5L scores, and a binary variable denoting whether the household member was in the intervention or control group. Manca et al (2005) highlighted the importance of adjusting for baseline utility scores in the regression to control for baseline EQ-5D imbalances between trial arms (368). The coefficient of the binary variable denotes the estimated QALY difference between groups. EQ-5D-5L scores were calculated using the UK tariff released provisionally in January 2016 as an alternative to the cross-walk algorithm (249).

Family member visits to GPs and practice nurses over a preceding 3 months were elicited in the 12 month follow-up questionnaire. In line with standard practice for costing health care visits, number of visits were multiplied with the most recently published PSSRU unit costs (Table 7.1), and then the total cost over 3 months was multiplied by 4 to estimate costs over 12 months. Family member costs were summed with the patient costs estimated in the primary analysis described in section 7.2. Family member medication costs or secondary care costs were not measured or included in this study.

Table 7.1 Unit costs of household member primary care visits

	Cost variables	Unit of measurement	Unit Cost (£)	Source
	General practitioner	Average consult of 11.7 minutes	45	a
	Practice nurse	Average consult of 15.5 minutes	14.5	a

a Curtis L. Unit Costs of Health and Social Care 2015. Canterbury: PSSRU, University of Kent; 2015 (370)

7.3.2. General approach for data analysis

The analysis was carried out by incorporating household member data into the standard analysis which used patient data. The analysis used the same time horizon as the primary evaluation, i.e. 12 months corresponding to the data collection period within the trial. As a result, no discount rate was applied to household member (and patient) costs and QALYs.

In all analyses undertaken for this study, missing data on household member costs and EQ-5D-5L scores was addressed using multiple imputation. Predictive mean matching was used to impute missing responses for household member costs, and EQ-5D-5L scores, using the independent variables age and gender. The process of predictive mean matching involves 'borrowing' a real value from a randomly chosen individual with complete data who has similar independent variable characteristics (369). The advantage of this approach is that it uses real observations to impute from, therefore retaining the original properties of the variables (i.e. discrete or continuous). As consistent with standard multiple imputation

practices, ten sets of imputations were generated per variable and a mean variable was generated to combine the ten sets into one final imputed variable (369).

In empirically estimating household member costs and QALYs, only the main household members were included. For two patients, household member data from a second household member was collected; in these cases only the household member expected to be impacted the most by spillover according to their relationship with the patient, were assigned as being the main household member. In these two cases, the spouse of the patient was deemed as being the main household member, as they were expected to be the primary informal carer for the patient and also expected to form a greater concordance in health behaviour change with the patient than a second household member.

As there were only two patients from whom data was collected from a second household member, this was insufficient to provide an empirical basis for estimating costs and QALYs among these members. Rather, where second household members were included in a scenario analysis, it was assumed that these second household members incurred the same health spillover cost/QALY effect as the average estimate for the main household members.

The following areas of methodological uncertainty for including health spillovers which were highlighted in section 7.1.2, will be addressed in this study:

(i) The proportion of patient households experiencing spillover (section 7.3.3)

(ii) The inclusion of spillovers among second household members as discussed in Chapter 2 (section 7.3.4).

(iii) Inclusion/exclusion of household member primary care utilisation costs (section 7.3.5).

(iv) The 'core' cost-effectiveness threshold used itself (conventional threshold applied by NICE in extra-welfarist economic evaluation of £20,000 per QALY) versus an empirically estimated threshold developed by researchers at the University of York of £12,936 per QALY (371). Also, the application of a reduction to the core thresholds of £20,000 and £12,936 per QALY, to account for the inclusion of QALYs beyond the patient to patients' household members (the rationale for doing this was discussed in Chapter 2). The methods for reducing the threshold in the analyses are described in section 7.3.6.

The following sections will describe how each of these methodological uncertainties were accounted for in this study.

7.3.3. Proportion of households experiencing health spillovers

In the primary economic evaluation (321), cost and QALYs were restricted to the standard NHS perspective only using the full sample of patients (n=577). Three sets of alternative analyses of the economic evaluation were carried out for this study. The first two sets of analyses summed estimates of patient costs and QALYs with household member costs and QALYs generated from intervention. The first set differed from the second set of analyses by making different assumptions about the proportion of household members who were

affected by spillovers. In the third set, cost-effectiveness was assessed only for patient-household member dyads (n=151), i.e. restricting the sample of patients included in analysis.

The analyses carried out for this study draw on the 'multiplier approach' for including health spillovers illustrated by Al-Janabi et al (78). The conventional decision rule for extra-welfarist economic evaluation is to approve an intervention if the incremental patient costs divided by the incremental patient QALYs are lower than a pre-specified threshold. After factoring in household member QALYs generated from an intervention, the authors derived the following amended decision rule:

$$\textbf{Patient ICER} * \frac{\textbf{Multiplier effect on health benefits displaced from intervention}}{\textbf{Multiplier effect on health benefits generated from intervention}} < \textbf{Threshold}$$

This study uses the same principles underlying the formula specified above, but more directly recalculates cost-effectiveness by recalculating the patient ICER denominator by adding household member QALYs to patient QALYs, and by multiplying the threshold by a factor from the literature to account for household member QALYs displaced from not funding another health intervention:

$$\frac{\textbf{Incremental costs of intervention}}{\textbf{Patient} + \textbf{ household member QALYs generated from intervention}} < \frac{\textbf{Threshold}}{\textbf{Displacement multiplier}}$$

It may be important to aggregate household member incremental costs and QALYs with patient incremental costs and QALYs in a NICE cost-utility analysis. By including household member health care utilisation costs potentially resulting from spillover, a more complete estimation of the costs that the NHS incurs from investing in a health intervention can be made. By including household member QALYs, decision makers can be guided towards judgements that maximise health across patients and their household members (157). The

methods by which main household member incremental costs and QALYs were included in the ICER calculations will now be presented. In the first set of analyses, all of the main household members in the overall patient sample were assumed to incur a spillover. In the second set, only the household members who participated in data collection were assumed to incur spillover costs and QALYs. Analysis 3 presents a dyadic analysis where incremental costs and QALYs were calculated across a subset of 151 patients and their 151 main household members. A further set of analyses in which spillovers for both the main household member and an additional (second) household member were included in the ICER calculations, are described in section 7.3.4.

Analysis 1: 428 household members included

The main problem with the household member data was missingness, as 277 of the 428 potentially eligible main household members did not participate in this study. Therefore an assumption was made for the first set of analyses, that the average health spillover estimated for the household members who participated in data collection, was the same for the household members who did not participate. In adapting the multiplier approach, estimates of cost and QALY change resulting from the telecoaching intervention for the main household members, were multiplied by the proportion of patients who have at least one household member. The resulting estimate of cost and QALY change for the main household members across the whole patient sample was then summed with the estimate of average patient cost and QALY change attributed to the telecoaching intervention, as illustrated in the ICER equation:

$$\mathbf{ICER}^{1} = \frac{\boldsymbol{\Delta costs(patient) + \ \Delta costs(HMs) * \frac{n\ patients\ with\ at\ least\ 1\ HM}{n\ patients\ in\ trial}}}{\boldsymbol{\Delta QALYs(patient) + \ \Delta QALYs(HMs) * \frac{n\ patients\ with\ at\ least\ 1\ HM}{n\ patients\ in\ trial}}}$$

[1] ICER numerator: Difference in NHS costs for patients between intervention and control groups (n=577) plus (difference in health care utilisation costs for household members between intervention and control groups*(Proportion of patients with at least one household member)).

ICER denominator: Between groups difference in follow-up patient QALYs adjusted for baseline patient EQ-5D-5L scores (n=577) plus (between groups difference in household member QALYs adjusted for baseline household member EQ-5D-5L scores*(Proportion of patients with at least one household member)).

Analysis 2: 151 household members included

The second set of analyses used the same multiplier approach as used in analysis 1, but when aggregating costs and QALYs, made the conservative assumption that household members who did not participate in data collection incurred no health spillover.

$$\mathbf{ICER^2 = \frac{\Delta costs(patient) + \Delta costs\ (HMs) * \frac{n\ participating\ household\ members}{n\ patients\ in\ trial}}{\Delta QALYs(patient) + \Delta QALYs\ (HMs) * \frac{n\ participating\ household\ members}{n\ patients\ in\ the\ trial}}}$$

A summary of the primary analysis and analysis 1 and 2 is provided in Table 7.2.

Table 7.2: Summary of primary analysis, and analyses where spillover is assumed for 428 and 151 household members respectively

Scenario	Health spillover methodology	Number of household members for which spillover included
Primary analysis	Not included	0
Analysis 1	Sum patient costs and QALYs with main HM costs and QALYs	428 (households where patients lived alone were excluded)
Analysis 2	Sum patient costs and QALYs with main HM costs and QALYs	151 (households where patients lived alone and also the other households which did not participate in the FIS were excluded)

[2] ICER numerator: Difference in NHS costs for patients plus (difference in health care utilisation costs for household members between intervention and control groups*(Proportion of patients with a main household member participating in the FIS)).

ICER denominator: Between groups difference in follow-up patient QALYs adjusted for baseline patient EQ-5D-5L scores (n=577) plus (between groups difference in household member QALYs adjusted for baseline household member EQ-5D-5L scores*(Proportion of patients with a main household member participating in the FIS)).

No probabilistic sensitivity analyses were undertaken to represent uncertainty of the point estimates in the deterministic analyses. This is because probabilistic sensitivity analyses depend on a bootstrapping process which can only be undertaken where there is full cost and QALY data for both patients and their household member, which requires all patients in the analysis to have data from a household member.

Analysis 3: dyadic approach (151 household members, 151 patients included)

As used in studies by Meeuwsen et al and Sturkenboom et al (221, 223), analysis 3 took a dyadic approach. This approach might be considered to be a less appropriate approach than analyses 1 and 2 for this particular case study, due to the substantially lower number of main household members that were recruited in the FIS (n=151) as compared with patients enrolled in the trial (n=577). However for some cost-utility analyses, this might be a preferred method for analysis where most or all patients have a household member recruited for data collection, in order to allow for straightforward aggregation of patient and household member costs and QALYs across each dyad (221, 223). Therefore, it is important to also present this as an alternative approach.

A cost-utility analysis of the intervention focusing on the 151 patient-household member dyads was carried out. Incremental cost-effectiveness ratios (ICERs) were calculated for the 151 dyads using the multiplier approach, and compared with the thresholds which are defined in section 7.3.6. These analyses were compared with an ICER illustrating the cost-

effectiveness of the intervention including just patient costs and QALYs, for the restricted sample of 151 patients at a threshold of £20,000 per QALY.

Table 7.3: Summary of dyadic analyses performed for this study

Scenario	Methodology used	Number of HMs
Base-case analysis	Patient costs and QALYs for restricted sample of patients (n=151)	0
Scenario analysis	Average estimates of summed patient (n=151) and household member (n=151) costs and QALYs	1

7.3.4. Inclusion of costs and QALYs among second household members

Additional scenario analyses were carried out to include not just the main household members in the analysis, but also the patients who had a second adult household member. In the patient baseline questionnaire, 11% of responding patients (61 out of 560 responders, with 17 non-responders) recorded that their household included 3 or more adult individuals in total. Therefore, for analysis 1, a total of 63 additional household members were added onto the 428 household members (so that 491 household members were included in total in the scenario analysis). It was then assumed that costs and outcome estimates were the same across all 491 household members, without differing between the main and second household members. This assumption was made because there was insufficient questionnaire data from second household members to provide empirically based estimates for costs and QALYs within this group. An equation to illustrate this methodology of including both main and second household members in the ICER is provided below:

$$\text{ICER}^{3} = \frac{\Delta\text{costs(patient)} + \Delta\text{costs (HMs)} * \frac{\text{n of main HMs + n of second HMs in total patient sample}}{\text{n patients in the trial}}}{\Delta\text{QALYs(patient)} + \Delta\text{QALYs (HMs)} * \frac{\text{n of main HMs + n of second HMs in total patient sample}}{\text{n patients in the trial}}}$$

7.3.5. Sensitivity analysis around costs

Further sensitivity analysis was carried out for the full sample and sub-sample analyses, to include and exclude household member health care costs (GP and nurse visits). There may be justification for including health care costs for household members as they fall appropriately under the NICE reference case which recommends including "resource costs that are under the control of the NHS" (p.46) (158) . Family members whose health improves as a result of intervention spillover may require fewer health care visits. A reason for excluding household member costs is that there were data limitations on these costs, as they had to be extrapolated from the reported 3 month estimates to cover a 12 month period, underlining the difficulties in collecting this data in practice. Another reason for excluding these costs is for aiding comparability with other studies, because studies do not conventionally include carer health care utilisation costs even when carer/household member QALYs are included (167).

[3] ICER numerator: Difference in NHS costs for patients between intervention and control groups (n=577) plus (difference in health care utilisation costs for household members between intervention and control groups*(Overall number of main and second household members divided by overall number of patients)).

ICER denominator: Between groups difference in follow-up patient QALYs adjusted for baseline patient EQ-5D-5L scores (n=577) plus (between groups difference in household member QALYs adjusted for baseline household member EQ-5D-5L scores*(Overall number of main and second household members divided by overall number of patients)).

7.3.6. Threshold deflation

A drawback of the existing economic evaluations identified from the systematic review in Chapter 2 was that none of these economic evaluations made any adjustment to the conventional decision threshold of £20,000 per QALY (158), when including health spillovers. This study used a range of alternative thresholds. First, an alternative threshold was used as proposed in a study by Al-Janabi et al, which deflated the threshold using a multiplier of 1.16 (78). This multiplier was drawn from empirical estimates which indicate that patient chronic illness on average generates a carer health spillover equivalent to 16% of the health loss of the patient(6, 372). However, the 1.16 multiplier was derived from estimates of health spillovers experienced in carers of chronically ill patients, and in particular does not factor in the lower proportional family health spillover produced from acute illness. The lower proportional health spillover produced from acute illness is due to the fact that the illness is short-term so that it is unlikely to induce mental health effects in family members. Therefore, another alternative lower multiplier of 1.10 was also applied in this study to the £20,000 per QALY threshold. This was an arbitrary adjustment that I made to deflate the NICE threshold according to the average health spillover across all illnesses and not just chronic illnesses.

Furthermore, a broader discussion on the suitability of the NICE decision threshold of £20,000 per QALY is ongoing. This threshold was set arbitrarily and with little empirical justification (371). One recent study attempted to make an empirical estimation of the 'best' decision threshold that should be adopted that would enable maximisation of health gains across all NHS patients, of £12,936 per QALY by Claxton et al (371). This threshold was

estimated through an empirical assessment of the relationship between the NHS budget and patient health outcomes. There was uncertainty about this estimation due to data limitations, and a possible lack of consideration of the long-run benefits to health systems from incentivising innovation by allowing for pharmaceutical companies to set higher prices for treatments (158, 162, 371, 373). It is important to note that the Claxton threshold estimate does not consider health spillover effects, so the multipliers of 1.10 and 1.16 may also be applied to Claxton's threshold. A comparison of the ICERs calculated from analyses 1 to 3 was made with all of the thresholds that are proposed here (£20,000, £20,000/1.10, £20,000/1.16, £12,936, £12,936/1.10 and £12,936/1.16 per QALY).

7.3.7. Probabilistic sensitivity analysis

For analysis 3, a probabilistic sensitivity analysis (PSA) was carried out on data where costs and QALYs for each of the 151 patient-household member dyads were summed across the dyad. Bootstrapping was used to calculate 1000 incremental cost-effectiveness ratios for 1000 samples of paired dyads in the dataset, with each pair consisting of a randomly selected dyad in the intervention group matched with a randomly selected dyad in the control group (367).

The proportion of the 1000 ICERs that were lower than a specified cost-effectiveness threshold was then calculated, to represent the probability of the intervention being cost-effective at the threshold. Cost-effectiveness acceptability curves were then generated, to

demonstrate the probability of intervention cost-effectiveness across a range of thresholds ranging from £0-40,000 per QALY, including the thresholds described in section 7.3.6 (374).

7.4. Results

7.4.1. Cost and QALY estimates for patients and household members

An imputation-based analysis was undertaken for this study meaning that there was a full set of cost and QALY data (either directly measured or imputed) for the 577 patients and 151 household members. Table 7.4 displays the estimates of cost and QALY differences which were used to calculate ICERs for the primary analysis and multiplier analyses.

Table 7.4: Estimated cost and QALY differences for patients and household members

Variable	Mean value intervention group	Mean value control group	Mean difference (Bootstrapped 95% CI)
Patient costs	£543.69	£517.46	£26.23 (-69.85 to 122.33)
Patient QALYs*	0.878	0.871	0.0069(-0.0038 to 0.0187)
Household member costs	£210.99	£197.61	£13.37 (-72.40 to 99.20)
Household member QALYs*	0.8393	0.8398	-0.0006 (-0.025 to 0.023)

*Mean values for patient/household member QALYs included an adjustment by the corresponding baseline patient/household member EQ-5D-5L score

Table 7.4 illustrates higher estimated costs and QALYs for patients receiving the intervention, and higher average costs of £13.37 and slightly lower QALYs of 0.0006 for household members of intervention patients. There was an absence of statistical significance and wide confidence intervals for all of the estimated cost and QALY differences.

Table 7.5 displays the estimates of GP and nurse costs for the 118 household members from whom elicitations were obtained for these costs in the 12-month questionnaire.

Table 7.5: GP and practice nurse costs for 118 household members who provided a valid response

Variable	Mean value intervention group	Mean value control group	Mean difference (Bootstrapped 95% CI)
GP costs	£183.66	£174.49	£9.17 (-93.51 to 111.85)
Practice nurse costs	£17.09	£21.10	-£4.02 (-19.93 to 11.90)

There were slightly higher estimated average GP costs of £9.17 and slightly lower average practice nurse costs of £4.02 generated over 12 months by intervention household members.

7.4.2. Investigation of the effect of applying different multipliers and thresholds

Table 7.6 displays the results estimating the cost-effectiveness of the telecoaching intervention after summing household member costs and QALYs to the ICER numerator and denominator respectively. The ICERs from these multiplier analyses were then compared against various threshold values to determine cost-effectiveness.

For all the multiplier analyses, the telecoaching intervention was cost-effective using any of the proposed thresholds of £11,151 per QALY or above. The highest ICER (£5,780 per QALY)

was for the analysis in which 491 household members' costs and QALYs were included. Conversely, lower ICERs were estimated for analyses where 151 patients and their main household members were analysed in dyads, and household member primary care costs were excluded.

Table 7.6: Cost-effectiveness estimates for multiplier analyses including household member costs and QALYs

Household members included (n)	Patients included (n)	Household member costs included?	Incremental cost per QALY (£/QALY)	Cost-effective at £20,000 per QALY threshold?	Cost-effective at £18,182 per QALY threshold?*	Cost-effective at £17,241 per QALY threshold?*	Cost-effective at £12,936 per QALY threshold?	Cost-effective at £11,760 per QALY threshold?	Cost-effective at £11,151 per QALY threshold?
491§	577	Y	£5780	✓	✓	✓	✓	✓	✓
491§	577	N	£4031	✓	✓	✓	✓	✓	✓
428	577	Y	£5502	✓	✓	✓	✓	✓	✓
428	577	N	£3992	✓	✓	✓	✓	✓	✓
151	577	Y	£4341	✓	✓	✓	✓	✓	✓
151	577	N	£3830	✓	✓	✓	✓	✓	✓
151†	151	Y	£2140	✓	✓	✓	✓	✓	✓
151†	151	N	£1144	✓	✓	✓	✓	✓	✓

*The £18,182, £17,241, £11,760 and £11,151 per QALY thresholds were derived by dividing the core thresholds (£20,000 per QALY and £12,936 per QALY) by 1.10 and 1.16

§ The sample of 491 household members comprised of 428 main household members and 63 second household members

† Results of the dyadic analyses of 151 patients and their main household member.

7.4.3. Analysis of participating patients in the family impact study

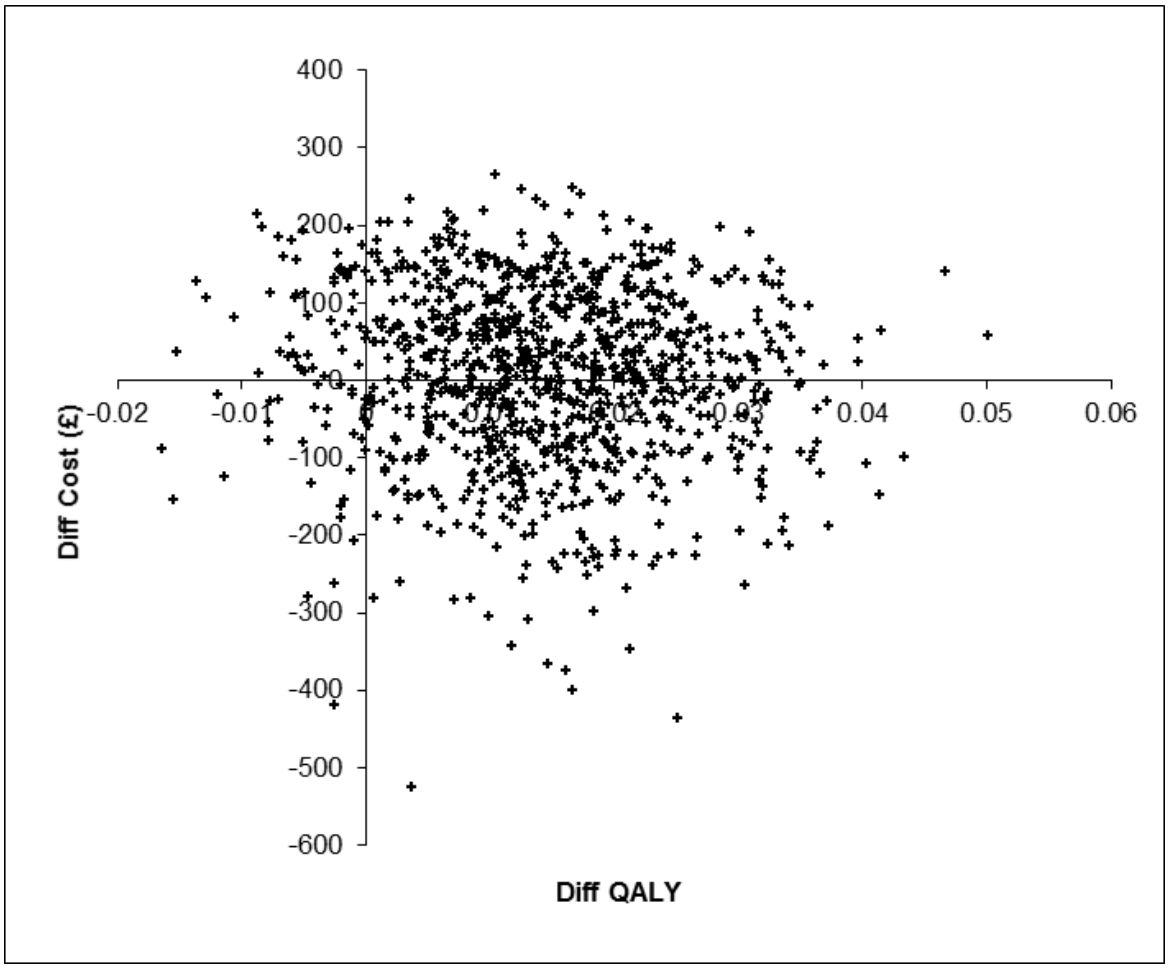
The incremental cost-effectiveness ratio (ICER) was recalculated for the sub-sample of patients whose household members participated in data collection (n=151). For the 151 patients, the telecoaching intervention was estimated to be on average £15.36 more expensive than usual care (s.d=119.50) and generated 0.014 additional QALYs (s.d=0.011). This resulted in a recalculated ICER for the 151 patients of £1097 per QALY (Table 7.7). From the patient perspective only, the patient QALYs generated from the telecoaching intervention for the sub-sample of 151 patients are much higher and resulting ICER considerably lower than for the patient QALY/ICER intervention estimates across the entire patient sample (Table 7.7).

Table 7.7: Cost-effectiveness estimates of telecoaching intervention for patients only

	ICER (cost (£) per QALY)	**Probability of telecoaching cost-effectiveness**
Full sample of patients (n=577)	£3659	82%
Sub-sample of patients (n=151)	£1097	86%

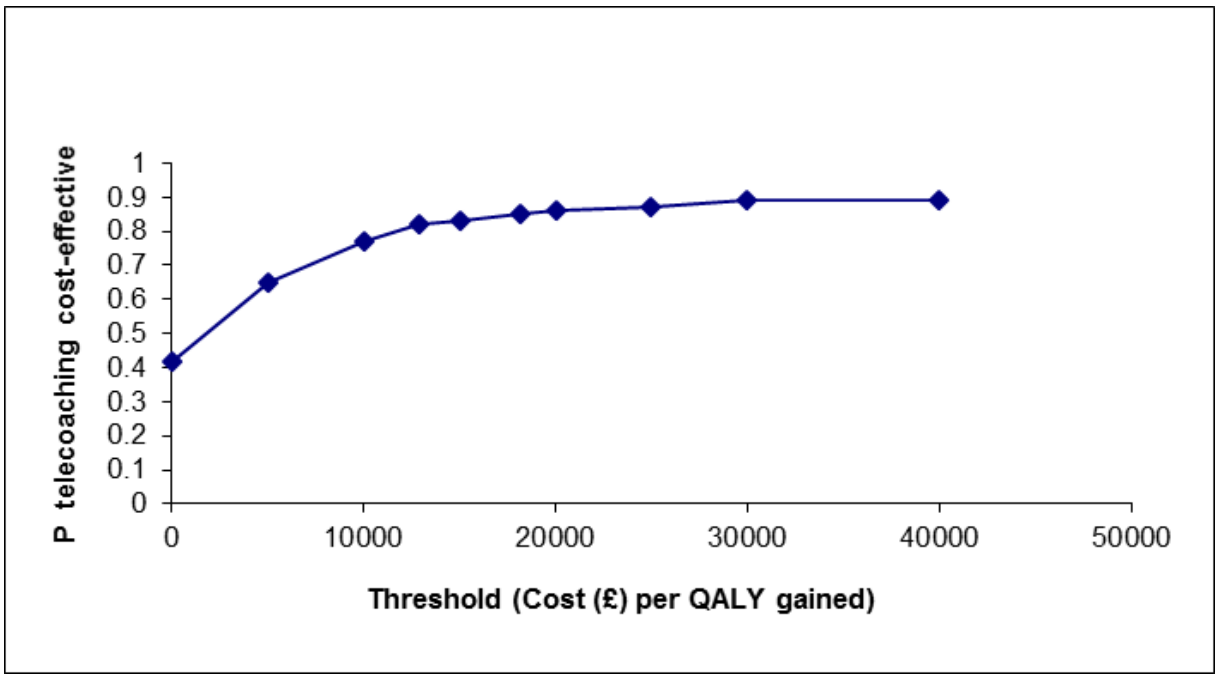
The cost-effectiveness plane graphically presents the 1000 bootstrapped cost and QALY differences between the intervention and usual care groups. Points in the eastern quadrants indicate simulations where positive intervention QALYs were estimated, and indicate higher intervention costs in the northern quadrants (and vice versa). The cost-effectiveness plane in Figure 7.1 demonstrates mostly positive QALY differences in favour of the telecoaching intervention from the perspective of the 151 patients, as most points are positioned in the east of the plane.

Figure 7.1: Cost effectiveness plane for the telecoaching intervention for 151 patients



The cost-effectiveness acceptability curve demonstrates the probability of the telephone coaching intervention being cost effective across a range of thresholds. Within the sub-sample of 151 patients, the estimated probability of the intervention being cost-effective is 86% at a £20,000 per QALY threshold (Figure 7.2).

Figure 7.2: Cost effectiveness acceptability curve of telecoaching intervention for 151 patients



7.4.4. Cost-effectiveness analysis of dyads

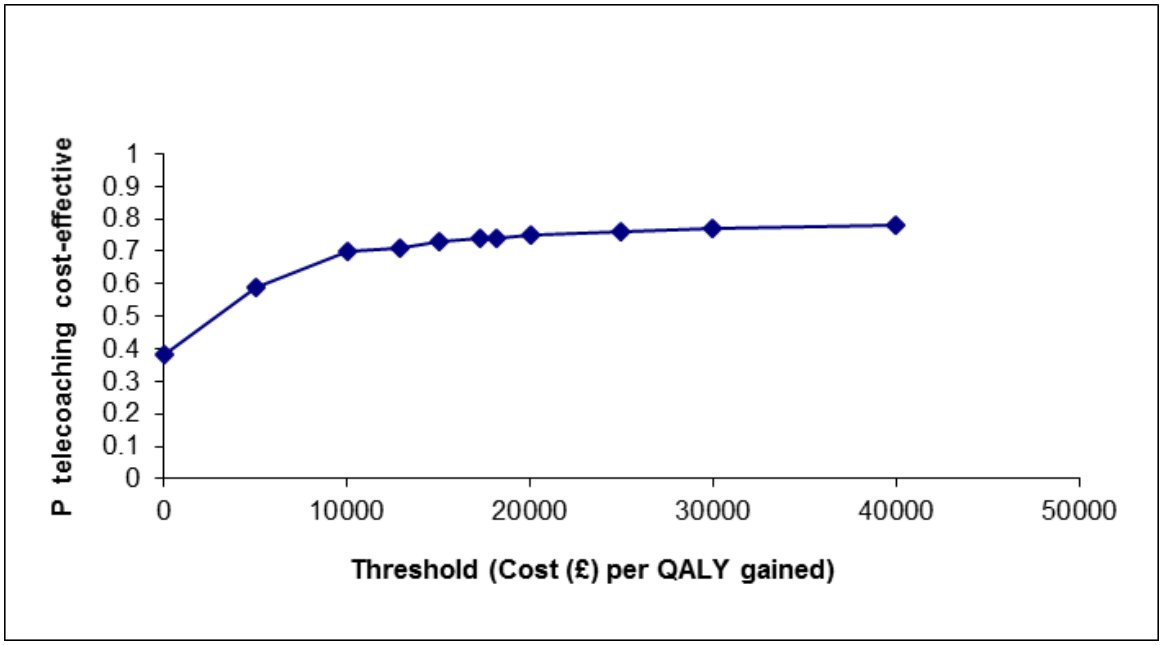
Table 7.6 also displays the cost-effectiveness analysis of the 151 patient-household member dyads. Inclusion of household member QALYs increased the ICER from £1097 to £1144,

relative to exclusion. Further inclusion of household member costs increased the ICER from £1144 to £2140 per QALY, relative to excluding these costs.

7.4.5. Probabilistic sensitivity analysis of dyads

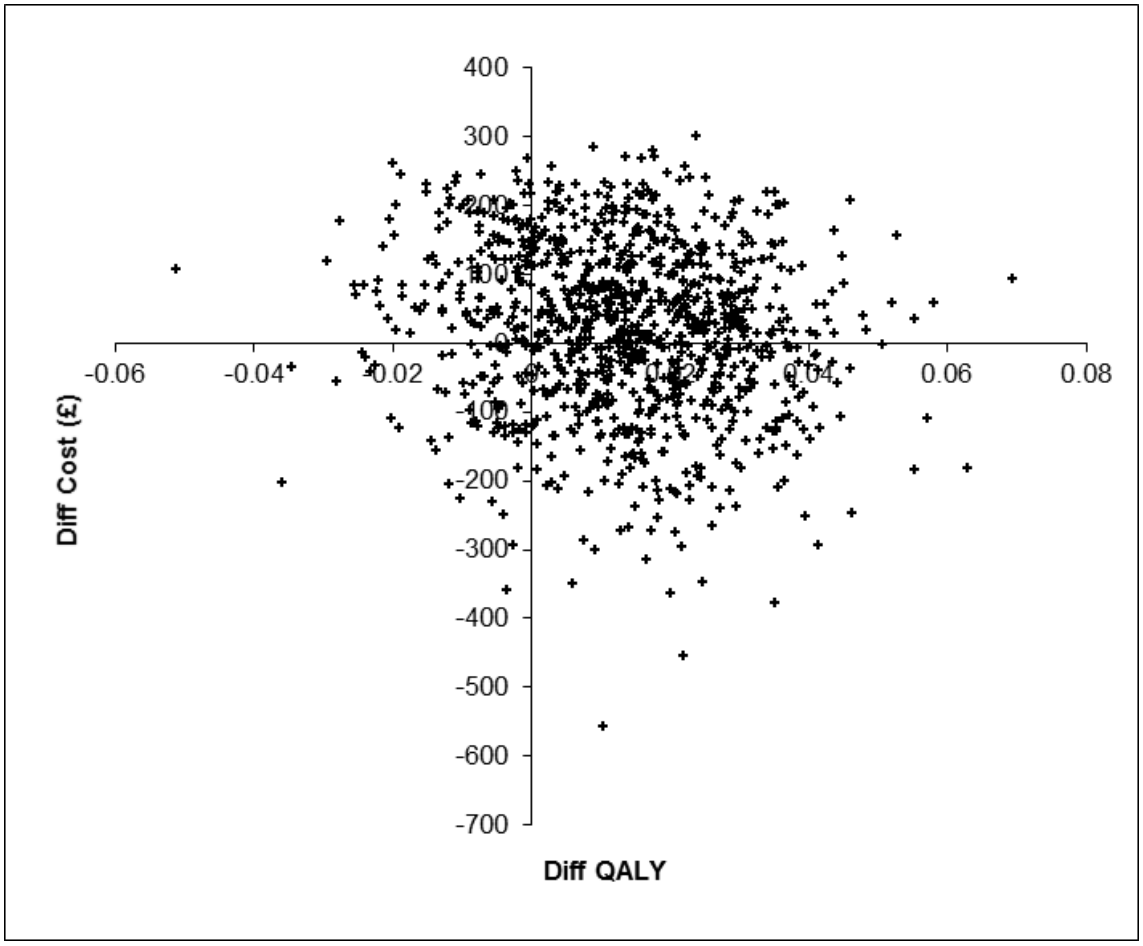
A cost effectiveness acceptability curve was generated for the analysis of 151 patient-household member dyads where both household member costs and QALYs were included (Figure 7.3). It is illustrated here that the telecoaching intervention has a 75% probability of being cost-effective at a threshold of £20,000 per QALY, 74% for both a threshold of £18,182 and £17,241 per QALY, 71% for both a threshold of £12,936 and £11,760 per QALY, and 70% at £11,151 per QALY.

Figure 7.3. Cost-effectiveness acceptability curve of COPD telecoaching intervention for 151 patient-household member dyads (household member costs and QALYs included)



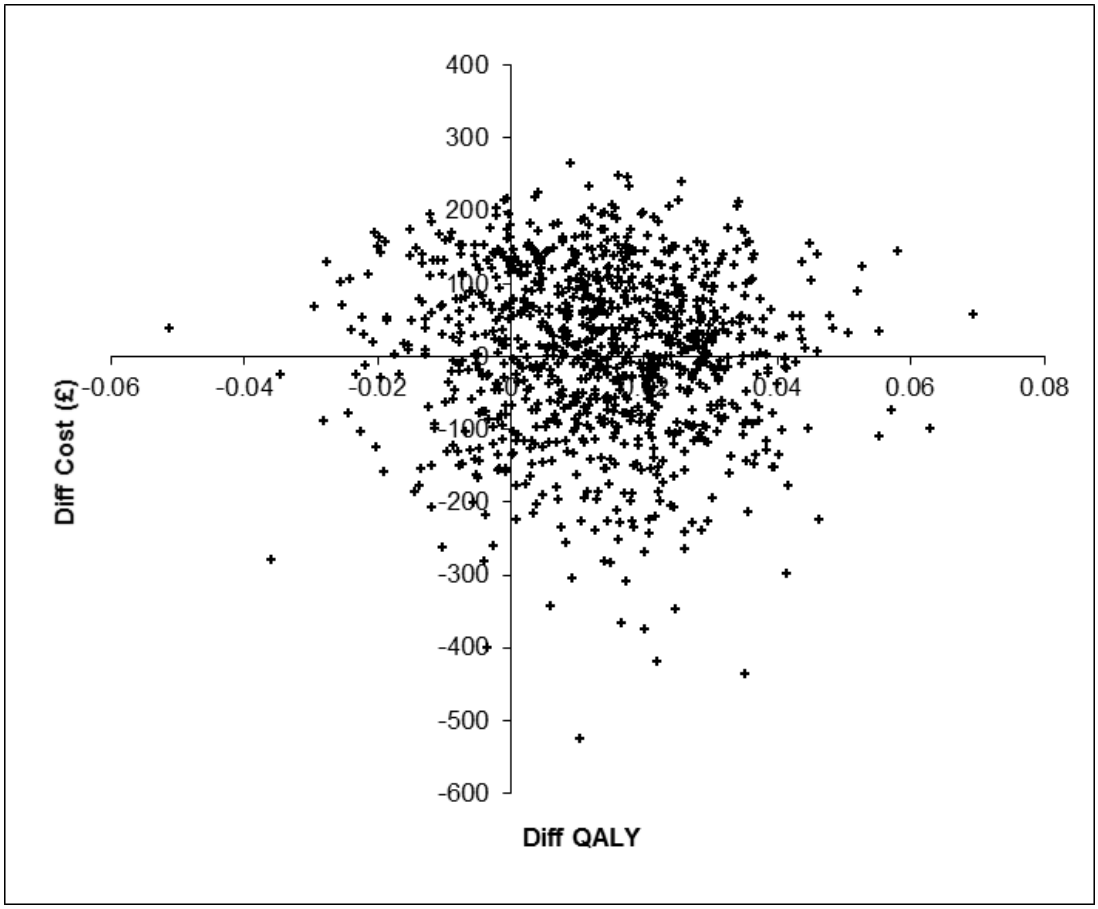
A cost effectiveness plane was also generated for the dyadic analysis including household member costs and QALYs (Figure 7.4). Most of the points were clustered in the eastern quadrants (where QALYs are positive), and particularly within the north-east quadrant. However, there were also more points in the western quadrants compared with the cost-effectiveness plane in Figure 7.1 where 151 patients were analysed without including household member costs and QALYs.

Figure 7.4. Cost-effectiveness plane of COPD telecoaching intervention for 151 patient-household member dyads (household member costs and QALYs included)



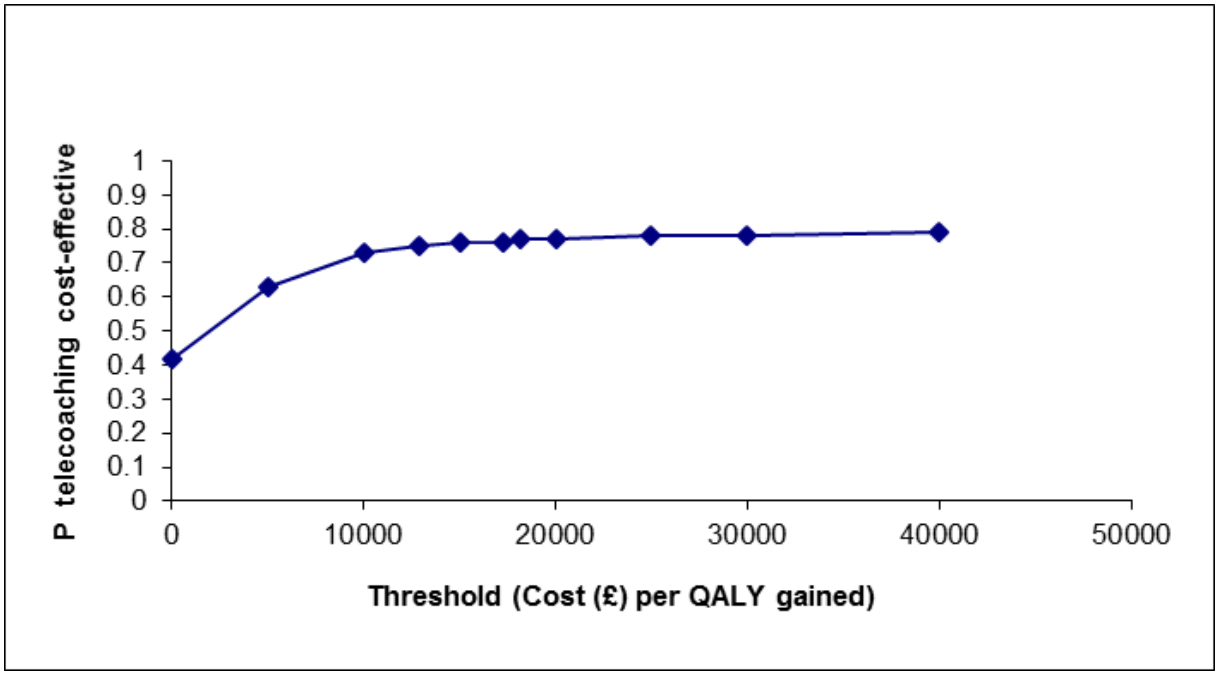
A cost effectiveness plane (Figure 7.5) and acceptability curve (Figure 7.6) were also generated for 151 patient-household member dyads where household member QALYs were included but household member costs were excluded. The cost-effectiveness plane here demonstrates similar dispersion compared with the cost-effectiveness plane where household member costs were included.

Figure 7.5. Cost-effectiveness plane of COPD telecoaching intervention for 151 patient-household member dyads (household member QALYs included, costs excluded)



The cost-effectiveness acceptability curve in Figure 7.6 illustrates that the telecoaching intervention has a 77% probability of being cost-effective using a decision threshold of £20,000 or £18,182 per QALY, 76% using a threshold of £17,241 per QALY, 75% using a threshold of £12,936 per QALY, and 74% at a £11,760 or £11,151 per QALY threshold.

Figure 7.6. Cost-effectiveness acceptability curve of COPD telecoaching intervention for 151 patient-household member dyads (household member QALYs included, costs excluded)



7.5. Discussion

Summary of main findings

In this study, it was found that the COPD telephone coaching intervention was cost-effective in the primary analysis which only considered NHS/PSS costs for patients and patient QALYs (using a threshold of £20000 per QALY), and in all the scenario analyses which additionally included household member costs and/or QALYs. The impact of including household member primary care costs and QALYs on the cost-effectiveness ratios without any adjustment to the threshold was small, but increased the ICERs in all analyses. Including household member costs was influential in the multiplier analysis because of the high magnitude of the incremental household member cost estimate (which was £13.37) relative to the incremental patient cost estimate (£26.23). Including household member QALYs was less influential in the multiplier analysis, because the magnitude of the incremental household member QALY estimate was small (less than 10% of the incremental patient QALY estimate). In the probabilistic sensitivity analysis, the probability of the intervention being cost-effective was reduced by including household member costs and QALYs.

Meaning and interpretation of findings

The negligible health spillover in this study is plausible given that the telecoaching intervention did not demonstrate clinical effectiveness for the COPD patients. However, the QALY difference between intervention and usual care within the 151 patients of participating family members, was quite large and positive despite not being statistically

significant, such that a low ICER of £1097 per QALY was estimated. There may have been a mixture of positive and negative health spillovers generated by the telecoaching intervention which provides a further explanation for the overall negligible health spillover. Although the negative effects of anxiety and strain on a COPD family member's health may have been alleviated by the telecoaching intervention to a degree, low burden caregiving is also known to induce positive feelings in COPD spouses and strengthen the relationship with the patient (320). It was seen in the qualitative free-text analysis from Chapter 6, that only a minority of respondents described that providing informal care was the single biggest impact of the mild COPD, perhaps indicating that most patients only required a small amount or no informal care. Patient illness may also promote an overall heightened attention to self-care among both non-carers and low burden carers (14, 40, 341).

Comparison with other studies

The estimate of household member QALYs in this study was marginally negative. When estimates of health spillover effects are negligible or negative, it is still important to incorporate these effects into analysis as was done here, in order to adopt a consistent analysis methodology across all evaluations. Also, a null finding is in itself informative and therefore should not be excluded from analysis reporting. Previous trial-based economic evaluations of occupational therapy interventions which have also included health spillovers estimated a carer health improvement which in fact exceeded the patient health improvement from intervention (223, 229). A number of factors may explain why interventions in which occupational therapists assisted patients with their disease

management, estimated a large health spillover effect relative to patient health effect. The family members assessed in these studies were all informal carers, they provided care for sicker patients (e.g. Parkinson's, dementia), and the carers received training from the occupational therapist on how to provide better care which alleviated carer burden (223, 229) .

Strengths and limitations

A strength of this study is that it illustrated a range of possible techniques which could be used to apply household member costs and outcomes within a trial-based economic evaluation. For instance, an intuitive approach was used by which patient costs and QALYs and household member costs and QALYs were summed together, in line with previous studies (221, 223). Also, an appropriate factor was applied to account for the non-existence of household spillover for the patients who lived alone.

The study is the first study to illustrate a range of techniques for including health spillover effects within an economic evaluation, including through the conduct of a probabilistic sensitivity analysis where patients and household members were analysed in dyads. A particularly novel element of this study is that it is the first cost-utility analysis to use a more appropriate choice of threshold while including health spillover effects. None of the 29 studies identified in the systematic review in Chapter 2 used a lower decision threshold for including health spillovers. However, this may be necessary to do, otherwise including health spillovers without any lowering of the threshold will result in more interventions being funded without any displacement in any other area of the health care budget, placing an

additional strain on NHS finances. However, there remains uncertainty about what value the multiplier for deflating the threshold should take.

The main weakness of this study was the limited number of household members who were enrolled into the FIS. This meant that there was a weaker basis for the estimations of household member costs and QALYs for the economic analysis. On the surface, it may appear to be reasonable to assume that non-participating household members' health is affected in the same way that participating household members' health is affected by the patients' COPD and associated interventions. However, as the intervention appeared to generate substantially more QALYs for the 151 patients whose household members participated in the study, this suggests that the household members in this study may have been unrepresentative of the household members of the total patient sample. The large confidence interval for the household member QALY estimate also brings to attention the considerable uncertainty around the estimate.

Another implication of the missing data on household members for analysis was that it was not possible to provide an empirical basis for estimating spillovers for household members other than the main household members. Instead, it was assumed in a set of scenario analyses that the second adult household members incurred the same health spillover as the main household members. However this assumption may be considered optimistic.

The aim of this study was to showcase appropriate methods for including health spillovers in a trial-based economic evaluation, in order to guide future researchers who wish to do this. This was done by illustrating a range of methods by which main household member incremental primary care costs and QALYs may be included in a cost-utility analysis. In the

first set of analyses, all of the 428 main household members were assumed to incur health spillover costs and QALYs in the ICER calculations. This was done because economic theory suggests it is important to include the health gains of interventions across all individuals who are affected (78). However, it may be inappropriate to assume that non-responding household members also incur a health spillover without any data to support this. This justified the approach for the second set of analyses, which only included spillover costs and QALYs for the 151 main household members who responded to the baseline survey.

The third set of analyses took a dyadic approach. Only 151 patient-household member dyads were included in the analysis, as these were the only dyads in which both the patient and the household member completed baseline questionnaires. 73% of patients (n=426) were simply dropped from the dyadic analysis as they did not have a participating household member. From the standard NHS perspective, dropping 426 patients from the analysis substantially improved the estimated cost-effectiveness of the intervention. The dyadic analyses were included in this study for the purposes of illustrating a methodology which may be adopted where most of the patients have a household member who is participating in data collection. The advantage that a dyadic analysis has over the multiplier approach for including health spillovers is that it enables a probabilistic sensitivity analysis to be conducted to explore cost-effectiveness uncertainty. However, in future studies where there are a considerable number of patients who live alone or do not have an informal carer or family member participating in data collection, avoiding this dyadic approach altogether is recommended to prevent the eliminating of substantial amounts of patient data from the analysis.

A further limitation of this study was that household member costs were extrapolated from a 3 months to a 12-month period. It was not possible to elicit data from household members in 6 month intervals to provide a more solid basis for the resource usage estimates (as was done for patients).

Implications of findings

In the study presented in Chapter 6, it was found that the patients who lived alone had a slightly worse EQ-5D-5L health status (0.87) than the patients who didn't (0.91). This may reflect that patients who experience loneliness from living alone or who do not have household support to assist in managing their chronic illness are as a consequence likely to have a lower health status (86, 375). The methodology that was adopted for this study potentially discriminates against conditions of the elderly who are more likely to live alone, by not factoring in a QALY multiplier for patients who live alone. However, from an equity standpoint, one may wish to promote the needs of such patients rather than do the opposite. Still, randomised trials should be effective in capturing the extra health status losses incurred over the trial among isolated patients resulting from lack of family support for their disease management. It also needs to be considered that by not including health spillovers, we are potentially discriminating against informal carers by not accounting for the health effects that they experience.

This study estimated small incremental household member primary care utilisation costs and negligible household member QALYs in the economic evaluation, and wide 95% confidence intervals around these estimates, which indicated considerable uncertainty. Uncertainty was

also highlighted as a general concern in measuring carer time costs in a study by Round et al (2015) (376). Uncertainty around carer/family member costs and QALYs could sway decision-makers towards making the wrong decisions, and therefore highlights a need to undertake probabilistic sensitivity analysis to account for the uncertainty. It was only possible in this study to carry out probabilistic sensitivity analysis in the dyadic analysis but not the multiplier analysis.

Conclusion

To conclude, this study demonstrated the application of the multiplier approach for including health spillovers in a trial-based economic evaluation. The exact analytical approach used for including health spillovers is likely to be context-specific and may not be obvious from the outset of the trial. Particularly, this study illustrated the potential importance of carrying out a separate analysis for the sub-sample of patients from whom household member data is collected.

CHAPTER 8: OVERALL DISCUSSION

Family members of chronically ill/disabled patients experience health losses from 'caring for' and 'caring about' a patient. Ideally, economic evaluations of health interventions should capture the health gains generated across *all* individuals whose health is impacted in a meaningful way by the intervention (patients and family members).

In this thesis, I have explored the methods which may be adopted for measuring health spillovers, collecting health spillover data and including health spillovers in economic evaluation. Two contrasting illnesses (meningitis and COPD) that potentially cause health spillovers on family members in different ways were used as case studies. In Chapters 3 and 4, the validity of the EQ-5D-5L and SF-6D for measuring health spillovers were compared. This was done by assessing the ability of the instruments to detect associations with variables predicted to generate health spillovers, using a large dataset of meningitis family members. In Chapters 5 and 6, the health spillover effect generated from a COPD telephone coaching intervention was estimated. This was done by collecting and analysing QALY data collected at baseline and 12 months follow-up from the household members of patients enrolled in the trial of the intervention. In Chapter 7, a range of approaches for including health spillovers in a cost-utility analysis were compared. In doing so, a range of assumptions were tested regarding the inclusion and exclusion of household member costs, choice of threshold, and number of household members included in analysis. The main findings of the studies are described below:

8. Motivation for this research

Guidelines for economic evaluation need to be drawn up outlining what is best practice for measuring health spillovers, and what is the appropriate methodology for including health spillovers in a cost-utility analysis. Exploration of the types of health interventions which are likely to generate a substantial health effect on family members (e.g. behavioural interventions) is also warranted. This PhD provided insight into these areas.

8.1. Key contributions of thesis

8.1.1. How to measure health spillovers (study 1)

In this study, it was found that both the EQ-5D-5L and the SF-6D exhibited construct validity for measuring health spillovers generated in family members of meningitis survivors. Within carers, it appeared that the EQ-5D-5L was more valid for detecting health spillovers generated from 'caring about' the patient, and the SF-6D more valid for detecting 'caring for' health spillovers. As documented in Chapter 1, chronic illnesses such as meningitis have an evident negative impact on the health (and especially mental health) of family members, which explains why the EQ-5D-5L and SF-6D were able to capture the spillover effects generated from meningitis. In the analysis of responsiveness, there was less evidence to suggest that the family member EQ-5D-5L and SF-6D were responsive to changes in patient health or caregiving hours over 12 months.

The responsiveness of the two instruments needs to be investigated in intervention studies, such as randomised trials which are used to inform health technology assessments. It may

be that generic health instruments are not responsive for capturing health spillovers in intervention studies due to the fact that the spillovers are not sufficiently large(12), and this area demands further research (244). Care-related quality of life instruments are likely to be more responsive to non-health spillover effects that carers experience from health interventions, although this has not been formally investigated. Furthermore, non-health spillover effects may be irrelevant to decision makers who are only concerned with maximising health effects.

8.1.2. Health spillovers of a COPD behaviour change (telephone coaching) intervention (study 2)

In this study, it was found that a telephone coaching intervention for COPD patients did not generate spillover effects on household members' primary (COPD-related quality of life) and secondary outcomes. The statistical analysis carried out by the main trial statistician seemed to indicate that the intervention had some degree of effectiveness in improving patients' COPD-related and health-related quality of life, and physical activity, although the null alternative for these outcomes could not be rejected. Another explanation for the null results for household members' outcomes may be that the participants with COPD only had a mild form of the condition and thus were mostly able to function independently, so that the intervention offered minimal scope to alleviate caregiving burden in household members. The patient-level and household-level findings were in agreement to the extent that patient health interventions with limited or no effectiveness would not be expected to

generate much of a knock-on effect (i.e. spillover) on the household. The qualitative findings suggested that many household members were emotionally impacted from worrying about the COPD patient. This indicates that if the intervention had been clinically effective for the COPD patients, this would have alleviated anxiety and distress for the household members who reported that the COPD symptoms and potential progression of the disease caused them to feel worried or concerned. Reduced symptoms of coughing and risk of mortality in the people with COPD which may result from successful behaviour change, have the potential alleviate the emotional burden of the household members who in this study qualitatively reported that these factors had caused them anxiety or distress. It was also found that there could potentially be a considerable amount of non-participation and missing data associated with household member data collection in patient randomised trials. Issues of missing data and the responsiveness of generic health instruments used for measuring health spillovers in randomised trials warrant further investigation.

8.1.3. How to include health spillovers in trial-based economic evaluations (study 3)

This particular case study of the COPD telecoaching intervention illustrated telecoaching cost-effectiveness when including or excluding health spillovers (and health spillover costs); even while factoring in a range of pessimistic cost-effectiveness threshold assumptions. The impact of including household member QALYs on the incremental cost-effectiveness ratios was small, because the magnitude of the household member QALY estimate was less than 10% of the magnitude of the patient QALY estimate. Within this case study, including household member primary care costs had more impact on the ICERs than including

household member QALYs. As with the effectiveness study described in section 8.1.2, missing data may have adversely impacted the relevance of the household member cost and QALY estimates. This may have been the case, given that the patient QALY estimate was very different and much larger for the sub-sample of patients whose household members participated in data collection than for the overall patient sample.

Patient QALYs improved in a non-significant way by the intervention. Conversely, including household member QALYs very slightly reduced the cost-effectiveness of the intervention. More generally, researchers may be inclined to exclude health spillovers from analysis when these discordant effects emerge. However, I would discourage the exclusion of health spillover effects on such grounds, so that health spillovers may be incorporated in a consistent and routine manner across all interventions. More generally, guidelines should be set which require researchers who have excluded health spillovers to provide a justification for their choice. For instance, there may be legitimate time or budget constraints faced by researchers in collecting spillover data, or low response rates from family member questionnaires may also prevent spillovers from being included in an economic evaluation (157). It may also be challenging to collect data from family members under 18 as they may lack the comprehension skills to complete assessments of their outcomes, although a youth-friendly version of the EQ-5D (the EQ-5D-Y) is available for use in people who are aged 8 to 18 years old (377).

This study highlighted the importance of including questions in the patient baseline questionnaire about whether the patient lives alone, and if not, how many household members the patient lives with. Obtaining this data from patients enabled appropriate

adjustment in this study to account for the patients who lived alone who resultantly did not generate a household health spillover. The systematic review that was conducted for Chapter 2 illustrated that few economic evaluations have included health spillovers. This may be due to uncertainty on the methods and techniques for collecting and including spillover data which were addressed in this study.

8.2. Strengths and limitations of this research

This thesis makes a contribution to the field. Two case studies were used of contrasting illnesses which presented the opportunity for a richer analysis. The main finding from the literature review chapters was that although health spillovers should ideally be systematically included in extra-welfarist economic evaluations, there are important challenges that need to be negotiated before this can be done. The three empirical studies for the thesis aimed to address some of these challenges.

The first empirical study demonstrated that the EQ-5D-5L and SF-6D are potentially valid instruments for measuring health spillovers using a large sample of family members of meningitis survivors. This is a novel study as no previous study has compared the validity of the EQ-5D-5L and SF-6D for measuring health spillovers in family members, or looked at the validity of a health status measure for detecting health spillovers in non-carers.

The second study was novel, as although a number of studies have examined the spillover on carers of interventions for chronic or infectious diseases as documented in the systematic review of Chapter 2, few have examined the potential for spillovers resulting from behaviour change interventions. Furthermore, the prospective study of health effects on close family members is rarely done even though trials provide the main input for economic evaluations.

The second study also presented the first full quantitative investigation of how a COPD intervention may generate health and health behaviour change beyond the patient (316). The study also highlighted a more general concern that estimates of household member QALYs in patient trials are likely to be more uncertain than estimates of the related patients' QALYs. The third study illustrated a methodology which may be used to include health spillovers in a trial-based economic evaluation, using a novel approach of adjusting the conventional NICE threshold and adjusting for the patients who live alone. A range of practical methodological problems that a health economist may face in including health spillovers were dealt with accordingly in the third study.

The empirical investigations for the thesis were nested within the specific case studies of meningitis and COPD. In order to explore spillovers and their incorporation in an economic evaluation, it was considered necessary to choose a randomised trial of a chronic illness (COPD) as a case study. The findings of the validity study may not be generalisable to certain illnesses. Meningitis encompasses a wide range of physical and psychological sequelae which may allow for the validity findings to be more broadly applied to other chronic illnesses which affect children, but less so for illnesses which affect older patients and their spouses. One might speculate that the SF-6D, which comprises of employment-related items, may exhibit higher validity for capturing carer spillovers in this study, than in a study of the spousal carers of older patients. This is because the spousal carers of older patients are more likely to be retired, compared with parents who provide care for children or adolescents with meningitis.The data collection period for the household members in the COPD case study was 12 months. This may have been too brief to capture the health spillover effects

generated from a health intervention, which are more likely to be generated over a longer period of accumulated psychological and caregiving stress.

In the validity study, the family member provided a proxy assessment of the meningitis patient's EQ-5D-5L score. Ideally, a future study in this area should provide self-report estimates from both patients and family members. Family members may not be able to accurately assess the patient's health status and particularly depression experienced in patients which may be hidden (324).

Only a minority of main household members (151 out of 428) were enrolled into the family impact of COPD study. The small sample size presented a considerable challenge in evaluating the health outcomes of household members. The missing nature of the data also weakened the basis for conducting the subsequent economic evaluation which included household member QALYs. There was a particular failure to obtain data from more than one household member per patient. A further important limitation of the economic evaluation study was that the assumptions that were made about threshold reduction to account for household member QALYs in a cost-utility analysis were to an extent arbitrary.

Two different tariffs were used in this thesis to calculate EQ-5D-5L scores. The cross-walk algorithm was used to calculate family member EQ-5D-5L scores for the validity analysis by mapping the responses onto the EQ-5D-3L value set. This is consistent with NICE's recent position statement which recommends the cross-walk algorithm for calculating EQ-5D-5L scores for a reference-case analysis, although NICE intends to review their position in 2018 (378). However, the new UK EQ-5D-5L tariff published in January 2016 was used to calculate household member EQ-5D-5L scores for the COPD analyses (249). This was done for

consistency purposes because the new tariff was also used to calculate the EQ-5D-5L scores for the COPD patients in the primary telephone coaching cost-effectiveness analysis conducted by the trial health economist. However, NICE has recommended that further research is needed on the implications of using the new tariff on the cost-effectiveness of health technologies across a range of diseases (378).

8.3. Recommendations

8.3.1. Recommendations for future research

Based on the findings of this thesis, future research activity could investigate the following areas:

Responsiveness of measures in relation to interventions

A future study could investigate responsiveness in relation to healthcare interventions rather than for an illness as was done for the responsiveness study in this PhD. This is because in health economics, we are mostly interested in capturing health spillover effects for the purposes of conducting economic evaluations of health interventions. The linked COPD patient-family member dataset from the PSM-COPD study could be used for a responsiveness investigation of the family member EQ-5D-5L (e.g. by using predictor variables relating to family member physical activity, stress, happiness and patient health). Also future studies could investigate validity in relation to spillovers generated by other health conditions besides meningitis, especially conditions affecting older patients and their

spousal carers. Absolute comparisons between the EQ-5D-5L and SF-6D in terms of family QALY estimates brought about by health interventions are also justified, to determine whether they can be used interchangeably for intervention trials.

Compare health-related and care-related quality of life measures

Future studies could compare the validity and responsiveness of both health-related and care-related quality of life measures for carers, and also compare the results of the two instruments when administered to carers in trials in terms of their impacts on cost-effectiveness ratios. This study only compared the validity of health-related quality of life measures. If care-related quality of life instruments are found to be much more responsive than health-related quality of life instruments when administered to carers in a trial setting, their use may be favoured over using health-related quality of life instruments, due to their greater sensitivity in quantifying differences for carers between trial arms. This greater responsiveness of care-related quality of life instruments may overcome the low statistical power in detecting and quantifying trial arm differences which are associated with the limited sample sizes of primary carers in trials. These limited sample sizes of primary carers may be the result of a proportion of trial patients either not having a primary informal carer or opting not to participate in data collection (as was observed within the COPD case study of the PhD).

Health spillovers of interventions for ill children

Future studies could investigate interventions for ill children which are likely to have a wider impact on the household in terms of affecting more than one parent and also siblings. By investigating this, we can further our understanding of which family members are most impacted by health spillovers from health interventions for sick and disabled children. It is important to consider that these family members may not necessarily live in the patient's house. The household perspective used in my study prevented the sub-group analysis of health spillover effects amongst the adult children of COPD patients who ordinarily live outside of the household.

Health spillovers for conditions other than COPD

Health spillovers for interventions across a wider range of conditions, for example severe COPD, mental illness, stroke and dementia, where the informal care and psychological burden on family members is expected to be large, could be investigated. This would further understanding of the magnitude of the health spillover effects which are generated from health interventions. In my study of mild/moderate COPD patients, the informal care needs of the patients appeared to be low.

Including health spillovers in a model-based economic evaluation

Although this PhD examined methodology for including health spillover effects in a trial-based economic evaluation, it was beyond the scope of the PhD to explore the methods for

including family QALYs in a model-based analysis. Model-based analyses extrapolate QALYs beyond the time horizon of a health intervention trial, and it remains unresolved what assumptions should be made for extrapolating health spillover effects and this may be context specific. For example, carers of patients recovering from a critical illness are less likely to report depression symptoms over time (47), but on the other hand carers of chronically ill patients may experience physical health impairment only 2 to 4 years after the patient first became ill (325). It may be wholly appropriate to extrapolate health spillover effects over a longer time horizon as carers' health may only deteriorate after experiencing care burden and stress over a period of time.

Including the health effects of bereaved family members in economic evaluation

An important question that was beyond the scope of this thesis is to theoretically explore the potential inclusion or exclusion of health effects among bereaved family members. If economic evaluations aim to maximise population health, they should account for the health losses of bereaved family members in addition to health spillovers on living family members. However within a randomised trial, it may be difficult on ethical grounds to collect data from the family members of patients who die during the trial.

The inclusion of carer time costs in economic evaluation

The US Panel on Cost-Effectiveness in Health and Medicine recommends that informal care costs are included in economic evaluation (194), and a future study could investigate the implications of this recommendation. Informal carer time costs in the UK are substantially valued at £132 billion per annum (19). It might therefore be hypothesised that including

carer time costs would have a more influential impact on cost-effectiveness ratios than including carer health-related QALYs; some cost-utility analyses from the systematic review in Chapter 2 illustrated this (208, 212).

The distributional implications of including spillover effects

The implications of including spillover effects in economic evaluation on the way the NHS budget is allocated across different groups in society may be explored in a future study. One particular area which could be examined is whether elderly people would lose out from the routine incorporation of spillover effects in economic evaluation. Although the elderly are more likely to receive informal care, they are also more likely to live alone, so the distributional implications from including health spillovers on the elderly remain unclear. It may also be necessary to include health spillovers for non-household family members or carers to prevent inequity for people who live alone.

8.3.2. Recommendations for future practice

It is argued in this thesis that a QALY is a QALY regardless of who it falls on, and that family members are not just passive agents whose costs and outcomes are irrelevant to decision makers. The Second US cost-effectiveness Panel in 2016 recommended that carer time costs should be included in economic evaluation along with carer QALYs in a base-case analysis (as well as "QALYs accrued among any other affected parties" allowing flexibility for the inclusion of non-carer QALYs) (194). These updated guidelines may stimulate a future increase in the number of economic evaluations from the USA which include carer QALYs.

In practice when including health spillovers in a trial-based economic evaluation, health economists should consider two options. Where over 80% of patients have a family member participating in data collection, the health economist should consider summing patient and family member QALYs across each dyad before computing averages. On the other hand, where less than 80% of patients in the trial have a participating family member, it is inappropriate to drop a substantial amount of patient data when undertaking a cost-utility analysis, and the multiplier approach should instead be taken which assumes a spillover for non-responding family members and no spillover for patients who live alone. This would require data collection from patient baseline questionnaires on whether the patient lives alone or not. This was an important piece of information that was integrated into the economic analysis that was carried out.

Future trials may choose to use a dyadic perspective rather than a wider household member perspective as used in this study, in order to adopt a simpler and more feasible procedure for collecting data and including health-related or care-related spillovers in a patient-family member analysis. Patients could be asked to pass on a questionnaire to their informal carer, or closest family member. This approach would also potentially enable data to be collected from patients who are in institutional care, or live separately from their relatives as is common for patients experiencing a severe mental illness or addiction disorder. However, it may be difficult for some patients to pass on a questionnaire to their closest family member if the family member does not provide regular care for the patient or see the patient very often (for example, for the family members who live in a different town or city to the patient). Patients could instead during trial recruitment be requested to provide the postal

address of their closest family member, so that the family member could then be contacted directly by the researcher.

As demonstrated in Chapter 7 and previous studies, a specific advantage of a dyadic perspective is that it lends to a probabilistic sensitivity analysis (221, 223). A dyadic perspective may be considered as a starting point for the routine inclusion of spillover outcomes. However further down the line, once a dyadic perspective has become more well established, decision makers may wish to cast the net wider by capturing spillovers generated across the extended family/social networks or both parents of child patients for the relevant interventions. A dyadic approach may have been appropriate in the context of the COPD telecoaching intervention because 88% of trial patients lived either alone or with just one household member.

The use of a carer perspective rather than a household perspective for costs and outcomes may also produce the additional challenge of needing to assess which diseases create situations where informal care is provided (307). The original motivation for this research largely stems from recognition of the burden that informal carers experience in society and which is currently ignored in NICE economic evaluations. Assuming a strictly carer perspective for including spillovers, it may thus be considered inappropriate and costly to implement data collection methods for interventions without a substantial carer population (166, 307). The size of the carer population may not be obvious from the outset of a trial, and a further complication in identifying the carer population is that family members (and particularly spouses) may not always perceive themselves to be carers. Even acute illnesses may create an informal care situation and health spillover effect, albeit for a short time

period (213, 239). Moreover it is important to adopt a consistent and systematic approach when choosing the interventions where health spillover data should be collected and analysed (167).

Finally, the health economist should consider collecting household member/carer outcomes over a longer time period in a trial. This is because it may take time before carers' health status is impacted by the prolonged strain of providing care; one study reported a lagged effect of caregiving on health status by 2 to 4 years (325). One solution could be to collect household member follow-up data 12 months after final follow-up data is collected for patients (i.e. 2 to 3 years after the start of the trial). This would however imply the delay of the HTA process for interventions by a year.

8.4. Conclusion

Impacts to family members and carers are currently neglected in NICE economic evaluations and UK health technology appraisal. In this thesis, it was found that there is potentially a scope for the routine inclusion of health spillover effects in economic evaluation. Various methods were identified that may be deployed for the measurement and inclusion of health spillover effects in economic evaluation. However, further research is required for exploring how and whether to include health spillovers systematically in NICE economic evaluations.

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Appendices

Appendix 2.1. Search strategy for systematic review of cost-utility analyses which have included health spillovers

Table 1. Keywords used in the search

Study Design keywords	Population keywords	Outcome keywords
Economic Evaluation	Family	QALY$
Cost utility	Families	Quality adjusted life year*
Cost effective	Network member$	Quality of life
Cost benefit	Household adj5 members$	Healthy years equivalent$
	Informal care$	Healthy life year$
	Unpaid care$	DALY$
	Carer$	EQ-*
	Caregiver$	SF*
	Relatives	HUI3
	Parent$	
	Spouse$	
	Spillover$	

The databases Medline, Embase, NHS EED and Econlit were searched on 5th October 2015 from origin of the databases to present. The keywords used in the search are listed in table 1. All studies which contained in their titles and abstracts one or more keyword from each of the outcome, population, and study design of interest in the review, were obtained in the search. This was done by using a Boolean search with AND/OR operators.

The search strategy that was used across the four databases was as follows:

cost effective* OR cost benefit OR cost utility OR economic evaluation

AND

QALY* OR quality adjusted life year* 0R quality of life OR DALY* OR healthy life year* OR healthy years equivalent* OR euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d) OR (hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII) OR (sf6D or sf 6D or short form 6D or shortform 6D OR sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension)

AND

family OR families OR network member* OR household adj5 member* OR “relatives” OR caregiver* OR carer* OR informal care* OR unpaid care* OR parent* OR spouse* OR spillover*

The screening of studies from the initial search to the final list of studies included in the review comprised of two stages: the initial title and abstract screening, and a further investigation of the remaining articles.

In stage 1, the title and abstract screening, articles were excluded if they met one or more of the following exclusion criteria:

- Exclude if they are not full economic evaluations (e.g. reviews, systematic reviews, clinical effectiveness studies, costing studies).
- Exclude if not an obvious cost-effectiveness analysis (no incremental cost per outcome)
- Exclude if not an obvious cost-utility analysis (no utility measure in list of outcomes)
- Exclude if they clearly and specifically relate to the economic evaluation of a family/carer intervention.
- Exclude if population terms (e.g. family, carer, informal care) were not mentioned in a relevant part of the abstract
- Exclude if conference abstract, study protocol, not English language

In stage 2, a further investigation of articles remaining from the screening in stage 1, articles were excluded if they met one (or more) of the following exclusion criteria:

- Does not use a measure of family member health utility
- Study meets any other exclusion criteria from Stage 1 of the review
- Study was unaccessible via the University of Birmingham/google search, and it was not explicitly specified in the title/abstract that family member or carer QALYs were

included in the study. If it was specified in the title and abstract, the lead author was contacted to access the study.

Embase search:

1	exp economic evaluation/
2	exp "cost utility analysis"/
3	exp "cost effectiveness analysis"/
4	exp "cost benefit analysis"/
6	exp quality adjusted life year/
7	exp "quality of life"/
8	DALY$.ti,ab.
9	healthy life year$.ti,ab.
10	healthy years equivalent$.ti,ab.
11	(euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d)).ti,ab.
12	(hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII).ti,ab.
13	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension).ti,ab.
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	5 and 14
16	(family adj5 member$).ti,ab.
17	network member$.ti,ab.
18	(household adj5 member$).ti,ab.
19	relatives.ti,ab.
20	exp caregiver/
21	informal care$.ti,ab.
22	unpaid care$.ti,ab.
23	carer$.ti,ab.
24	caregiver$.ti,ab.
25	spouse$.ti,ab.

26	exp parent/
27	spillover$.ti,ab.

(cost effective* or cost benefit or cost utility or economic evaluation) AND (QALY* OR quality adjusted life year* 0R quality of life OR DALY* OR healthy life year* OR healthy years equivalent* OR euroqol or euro qol or eq5d or eq 5d or eq-5d or (euro adj qol) or (eur adj qual) or (eq adj 5d) OR (hui3 or hui 3 or health utilities index mark 3 or health utilities mark three or hui III or huiIII) OR (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form sixD or sf-6d or 6d or 6-d or 6 dimension)) AND (family OR families OR network member* OR household adj5 member* OR “relatives” OR caregiver* OR carer* OR informal care* OR unpaid care* OR parent* or spouse* or spillover*) IN NHSEED

EMBASE n=1999 Medline=673 Econlit =24 NHSEED=574 (approx.)

Appendix 2.2. Data extraction forms for the systematic review of cost-utility analyses which include health spillover effects

Title

Treating alcoholism reduces financial burden on caregivers and increases quality adjusted life years

Author	**Publication Year**
Salize, H. J., Jacke, C., Kief, S., Franz, M., Mann, K.	2013

Type of analysis	**Intervention**	**Comparator**	**Patients**
Before and after study	Alcohol dependence treatment in outpatient and inpatient settings	None	Alcoholic patients

Rationale Psychosocial burden on family members is important to consider

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
One carer/relative of patient	WHO-BREF	Base case

Family member costs? Which ones Not included (health care perspective)

Family member QALYs information

48 carers and relatives . n=24 family members of inpatients . n=24 family members of outpatients.

Method for combining patient and family member QALYs

N/A. Only QALYs of family members assessed (patient QALYs not measured and excluded in analysis

Size of health spillovers, impact on ICER

Intervention cost per QALY for outpatient treatment = 5470 euros < 30 000 euros (threshold)

Intervention cost per QALY for inpatient treatment = 37601 euros > 30 000 euros (threshold)

Other comments

Authors acknowledge that patient QALYs should be aggregated with family members to reflect total health gains to family in ICER. Patient QALYs weren't measured in this 'exploratory' study that focused on family members.

Nevertheless treatment is cost-effective for family members alone of outpatients, even when patient QALYs are excluded.

Title

Cost-effectiveness of one year dementia follow-up care by memory clinics or general practitioners: economic evaluation of a randomised controlled trial

Author	**Publication Year**
Meeuwsen, E., Melis, R., Van Der Aa, G.	2013

Type of analysis	**Intervention**	**Comparator**	**Patients** Dementia
Trial based (RCT)	Care by 'specialist' memory clinic (patient focused)	Usual care by GP	

Rationale Societal perspective. Also carers filled out questionnaires for themselves as well as on behalf of the patient.

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Primary carers	EQ-5D	Base case and scenario

Family member costs?

Carer productivity losses (and patient productivity losses)

Family member QALYs information.

N=175 patients and their primary carer. In final analysis n=160 pairs evaluated. One carer died. One carer did not fill out the questionnaire. 11 pairs dropped out because they considered participation in the study to be too burdensome. One carer was not present during the measurements.

Method for combining patient and family member QALYs

Patient and carer QALYs summed

Scenario analysis 1: Patient and carer costs. Only patient QALYs. Scenario analysis 2: Cost and QALY of patient only. Scenario analysis 3: Cost and QALY of carer only

Size of health spillovers, impact on ICER

There was no difference in QALYs for both patients and carers between intervention and comparator arms of trial. Therefore including/excluding carer QALYs did not have much impact to results in the base case and scenario analyses.

Other comments

Cost-effectiveness acceptability curve were a different shape for scenario analysis 2 (costs and QALYs of patient only) compared to the other scenario analyses, this was noted by the authors but not explained further.

Title

Budget impact and cost effectiveness of including a pentavalent rotavirus vaccine in the new Zealand childhood immunization schedule.

Author		**Publication Year**	
Milne, R. J., Grimwood, K.		2009	
Type of analysis Model-based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5

Rationale Enables comparison with other rotavirus economic evaluations in other countries

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Carers (parents)	EQ-5D	Base case and scenario

Family member costs?

Carer productivity and transportation costs included in societal perspective

Family member QALYs information.

Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

Method for combining patient and family member QALYs

Several scenario analyses which undertook alternative perspectives for costs (from health care or government perspective)

In another scenario analysis, the disutility of two caregiving parents was included instead of one carer.

Size of health spillovers, impact on ICER

Scenario analysis : 2 carers disutility instead of one carer. Including this second carer reduces ICER by 45%.

Other comments

Title

Probabilistic Markov Model estimating cost effectiveness of methylphenidate osmotic release oral system versus immediate release methylmenidate in children and adolescents: which information is needed?

Author	**Publication Year**
Schawo, S., van der Kolk, A., Bouwmans, C.,	2015

Type of analysis	**Intervention**	**Comparator**	**Patients**
Model based	OROS	IR methylmenidate	Children and adolescents with ADHD

Rationale ADHD can be particularly stressful on the family of the patient. Literature in the area of including health spillovers in economic evaluation is emerging.

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Whole family	EQ-5D	Base case

Family member costs?

Carer productivity and transportation costs included in societal perspective

Family member QALYs information.

QALYs on the family (closest 4 family members of the patient) was estimated to be 48% of the patient QALY gains from vaccination. This estimate was based on a cross-sectional study by Al-Janabi that surveyed 1600 family members of meningitis survivors. A regression model was used to determine the magnitude of the association between family member health and patient health. Although meningitis and ADHD are very different illnesses, the authors made no adjustment to this 48% calculation.

Authors also mentioned study from van der Kolk which used EQ-5D. Measured utility of 618 children and 590 caregiving parents of children with ADHD. Estimated that suboptimal/stopping treatment is associated with carer utility reduction of 0.02. However this study, although mentioned in the methods, does not appear to have been used in the analysis to estimate carer utility.

Method for combining patient and family member QALYs

Base case: Includes carer costs, includes carer utility. Scenario 1: Costs of carers excluded Scenario 2: Utility of carers excluded

Size of health spillovers, impact on ICER

The study by Al-Janabi estimated total family spillover to be 48% of the utility loss incurred by

children with developmental problems. Therefore, the authors multiplied patient QALYs by 1.48 to estimate total QALYs for the base case analysis.
Other comments For some reason costs also change slightly when carer utility is excluded in scenario 1, although it is unclear why this should happen.

Title

Re-evaluating cost-effectiveness of universal meningitis vaccination (Bexsero) in England: modelling study

Author Christensen, H., Trotter, C. L., Hickman, M		**Publication Year** 2014	
Type of analysis Model-based	**Intervention** Meningitis vaccination programme	**Comparator** No vaccination	**Patients** All infants in England vaccinated

Rationale Health care perspective

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Whole family (4 family members)	EQ-5D	Scenario

Family member costs? Not measured/included

Family member QALYs information.

QALYs on the family (closest 4 family members of the patient) was estimated to be 48% of the patient QALY gains from vaccination. This estimate was based on a cross-sectional study by Al-Janabi that surveyed 1600 family members of meningitis survivors. A regression model was used to determine the magnitude of the association between family member health and patient health.

The QALYs lost to bereaved family members were also included in the analysis. This was done using a different study that estimated impact of child death on bereaved parents. The QALY loss to bereaved family members was estimated to be 9% of the QALY losses to the child who died.

Method for combining patient and family member QALYs Family member QALY losses included in a scenario analysis (excluded in the base case)

Size of health spillovers, impact on ICER

By including family QALYs, the vaccination cost-effective price increased from £8 to £11 per dose.

Other comments

Title

Economic evaluation of Occupational Therapy in Parkinson's Disease: A randomised controlled trial

Author Sturkenboom, I. H., Hendriks, J. C., Graff, M. J.		**Publication Year** 2015	
Type of analysis Trial-based	**Intervention** Occupational Therapy	**Comparator** No occupational therapy (usual care)	**Patients** Parkinson's disease

Rationale Societal perspective

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Primary carers	EQ-5D	Not stated

Family member costs? Carer productivity losses were excluded in the primary analysis. Although the authors tried to measure these, there was a substantial amount of missing data that prevented their estimation. However carer health care utilisation costs were estimated.

Family member QALYs information.

189 patients, 178 carers. A primary carer of a patient would participate if willing and available.

Method for combining patient and family member QALYs

Three analyses performed: It was unclear what the overall method was that was used. It appears that the authors may have used the same perspective for both costs and outcomes (e.g. carer only perspective calculated a NMB using carer costs and carer outcomes only).

1) Patient only. Experiences EQ-5D gain of 0.02 from intervention
2) Carer only. Experiences EQ-5D gain of 0.04 from intervention
3) Patient-carer pairs. This was a complete case analysis in which only patient-carer dyads were included (patients without a carer participating in the study were excluded). Patient and carer QALYs appear to be aggregated (utility gain of 0.05 from intervention).

Size of health spillovers, impact on ICER

The gains to the carer from occupational therapy were estimated to be larger (+0.04) than the gains to the patient (+0.02); however neither of these gains were statistically significant when assessed separately (or when aggregated across patient-carer dyads).

Other comments

Title Health economics of rotavirus immunization in Vietnam: potentials for favorable cost-effectiveness in developing countries			
Author *Tu HA, Rozenbaum MH, Coyte PC, Li SC, Woerdenbag HJ, Postma MJ*		**Publication Year** 2012	
Type of analysis Model based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5
Rationale Carers play an important role in infant rotavirus			
Groups of family members considered in analysis Parents	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Scenario	
Family member costs? Indirect costs were included in societal perspective, but these costs were not specified by the authors			
Family member QALYs information. Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs Base case: child only. Probability of vaccination being cost effective is 67% Scenario 1: including QALYs of one carer increase probability of cost-effectiveness to 70% Scenario 2: including QALYs of two carers increase probability of cost-effectiveness to 74%			
Size of health spillovers, impact on ICER Small impact of including spillover effect Perhaps because the rotavirus causes far more deaths in this developing country setting (1660 in a birth cohort), so the QALY losses for patients far outweigh the carer spillover QALY losses in this setting.			
Other comments			

<table>
<tr><td colspan="4">Title Cost-effectiveness of universal rotavirus vaccination in reducing rotavirus gastroenteritis in Ireland</td></tr>
<tr><td colspan="2">Author Tilson L, Jit M, Schmitz S, Walsh C, Garvey P, McKeown P, Barry M</td><td colspan="2">Publication Year 2011</td></tr>
<tr><td>Type of analysis
Model-based</td><td>Intervention Rotavirus vaccination</td><td>Comparator No vaccination</td><td>Patients Children aged under 5</td></tr>
<tr><td colspan="4">Rationale Base case analysis justified excluding carers on the basis that economic evaluations generally do not include carer QALYs. Scenario analysis justified on the basis that carer QALYs included in rotavirus economic evaluations in other countries- justifying the approach in this Irish study to enable comparability with other countries.</td></tr>
<tr><td colspan="2">Groups of family members considered in analysis
One parent (primary carer)</td><td>Measure of FM health

EQ-5D</td><td>Type of analysis where FM health included Scenario</td></tr>
<tr><td colspan="4">Family member costs? Direct (private GP) and indirect (productivity loss) costs considered</td></tr>
<tr><td colspan="4">Family member QALYs information

Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.</td></tr>
<tr><td colspan="4">Method for combining patient and family member QALYs See below</td></tr>
<tr><td colspan="4">Size of health spillovers, impact on ICER

Base case analysis uses a health care perspective and utilities for the child only.

Scenario analysis 1. Including the QALYs lost by one carer reduces ICER from base case analysis by 45%.

1. Scenario analysis 2. For the societal perspective, the informal carer work losses were included, carer utility losses excluded.
2.
3. Scenario analysis 3. Societal perspective. Work losses, as well as one carer utility losses included. This adjustment reduces ICER from scenario analysis 2 by 45%.</td></tr>
<tr><td colspan="4">Other comments</td></tr>
</table>

The cost effectiveness of rotavirus vaccination: comparative analyses for five European countries and transferability in Europe			
Jit, M., Bilcke, J., Mangen, M. J. J.		**Publication Year** 2009	
Type of analysis Model based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5
Rationale Senecal study collected data on utilities of children and carers – thereby providing the impetus to include carers in QALY estimates			
Groups of family members considered in analysis Parents (informal carers)	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case (health care perspective)	
Family member costs? Yes, productivity losses and out-of-pocket expenses for parents (e.g. extra nappies) included in the societal perspective (scenario analysis)			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs Base case analysis (health care perspective): one carer QALYs included, carer costs excluded, makes 'realistic' adjustment to child and carer QALYs from Senecal study (50% reduction for the home-treated cases) Scenario analysis 1: (health care perspective): carer costs and QALYs excluded Scenario analysis 2 (societal perspective): one carer included, carer costs included Scenario analysis 3 (using most favourable assumptions for vaccinating): two carers included, no reduction adjustment of the QALY losses from Senecal study for home-treated cases.			
Size of health spillovers, impact on ICER Scenario analysis: Excluding carer approximately doubles ICER from the base case analysis. Including a second carer approximately halves ICER from base case.			
Other comments The inclusion of carer costs (productivity and out-of-pocket) has a substantial impact on cost effectiveness of vaccination in some countries. The adjustment in QALYs for home-treated cases is assumed to be 50% of the utility losses from			

the Senecal study for both children and carers in base-case analysis. This assumption was made due to an absence of data for utilities of home treatment cases. However in reality, children and carer utilities may not be perfect linear functions of each other.

Cost effectiveness of Donepezil in the Treatment of Mild to Moderate Alzheimer's Disease: A UK Evaluation Using Discrete-Event Simulation			
Denis Getsios, Steve Blume, K Ishak and Grant Maclaine		**Publication Year** 2010	
Type of analysis Model based (discrete event simulation)	**Intervention** Donepezil	**Comparator** No treatment	**Patients** Alzheimer's disease
Rationale Not stated			

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
One carer	SF-36	Base case (in both health care and societal perspectives)

Family member costs? Yes, carer productivity losses included in societal perspective

Family member QALYs information

Patient and carer QALYs were estimated using data from several different donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed by the authors using the data from 3 donepezil clinical trials.

Method for combining patient and family member QALYs

Two perspectives used: health care payer and societal perspective.

In health care payer perspective – health care (mainly NHS) costs, sum of patient and carer QALYs

In societal perspective – health care costs plus carer productivity costs , sum of patient and carer QALYs

Size of health spillovers, impact on ICER

Carer QALY gains from donepezil were only estimated to be approximately 10% of patient QALY gains.

Including carer productivity losses was a more influential parameter; the reduction in costs to carers was estimated to be approximately equivalent to the reduction in costs to the health care provider, from administering donepezil.

Other comments

Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation			
Hartz S, Getsios D, Tao S, Blume S, Maclaine G		**Publication Year** 2012	
Type of analysis Model based (discrete event simulation)	**Intervention** Donepezil	**Comparator** Memantine or no treatment	**Patients** Alzheimer's Disease
Rationale Alzheimer's disease imposes 'burden' on carers			
Groups of family members considered in analysis One carer	**Measure of FM health** SF-36	**Type of analysis where FM health included** Base case (in both health care and societal perspectives)	
Family member costs? Yes, carer productivity losses included in societal perspective			
Family member QALYs information Patient and carer QALYs were estimated using data from several different donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed by the authors using the data from 3 donepezil clinical trials.			
Method for combining patient and family member QALYs Two perspectives used: health care payer and societal perspective. In health care payer perspective – health care costs, sum of patient and carer QALYs In societal perspective – health care costs plus carer productivity costs , sum of patient and carer QALYs			
Size of health spillovers, impact on ICER Carer QALY gains from donepezil were only estimated to be approximately 10% of patient QALY gains Including carer productivity losses was an influential parameter ,although not as influential as in the UK-based studies by Getsios et al evaluating donepezil and early assessment. The reduction in costs to carers was estimated to be approximately 40% of the reduction in costs to the health care provider, from the administration of donepezil.			
Other comments			

An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom			
Getsios D, Blume S, Ishak KJ, MacLaine G, Hernandez L		**Publication Year** 2012	
Type of analysis Model based (discrete event simulation)	**Intervention** Early assessment and donepezil	**Comparator** Without early assessment; or without donepezil after diagnosis	**Patients** Alzheimer's disease
Rationale Alzheimer's disease has 'profound' effects on carers			
Groups of family members considered in analysis One carer	**Measure of FM health** SF-36	**Type of analysis where FM health included** Appears to be included in both base case analyses	
Family member costs? Yes, carer productivity losses included in societal perspective			
Family member QALYs information Patient and carer QALYs were estimated using data from several different donepezil trials. The regression model for patient QALYs came from an external study; a new regression model for carer QALYs was developed by the authors using the data from 3 donepezil clinical trials.			
Method for combining patient and family member QALYs Two perspectives used: health care payer and societal perspective. In health care payer perspective – NHS costs and QALYs (although unclear whether QALYs were aggregated to include carers under this perspective) In societal perspective – NHS costs plus carer productivity costs , and patient + carer QALYs (summed).			
Size of health spillovers, impact on ICER Under the societal perspective, including carer QALYs reduced the ICER of the early assessment intervention by 12-15% (depending on the comparator that was used). Including carer productivity losses had a more substantial effect on the ICER in the societal perspective. The inclusion of these productivity losses effectively more than halved the ICERs for both interventions.			
Other comments			

The cost-effectiveness of rotavirus vaccination in Australia			
Author *Newall A T, Beutels P, Macartney K, Wood J, MacIntyre C R*		**Publication Year** 2007	
Type of analysis Model-based	**Intervention** Rotavirus vaccination (Rotarix and Rotateq)	**Comparator** No vaccination	**Patients** Children aged 5 years or under
Rationale Carers were estimated in the same study that measured patient QALYs, enabling their inclusion			
Groups of family members considered in analysis Parents	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
4. **Family member costs** Yes, productivity losses			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs See below			
Size of health spillovers, impact on ICER Base case analysis (health care perspective): QALYs for the child and the primary carer were considered. Societal perspective: Included productivity losses for the carers; but only QALYs for the child included (carer QALYs excluded to prevent double counting). Under this perspective, vaccination was a dominant strategy (reduced total costs, increased QALYs). Further scenario analysis: The inclusion of QALY gains from two carers, rather than one, substantially improved the cost-effectiveness of the two vaccinations. For example including two carers instead of one reduced the ICER of Rotarix from $60000 to $40000.			
Other comments			

<table>
<tr><td colspan="4">Title Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease</td></tr>
<tr><td colspan="2">Author Neumann P J, Hermann R C, Kuntz K M, Araki S S, Duff S B, Leon J, Berenbaum P A, Goldman P A, Williams L W, Weinstein M C</td><td colspan="2">Publication Year

1999</td></tr>
<tr><td>Type of analysis
Model-based</td><td>Intervention Donepezil</td><td>Comparator No drug treatment</td><td>Patients Alzheimer’s Disease</td></tr>
<tr><td colspan="4">Rationale Carers were administered the quality of life instrument for the patient; are therefore positioned to self-report their own quality of life</td></tr>
<tr><td>Groups of family members considered in analysis Primary carers</td><td>Measure of FM health

HUI:2</td><td colspan="2">Type of analysis where FM health included Scenario analysis</td></tr>
<tr><td colspan="4">5. Family member costs? Yes, time losses</td></tr>
<tr><td colspan="4">Family member QALYs information

Carer QALYs were measured in a cross-sectional study using the HUI:2 in a sample of 528 carers of people with Alzheimer's disease, stratified by disease severity (201 mild, 175 moderate and 142 severe) and care setting (354 community and 164 nursing home). Carers both proxy reported the health of the patients, and also their own health utility.</td></tr>
<tr><td colspan="4">Method for combining patient and family member QALYs In the conventional base case analysis only patient QALYs were considered. In a scenario analysis carer QALYs were added.</td></tr>
<tr><td colspan="4">Size of health spillovers, impact on ICER QALYs for carers were generally invariant to severity of patient illness and setting of patient treatment, and therefore had little impact on the cost effectiveness ratio when applied in the scenario analysis.</td></tr>
<tr><td colspan="4">Other comments</td></tr>
</table>

Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia

Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, Gutierrez H, Satram-Hoang S, Keating MJ	**Publication Year** 2012

Type of analysis Trial based	**Intervention** R-FC	**Comparator** FC	**Patients** Adult leukemia patients (average age = 61 years)

Rationale Including health of family members represents a new development in cost-effectiveness research

Groups of family members considered in analysis	**Measure of FM health**	**Type of analysis where FM health included**
Spouses/partners	Time trade-off (direct elicitation)	Societal perspective

Family member costs? Yes, included also in the societal perspective

Family member QALYs information

Carer costs and outcomes were excluded in the payer perspective, and were included in the societal perspective. Carer outcomes were included in terms of the utility values of spouses/partners of patients. The utility values of spouses of patients were derived from a study by Basu that estimated the utility losses incurred among spouses of patients with prostate cancer, depending on how much the cancer progressed, and also disutility resulting from the patient dying. Although prostate cancer is a different type of cancer to Chronic Lymphocytic Leukemia (CLL), the Basu study was used as a proxy to estimate spillover of CLL on the spouse.

Method for combining patient and family member QALYs Utility decrements were summed for the patient and the spouse in each of the 3 states of the Markov model. These 3 states were progression free survival (estimated decrement to spouse=0.18, progressive illness (0.40) and death (0.60). A 1-year bereavement period was assumed for the spouse of a patient that died.

Size of health spillovers, impact on ICER

R-FC produced 1.15 more QALYs than FC when considering only patient QALYs. However by aggregating spouse/partner QALYs with patient QALYs, R-FC produced only 1.03 more QALYs than FC. The reason for this reduction is because the overall impact of R-FC in extending the patient's life expectancy compared to FC was estimated to result in an overall more negative impact on the spouse as a result of a longer duration of spillover.

Other comments

Title Impact of transmission dynamics on the cost-effectiveness of rotavirus vaccination			
Author *Shim E, Galvani AP*		**Publication Year** 2009	
Type of analysis Model-based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5
Rationale Not stated			
Groups of family members considered in analysis One parent	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
Family member costs? Yes, carer time losses included in societal perspective			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs No explicit base case was set out, although main finding was that vaccination was cost-effective when considering QALYs for the child and one carer (but not cost-effective when considering QALYs for child only).			
Size of health spillovers, impact on ICER 6. Including one carer approximately halves the ICER in both health care and societal perspectives. ***7.***			
Other comments Societal perspective also included the 'lifetime productivity loss of a child death'- $1.3 million loss in expected future earnings of a child who died.			

Title Cost-effectiveness of a 3-dose pneumococcal conjugate vaccine program in the province of Quebec, Canada			
Author *Poirier B, De Wals P, Petit G, Erickson LJ*		**Publication Year** 2009	
Type of analysis Model-based	**Intervention** Pneumococcal conjugate vaccine programme	**Comparator** No vaccination	**Patients** Invasive pneumococcal disease (all ages)
Rationale Not stated			
Groups of family members considered in analysis One carer (parent)	**Measure of FM health** Not stated	**Type of analysis where FM health included** Base case	
8. **Family member costs?** Yes, costs of disease on the family were included. Carer time losses do not appear to be included.			
Family member QALYs information The disutility associated with pneumococcal disease during the acute phase was assumed to be the same for the patient and one carer. This assumption is based on an unpublished study.			
Method for combining patient and family member QALYs Not stated			
Size of health spillovers, impact on ICER Scenario analysis- child only (excluded the carer). This adjustment resulted in a small increase in the ICER from 18000 dollars to 20000 dollars.			
Other comments			

Socio-economic modelling of rotavirus vaccination in Castilla y Leon, Spain			
Author *Perez-Rubio A, Luquero FJ, Eiros Bouza JM, Castrodeza Sanz JJ, Bachiller Luque MR, de Lejarazu RO, Sanchez Porto A*		**Publication Year** 2011	
Type of analysis Model based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged 5 years or under
Rationale Not stated			
Groups of family members considered in analysis Both parents	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
9. Family member costs? Yes, productivity losses			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYS Base case: Patient and QALY losses for *two* parents were included.			
Size of health spillovers, impact on ICER Not explicitly set out, although including QALY losses for two carers (i.e. both parents) effectively will reduce the ICER for rotavirus vaccination by around 70%, compared with excluding these carers.			
Other comments			

Treatment of childhood anxiety disorder in the context of maternal anxiety disorder: a randomised controlled trial and economic analysis			
Author Creswell C, Cruddace S, Gerry S, Gitau R, McIntosh E, Mollison J, Murray L, Shafran R		**Publication Year** 2015	
Type of analysis Trial based	**Interventions** Treatment of mother's anxiety and her interaction with child, in addition to the comparator treatment that only treats the child	**Comparator** Treatment of child only	**Patients** Mother-child dyads both experiencing anxiety disorder
Rationale The interventions are multi-faceted conferring benefits on both mother and child			
Groups of family members considered in analysis Child	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
10. **Family member costs?** Primary analysis was from health care provider perspective, however costs were measured for both mother and children for time off work to enable a potential future analysis with a societal perspective			
Family member QALYs information Children and mother EQ-5D scores were elicited at the start and the end of the trial, with around 70 mothers and children in each treatment arm. Since patients were recruited in dyads there was no difference in the sample sizes obtained between mothers and children.			
Method for combining patient and family member QALYs In the cost-utility analysis, child QALYs were only included (i.e. the QALYs children experienced from the spillover of the interventions administered to the mother), but QALYs of the mothers who directly received the interventions were excluded.			
Size of health spillovers, impact on ICER Neither the mother or child experienced statistically significant health improvements over the trial period from the interventions.			
Other comments			

Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: a cost-effectiveness analysis			
Author *Little S E, Caughey A B*		**Publication Year** 2005	
Type of analysis Model-based	**Intervention** Acyclovir prophylaxis	**Comparator** No drug therapy (standard care)	**Patients** Neonates
Rationale The model adopts perspective of QALYs lost to both mothers and children, and not for any other family members. Utility losses include disabled children, death of mother, bereavement effect on mother, and also the spillover utility loss mothers incur from caring for neurologically impaired child.			
Groups of family members considered in analysis Mothers	**Measure of FM health** Direct elicitation (standard gamble and time trade-off)	**Type of analysis where FM health included** Base case	
Family member costs? Direct lifetime costs of having a child with cerebral palsy were considered, indirect costs excluded			
Family member QALYs information The maternal utility decrement when a child had either moderate or severe neurologic impairment was applied of 0.17, using an estimate from the literature of the utility decrement for the mother from having a child with Down syndrome. This utility for Down's syndrome is not specific for the health states analysed in the model and was used as a proxy estimate. A maternal utility decrement of 0.07 was also applied when the child died.			
Method for combining patient and family member QALYS QALYs for the mother and child were summed.			
Size of health spillovers, impact on ICER Mother and child QALYs were not presented in a disaggregated form so this could not be ascertained			
Other comments			

Cost and cost-effectiveness of childhood vaccination against rotavirus in France			
Author *Melliez H, Levybruhl D, Boelle P Y, Dervaux B, Baron S, Yazdanpanah Y*		**Publication Year** 2008	
Type of analysis Model based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged 3 years or under
Rationale Study that measured patient QALYs also measured carer QALYs; enabling them to be included			
Groups of family members considered in analysis One carer	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
Family member costs? No, deliberately excluded. The authors justified the exclusion of indirect costs (i.e. productivity losses), as necessary in order to prevent double counting, as carer QALYs were considered instead.			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs It was not made explicit how patient and carer QALYs were combined.			
Size of health spillovers, impact on ICER Not explored explicity.			
Other comments			

Evaluating rotavirus vaccination in England and Wales. Part II: The potential cost-effectiveness of vaccination			
Jit M, Edmunds W J		**Publication Year** 2007	
Type of analysis Model-based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5 years
Rationale NICE specifies that utility losses should be extended to include carers			
Groups of family members considered in analysis Parents (two carers)	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
Family member costs? Excluded in base case, included in scenario analysis			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs Base case: summed QALY losses for patients and their two carers. Excluded carer productivity losses Scenario analysis 1: Included carer QALYs and also included carer productivity losses.			
Size of health spillovers, impact on ICER A sensitivity analysis was carried out across the 95% confidence interval for carer QALYs. It was found that the ICER is particularly sensitive to carer QALYs when they are varied across the full 95% confidence interval. It should be highlighted that the 95% confidence interval for carer QALYs exhibited much more uncertainty (greater width) than the patient QALYs from the Canadian study.			
Other comments Assumed that all infants have two carers (parents)			

<table>
<tr><td colspan="4">End of life care interventions: an economic analysis</td></tr>
<tr><td colspan="2">Authors Pham, B., Krahn, M.</td><td colspan="2">Publication Year: 2014</td></tr>
<tr><td>Type of analysis
Model based</td><td>Interventions Patient focused interventions were palliative team care, and patient care planning discussions</td><td>Comparator
Usual end-of-life care</td><td>Patients
Terminally ill/dying</td></tr>
<tr><td colspan="4">Rationale This study evaluated an array of end-of-life care interventions including patient-focused interventions, some multi-faceted interventions and an intervention specific to carers.</td></tr>
<tr><td colspan="2">Groups of family members considered in analysis
One informal carer</td><td>Measure of FM health
EQ-5D</td><td>Type of analysis where FM health included: Base case</td></tr>
<tr><td colspan="4">Family member costs? Not included</td></tr>
<tr><td colspan="4">Family member QALYs information These were derived from an external study that measured QALY values using elicitations from 921 carers, who were then compared with matched population based QALY scores, to calculate a QALY loss. Regression analysis was also performed to establish the magnitude of QALY loss for carers identified as ‘finding it difficult to have a break from caregiving’.</td></tr>
<tr><td colspan="4">Method for combining patient and family member QALYs

Three QALY decrements were applied to family members: from experiencing bereavement, from caregiving, and from having a break from caregiving. These QALY decrement estimates were obtained from external studies.</td></tr>
<tr><td colspan="4">Size of health spillovers, impact on ICER

The patient-focused end-of-life interventions were estimated to produce small gains on QALDs of carers (<10% of patient QALD gains). The authors explained that in-home palliative team care enabled the carer to have a break from caregiving resulting in small carer QALD gains. For the patient care planning discussions, the authors did not indicate why carers incurred small gains in QALDs.</td></tr>
<tr><td colspan="4">Other comments The external study that was used to identify the QALY loss to carers (In pursuit of QALY weights for relatives by Davidson et al), did not find a statistically significant association between having a break from caregiving and higher carer utility (p=0.534); however this parameter was still used in the modelling by Pham and Krahn.</td></tr>
</table>

Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK			
Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J		**Publication Year** 2008	
Type of analysis Model based	**Intervention** Natalizumab	**Comparators** Interferon-B, glatiramer acetate, and best supportive care	**Patients** Multiple Sclerosis
Rationale Previous studies have shown that MS has a major impact on family members, with disease severity correlated with carer depression.			
Groups of family members considered in analysis One carer	**Measure of FM health** Not stated	**Type of analysis where FM health included** Base case	
Family member costs? Excluded in base case, included in scenario analysis			
Family member QALYs information. The utility for carers was derived from a study of Alzheimer's disease carers. Even though Alzheimer's disease and multiple sclerosis are different illnesses, the impact of these diseases on carers was assumed to be the same. A scale was extrapolated from this study to represent carer disutility according to the severity of patient MS (ranging from 0.00 for patients with low-level MS to 0.14 for patients with the most severe MS).			
Method for combining patient and family member QALYs In the base-case analysis the utility of carers was included. In an alternative scenario analysis, the utility of carers was excluded.			
Size of health spillovers, impact on ICER Excluding carer disutility in the scenario analysis led to a small increase in the ICER from £2300 to £2500 per QALY.			
Other comments			

Cost-effectiveness of a pentavalent human-bovine reassortant rotavirus vaccine for children <=5 years of age in Taiwan			
Itzler RF, Chen PY, Lac C, El Khoury AC, Cook JR		**Publication Year** 2011	
Type of analysis Model-based	**Intervention** Rotavirus vaccination	**Comparator** No vaccination	**Patients** Children aged under 5 years
Rationale Authors acknowledge that inclusion of carer QALYs is 'controversial'			
Groups of family members considered in analysis 1.9 parents per child with rotavirus	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case	
Family member costs? Societal perspective includes carer costs in terms of lost work time.			
Family member QALYs information Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 and the VAS on behalf of the patient (Itzler et al used the VAS elicitations for the base case analysis), and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.			
Method for combining patient and family member QALYs Two perspectives adopted: health care and societal. Health care perspective: Health care costs, patient and carer QALYs. Societal perspective: Health care and carer costs, patient and carer QALYs			
Size of health spillovers, impact on ICER In this study the authors used an estimate for patient QALYs that was much higher than the other rotavirus economic evaluations included in this review- by using the VAS estimate of patient QALYs as opposed to the HUI:2 estimate. This VAS estimate was taken from the Canadian study and is 3-fold higher than the HUI:2 estimate. Therefore, this would suggest that the inclusion of carer QALYs was of relatively less influence in this economic evaluation compared to many of the other studies that were included in this review.			
Other comments			

11.

Occupational therapy compared with social work assessment for older people: an economic evaluation alongside the CAMELOT randomised controlled trial			
Flood C, Mugford M, Stewart S, Harvey I, Poland F, Lloyd-Smith W		**Publication Year** 2005	
Type of analysis Trial-based	**Intervention** Occupational therapy	**Comparator** Social work assessment	**Patients** Frail older patients (aged 65 and over) living in their own homes
Rationale Carers' involvement is key to the welfare of the patients			
Groups of family members considered in analysis Carers	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Not included in the synthesis of costs and benefits	
Family member costs? Carers' out-of-pocket household costs included, work related time costs excluded.			
Family member QALYs information 321 patients were included in the analysis. However, only 113 carers were included in the analysis. This is because there was less than full data for carers at baseline and follow-up, which authors acknowledged made analysis from carer perspective difficult. In both trial arms, around 65% of carers were female, and carers were on average aged 69, suggesting that most carers were the spouse of the patient.			
Method for combining patient and family member QALYs Although carer QALYs were measured, it appears that they were not included in the synthesis of benefits.			
Size of health spillovers, impact on ICER There was no statistically significant difference in EQ-5D scores between the intervention and comparator arms of the trial, for both patients (p=0.29), and for carers (p=0.194).			
Other comments			

<table>
<tr><td colspan="4">Effectiveness and cost-effectiveness of pediatric rotavirus vaccination in British Columbia: a model-based evaluation</td></tr>
<tr><td colspan="2">Fisman DN, Chan CH, Lowcock E, Naus M, Lee V</td><td colspan="2">Publication Year

2012</td></tr>
<tr><td>Type of analysis
Model-based</td><td>Intervention Rotavirus vaccination</td><td>Comparator No vaccination</td><td>Patients
Children aged 5 years or under</td></tr>
<tr><td colspan="4">Rationale Not stated</td></tr>
<tr><td>Groups of family members considered in analysis

Parent/s</td><td>Measure of FM health
EQ-5D</td><td colspan="2">Type of analysis where FM health included Base case</td></tr>
<tr><td colspan="4">Family member costs? No (health care perspective)</td></tr>
<tr><td colspan="4">Family member QALYs information

Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

It is unclear from both the Canadian study and this study, whether the authors are including QALYs for one parent, or for both parents.</td></tr>
<tr><td colspan="4">Method for combining patient and family member QALYs

Aggregation</td></tr>
<tr><td colspan="4">Size of health spillovers, impact on ICER Not stated or explored</td></tr>
<tr><td colspan="4">Other comments Authors declare that there is limited information about the health utilities associated with rotavirus vaccination.</td></tr>
</table>

Cost-effectiveness of rotavirus vaccination: exploring caregiver(s) and "no medical care" disease impact in Belgium

Author *Bilcke J, Van Damme P, Beutels P*		**Publication Year** 2009	
Type of analysis Model based	**Intervention** Rotavirus vaccination (Rotarix and Rotataq)	**Comparator** No vaccination	**Patients** Children aged 7 years or under

Rationale Although the authors included these, they also discussed the 'considerable uncertainty' about best practice for including family member QALYs in economic evaluation.

Groups of family members considered in analysis One parent	**Measure of FM health** EQ-5D	**Type of analysis where FM health included** Base case

12. **Family member costs** Yes, productivity losses included in societal perspective

Family member QALYs information

Utility estimates were based on a cross-sectional Canadian study for children and carers (parents) who attended their GP for rotavirus gastroenteritis. Carers completed the HUI:2 on behalf of the patient, and the EQ-5D questionnaire to evaluate their own utility loss over a two-week period.

The authors also made an assumption that parents who did not seek professional medical treatment for their child's rotavirus incurred only 50% of the utility decrement compared to parents that did seek medical treatment (from the Canadian study).

Method for combining patient and family member QALYs

Health care perspective- included QALYs for children and one parent, and excluded carer productivity losses; justified as necessary to prevent double counting

Societal perspective- included QALYs for children only, and included carer productivity losses

Size of health spillovers, impact on ICER

Scenario analysis was carried out that evaluated impact of excluding carer QALYs under the health care payer perspective. The probability of Rotarix being cost-effective was reduced dramatically from 81% to 8% as a result of excluding carer QALYs. Conversely, another scenario analysis found that including QALYs of two carers instead of one increased the probability of Rotarix being cost-effective from 81% to 97%.

Other comments Authors included one carer instead of two, because not all families are two-parent families.

<table>
<tr><td colspan="4">Use of models to identify cost-effective interventions: pertussis vaccination for pediatric health care workers</td></tr>
<tr><td colspan="2">Greer AL, Fisman DN</td><td colspan="2">Publication Year 2011</td></tr>
<tr><td>Type of analysis
Model-based</td><td>Intervention Pertussis vaccination</td><td>Comparator No vaccination</td><td>Patients All neonates</td></tr>
<tr><td colspan="4">Rationale Not stated</td></tr>
<tr><td>Groups of family members considered in analysis
Parents (mother and father)</td><td>Measure of FM health Direct elicitation (standard gamble and time trade-off)</td><td colspan="2">Type of analysis where FM health included Base case</td></tr>
<tr><td colspan="4">Family member costs? Yes, parent time losses appear to be accounted for in terms of visiting hospital, but time losses associated with prolonged illness of child (i.e. spillover) were excluded.</td></tr>
<tr><td colspan="4">Family member QALYs information.

Utilities were estimated for parents (both mother and father) and children. For the mother and father, a utility decrement was applied if the child died, and a larger utility decrement was applied if the child survived with a neurologic disability. These utility decrements appear to be taken from another economic evaluation (Little and Caughey) that was also identified in this review. In the model, the authors also took into account the proportion of single-parent households in the population (15%)</td></tr>
<tr><td colspan="4">Method for combining patient and family member QALYs Not stated</td></tr>
<tr><td colspan="4">Size of health spillovers, impact on ICER

Not stated or explored</td></tr>
<tr><td colspan="4">Other comments</td></tr>
</table>

Appendices 3.1-3.3 detail the construct validity and responsiveness results where multiple family members of the same patient were included.

Appendix 3.1. Effect sizes for tests of construct validity of the EQ-5D-5L and SF-6D for measuring spillovers in full sample

Constructs associated with family member health spillover	**FAMILY MEMBER INDEX SCORES**	
	EQ-5D-5L	**SF-6D**
'Caring about' hypotheses for non- carer sub-sample (n=815)		
Patient EQ-5D-5L	0.20***	0.15***
Patient VAS	0.18***	0.21***
Patient Mobility	-0.08*	-0.04
Patient Self-Care	-0.13***	-0.12**
Patient Usual activity	-0.09*	-0.11**
Patient Anxiety	-0.21***	-0.18***
Patient Pain	-0.16***	-0.11**
Family life	-0.23	-0.48***
Social life	-0.46**	-0.55***
Exercise	-0.81**	-0.65***
Personal health	-0.83***	-0.71***
Hypotheses for carer sub-sample related to 'caring about' or 'caring for' the patient (n=238)		
Patient EQ-5D-5L	0.27***	0.10
Patient VAS	0.22***	0.13*
Patient mobility	-0.20**	-0.05
Patient self-care	-0.19**	-0.08
Patient usual activity	-0.22***	-0.06
Patient anxiety	-0.09	-0.15*
Patient pain	-0.14*	-0.06
Family life	-0.30*	-0.17
Social life	-0.38***	-0.40**
Exercise	-0.50**	-0.46**
Personal health	-0.82***	-0.58*
Hypotheses for carer sub-sample solely related to 'caring for' the patient (n=238)		
Hours of care provided	-0.21***	-0.21***
Carer Experience Scale	0.24**	0.25**
Shares house	-0.15	-0.09
Daily care	-0.01	-0.41*
Main carer	-0.03	-0.53**
Provides majority of care	-0.03	-0.22
Provides personal care	0.21	0.24
Impact of meningitis on work	-0.26**	-0.48**
Impact of meningitis on finances	-0.16**	-0.17*
Provides constant supervision	-0.22	-0.31

Appendix 3.2: Tests of responsiveness of the family member (FM) EQ-5D-5L and SF-6D for the full sample of non-carers

Patient EQ-5D-5L	FM EQ-5D-5L 2012 baseline (mean)	FM EQ-5D-5L 2013 follow-up (mean)	Difference between follow-up and baseline EQ-5D-5L (95% CI)	Effect size (Cohen's D)	n
Improved	0.83	0.83	0.00 (-0.03, 0.03)	0.01	60
No change	0.91	0.88	-0.03* (-0.04, -0.01)	-0.19	295
Worsened	0.86	0.82	-0.04* (-0.06, -0.02)	-0.16	138

Patient EQ-5D-5L	FM SF-6D 2012 baseline (mean)	FM SF-6D 2013 follow-up (mean)	Difference between follow-up and baseline SF-6D (95% CI)	Effect size (Cohen's D)	n
Improved	0.76	0.75	-0.01 (-0.04, 0.01)	-0.11	56
No change	0.81	0.79	-0.02** (-0.03, -0.01)	-0.15	270
Worsened	0.77	0.76	-0.01 (-0.03, 0.01)	-0.06	126

*p<0.05, **p<0.01, ***p<0.001

§ Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large.

Appendix 3.3: Tests of responsiveness of the carer EQ-5D-5L and SF-6D (full sample)

	Carer EQ-5D-5L 2012 baseline (mean)	Carer EQ-5D-5L 2013 follow-up (mean)	Difference between follow-up and baseline EQ-5D-5L (95% CI)	Effect size (Cohen's D)	n
Patient EQ-5D-5L					
Improved	0.78	0.82	0.04 (-0.04, 0.11)	0.18	26
No change	0.85	0.84	-0.01 (-0.03, 0.01)	-0.07	70
Worsened	0.79	0.74	-0.05* (-0.09, 0.00)	-0.19	50
Hours of care provided ('caring for' the patient)					
Less care	0.80	0.77	-0.03 (-0.07, 0.01)	-0.13	35
No change	0.83	0.83	0.00 (-0.04, 0.03)	-0.01	40
More care	0.85	0.80	-0.06* (-0.10, -0.01)	-0.37	27
	Carer SF-6D 2012 baseline (mean)	**Carer SF-6D 2013 follow-up (mean)**	**Difference between follow-up and baseline SF-6D (95% CI)**	**Effect size (Cohen's D)**	**n**
Patient EQ-5D-5L					
Improved	0.72	0.70	-0.02 (-0.08, 0.04)	-0.15	25
No change	0.73	0.71	-0.02 (-0.04, 0.00)	-0.15	69
Worsened	0.70	0.67	-0.03 (-0.06, 0.00)	-0.25	48
Hours of care provided for patient ('caring for' the patient)					
Less care	0.69	0.67	-0.02 (-0.06, 0.02)	-0.15	32
No change	0.73	0.72	-0.01 (-0.04, 0.02)	-0.07	41
More care	0.74	0.68	-0.05* (-0.10, -0.01)	-0.48	24

*p<0.05, **p<0.01, ***p<0.001

§ Cohen's D effect sizes of between 0.2 and 0.5 are considered small, 0.5 and 0.8 moderate and > 0.8 large.

Appendix 3.4. Questionnaires administered to the family members of meningitis survivors

UNIVERSITY OF BIRMINGHAM

Meningitis Research Foundation

Family impact of meningitis and septicaemia

This questionnaire is part of a government-funded research study into the impact of meningitis. If you are a relative, partner or friend of a person affected by meningitis or septicaemia we would be very grateful if you could complete the questionnaire.

This research will help us to understand the impact that meningitis and septicaemia can have on relatives and friends of the person affected. This information will be useful for those making decisions about funding preventative vaccines and other care in this area.

More information about the study can be found in the enclosed letter and information sheet.

The questionnaire should take about 20 minutes to complete.

For office use only:

Study ID

Your consent to take part in the study

Before completing this survey please read the information sheet and complete part 1 and, if applicable, part 2 of the consent section below.

PART 1: CONSENT

1a) I agree to the University of Birmingham recording and processing the information I have provided in this questionnaire and...

I am 16 or over	**OR**	☐ 0
I am 13-15 and have also included an assent form from my parent or guardian		☐ 1

This information will be held and processed for non-commercial research and to contact you about other voluntary research studies (but only if you tick a box below).

1b) Would you be willing to be contacted by the University of Birmingham about other voluntary research studies?

Yes (please complete address in Part 2)	☐ 0
No	☐ 1

1c) I understand that the information will be used only for the purposes set out in the statements above, and my consent is conditional upon the University complying with its obligations under the Data Protection Act. I understand that I am able to withdraw from the study at any time, without giving a reason.

Signature…… Date……..

Name (please print)……

PART 2: CONTACT DETAILS

Could you put your contact details below if...

- You have received this questionnaire from a friend or relative. We can then directly send you next year's shorter follow-up survey and the Meningitis Research Foundation can contact you about support in your area.

AND/OR

- You are willing to be contacted directly about other voluntary University of Birmingham research studies.

Postal address ……

……

……

Email address ……

Thank you for taking the time to participate in this research. We are very grateful.

SECTION A. Questions about the person affected by meningitis or septicaemia

The questions in section A are about the person you know who has had meningitis or septicaemia. If this applies to more than one person, please focus on the individual who has been affected most severely.

1. Is the person affected female or male?

Female ☐0

Male ☐1

2. What is their date of birth?

☐☐/☐☐/☐☐☐☐

D D M M Y Y Y Y

3. What is your relationship to the person affected? You are...

their parent ☐1

their brother or sister ☐2

their husband, wife or partner ☐3

their grandparent ☐4

a friend ☐5

other (please state below) ☐6

_____

4. Do you share a house with the person affected?

Yes ☐0

No ☐1

5. How many people share your house? (Including you and, if relevant, the person affected)

_____ adults (18 or over)

_____ children (17 or under)

6. In general, how often do you see the person affected?

Every day ☐1

Most days ☐2

1, 2 or 3 days a week	☐ 3
1, 2 or 3 days a month	☐ 4
A few days per year	☐ 5
Once a year or less	☐ 6

7. How long ago did the person affected contract meningitis or septicaemia?

_____ years and _____ months

8**. Under each heading please tick one box that you think best describes the person's health <u>today</u>.**

MOBILITY

They have no problems in walking about	☐1
They have slight problems in walking about	☐2
They have moderate problems in walking about	☐3
They have severe problems in walking about	☐4
They are unable to walk about	☐5

SELF CARE

They have no problems in washing and dressing themselves	☐1
They have slight problems in washing and dressing themselves	☐2
They have moderate problems in washing and dressing themselves	☐3
They have severe problems in washing and dressing themselves	☐4
They are unable to wash and dress themselves	☐5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

They have no problems in doing their usual activities	☐1
They have slight problems in doing their usual activities	☐2
They have moderate problems in doing their usual activities	☐3
They have severe problems in doing their usual activities	☐4
They are unable to do their usual activities	☐5

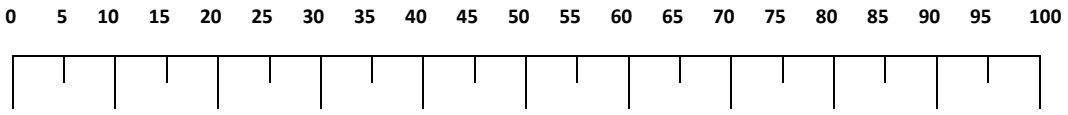
PAIN/DISCOMFORT

They have no pain or discomfort	☐1
They have slight pain or discomfort	☐2
They have moderate pain or discomfort	☐3
They have severe pain or discomfort	☐4
They have extreme pain or discomfort	☐5

ANXIETY/DEPRESSION

They have no anxiety or depression	☐1
They have slight anxiety or depression	☐2
They have moderate anxiety or depression	☐3
They have severe anxiety or depression	☐4
They have extreme anxiety or depression	☐5

9. How would you rate their health today, where 0 is the worst health you can imagine and 100 is the best health you can imagine? Please do this by drawing an X on the scale to indicate how good, or bad, their health state is today and write the number in the box below.



0 = 100 =

the worst health you can imagine the best health you can imagine

Their health today = _____

10. Compared to 12 months ago, how would you rate their health <u>today</u>?

Much better than 12 months ago	☐ 1
Somewhat better than 12 months ago	☐ 2
About the same	☐ 3
Somewhat worse than 12 months ago	☐ 4
Much worse than 12 months ago	☐ 5

11. Please would you put a tick next to any after effects that the person affected has. (Please tick all that are applicable)

Behavioural, psychological or emotional problems	☐
Mild or moderate learning difficulties	☐
Severe learning difficulties (that would prevent attending mainstream school even with educational support)	☐
Speech or language problems	☐
Hearing loss in one ear	☐
Hearing loss in both ears	☐
Sight loss	☐
Other visual impairment	☐
Seizures or fits	☐
Hydrocephalus (water on the brain)	☐
Hypotonia (reduced muscle strength or tone)	☐
Motor deficits (such as severe problems moving limbs)	☐
Incontinence	☐
Balance problems	☐
Pain (even after taking medication)	☐
Amputations	☐
Scarring or tissue damage	☐
Abnormal bone growth	☐
Arthritis or severe limb or joint pain	☐
Kidney damage	☐
Other (please specify) _____	

12. Did the person affected contract meningitis or septicaemia?

Meningitis	☐ 1
Septicaemia	☐ 2
Both meningitis and septicaemia	☐ 3

13. Which bug caused the meningitis or septicaemia? (If known, e.g. "meningococcal B").

Section B. Questions about any help or support you provide

___

_____

The questions in section B are about any <u>care</u> you provide for the person, <u>as a result of their meningitis or septicaemia and any after effects</u>.

1. In a typical week, please state roughly how many hours, on average, you spend on the activities below as a result of their meningitis or septicaemia and any after effects.

Assisting the person with daily living ..... _____hours/week
(e.g. helping with personal care, going to the toilet, eating, communication, moving around, therapy)

Organisational support for the person affected..... _____hours/week
(e.g. help with outings, visits to health and care professionals, organising assitance, taking care of finances)

Extra household activity..... _____hours/week
(e.g. additional work on food preparation, cleaning, laundry, home maintenance)

Other care activity (please state what the activities are below)..... _____hours/week

_____

If you do not provide any extra care for the person, as a result of their meningitis or septicaemia, please go straight to section C, otherwise please continue.

2. In general, do you provide care for this person every day?

Yes ☐0
No ☐1

3. Do any of the statements below refer to your caring role? (Please tick any that apply)

I provide the majority of the person's care ☐1
I feel responsible for the person's care ☐2
I make decisions about the person's care ☐3

I am the closest individual to the person ☐4

4. Do you provide constant day-time supervision for this person?

Yes, on my own ☐1
Yes, with assistance from others ☐2
No, someone else does ☐3
No, they do not require it ☐4

5. Do any people, other than you, provide care for this person?

No ☐0
Yes ☐1
(if yes, please indicate roughly how many hours below)

Relatives of the person affected _____hours/week
Friends of the person affected _____hours/week
Paid carers _____hours/week

6. Are you the main carer for this person?

Yes ☐0
No ☐1

7. <u>Compared to 12 months ago</u>, has there been any change in the <u>amount</u> of care you provide? (For example, are you involved in fewer caring tasks, or does the care now require less time or effort?)

I now provide a great deal more care ☐1
I now provide somewhat more care ☐2
There has been no change ☐3
I now provide somewhat less care ☐4
I now provide a great deal less care ☐5

8. <u>Since you started providing care</u>, has there been any change in the <u>amount</u> of care you provide? (For example, are you involved in fewer caring tasks, or does the care now require less time or effort?)

I now provide a great deal more care ☐1
I now provide somewhat more care ☐2
There has been no change ☐3
I now provide somewhat less care ☐4
I now provide a great deal less care ☐5

9. <u>Since you started providing care</u> have there been <u>frequent</u> or <u>unpredictable</u> changes in any of the following aspects of the care you provide? (Please tick any statements that apply).

The amount of care you provide ☐
The care tasks that you are involved in ☐
Your caring role ☐
The effort or difficulty of care ☐

10. Please think about the time when you started to provide care for the person affected and tick the box that best applies to your situation.

I had options in terms of who provided <u>all</u> of the care	☐ 1
I had options in terms of who provided <u>some</u> of the care	☐ 2
I had <u>no</u> options in terms of who provided the care	☐ 3

11. If you ticked 'I had *<u>no</u>* options in terms of who provided the care', please tick any boxes below that applied to your situation.

I had no options, because I was the most suitable person	☐
I had no options, because I felt it was my duty	☐
I had no options, because there was no-one else to help	☐
I had no options, because there was no money for paid care	☐
I had no options, because of another reason (stated below)	☐

_____

12. Do you have any <u>ongoing concerns</u> about the future health and needs of the person affected? (Please tick all areas that you have concerns about).

Their future health	☐
Their future development (including educational and social)	☐
The care that I will need to provide	☐
The care that others will need to provide	☐
The financial costs of care	☐
Other (please state below)	☐

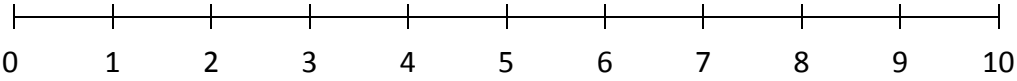
_____

13. How much strain do you feel caring for the person affected puts you under at the moment?

Please put a mark on the scale below that indicates how how much strain you feel caring for the person affected puts you under at the moment.

On the scale below, '0' means that you feel that caring for the person at the moment puts you under no strain; '10' means that you feel that caring for the person puts you under far too much strain

not at all straining ***much too straining***



14. Thinking about your <u>current</u> experience of caring for this person, please tick one box for each group to indicate which statement best describes your current caring situation.

ACTIVITIES OUTSIDE CARING *(Socialising, physical activity and spending time on hobbies, leisure or study)*

You can do most of the other things you want to do outside caring ☐1
You can do some of the other things you want to do outside caring ☐2
You can do few of the other things you want to do outside caring ☐3

SUPPORT FROM FAMILY AND FRIENDS *(Personal help in caring and/or emotional support from family, friends, neighbours or work colleagues)*

You get a lot of support from family and friends ☐1
You get some support from family and friends ☐2
You get little support from family and friends ☐3

ASSISTANCE FROM ORGANISATIONS AND THE GOVERNMENT *(Help from public, private or voluntary groups in terms of benefits, respite and practical information)*

You get a lot of assistance from organisations and the government ☐1
You get some assistance from organisations and the government ☐2
You get little assistance from organisations and the government ☐3

FULFILMENT FROM CARING *(Positive feelings from providing care, which may come from: making the person you care for happy, maintaining their dignity, being appreciated, fulfilling your responsibility, gaining new skills or contributing to the care of the person you look after)*

You mostly find caring fulfilling ☐1
You sometimes find caring fulfilling ☐2
You rarely find caring fulfilling ☐3

CONTROL OVER THE CARING *(Your ability to influence the overall care of the person you look after)*

You are in control of most aspects of the caring ☐1
You are in control of some aspects of the caring ☐2
You are in control of few aspects of the caring ☐3

GETTING ON WITH THE PERSON YOU CARE FOR *(Being able to talk with the person you look after, and discuss things without arguing)*

You mostly get on with the person you care for ☐1
You sometimes get on with the person you care for ☐2
You rarely get on with the person you care for ☐3

Section C. Questions about you

The questions on this page are about you. All personal details will be treated in confidence.

1. Are you female or male?

- Female ☐ 0
- Male ☐ 1

2. How old are you? _____ years old

3. How would you describe your ethnicity?

- White ☐ 1
- Black or Black British ☐ 2
- Asian or Asian British ☐ 3
- Mixed (please specify below) ☐ 4

_____

- Other (please specify below) ☐ 5

_____

4. What is your highest level of educational or technical qualification?

- None ☐ 1
- GSCE, O-level, NVQ level 1 or equivalent ☐ 2
- AS-level, A-level, NVQ level 2 or equivalent ☐ 3
- Degree level or equivalent ☐ 4

5. Which of these activities describes what you are doing at present? (Please tick all boxes that apply)

- Paid employment (30hrs+ per week) ☐
- Paid employment (<30hrs per week) ☐
- Voluntary work ☐
- Looking after home & family ☐
- Full-time carer ☐
- Wholly retired from work ☐
- Unemployed and available for work ☐
- Self-employed ☐
- Permanently sick or disabled ☐
- In full-time education or training scheme ☐

Now we would like to know a little about your health and wellbeing. Unless stated, please answer the questions in a general sense (i.e. not necessarily associated with the person affected or any caring responsibilities you may have).

6. Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about	☐ 1
I have slight problems in walking about	☐ 2
I have moderate problems in walking about	☐ 3
I have severe problems in walking about	☐ 4
I am unable to walk about	☐ 5

SELF CARE

I have no problems in washing and dressing myself	☐ 1
I have slight problems in washing and dressing myself	☐ 2
I have moderate problems in washing and dressing myself	☐ 3
I have severe problems in washing and dressing myself	☐ 4
I am unable to wash and dress myself	☐ 5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

I have no problems doing my usual activities	☐ 1
I have slight problems doing my usual activities	☐ 2
I have moderate problems doing my usual activities	☐ 3
I have severe problems doing my usual activities	☐ 4
I am unable to do my usual activities	☐ 5

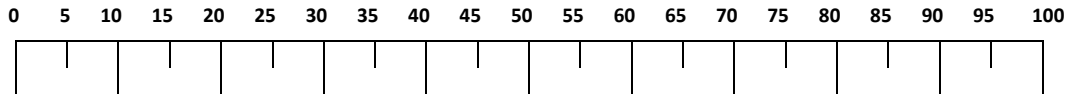
PAIN/DISCOMFORT

I have no pain or discomfort	☐ 1
I have slight pain or discomfort	☐ 2
I have moderate pain or discomfort	☐ 3
I have severe pain or discomfort	☐ 4
I have extreme pain or discomfort	☐ 5

ANXIETY/DEPRESSION

I have no anxiety or depression	☐ 1
I have slight anxiety or depression	☐ 2
I have moderate anxiety or depression	☐ 3
I have severe anxiety or depression	☐ 4
I have extreme anxiety or depression	☐ 5

7. How would you rate your health today, where 0 is the worst health you can imagine and 100 is the best health you can imagine? Please do this by drawing an X on the scale to indicate how good, or bad, your health state is today and write the number in the box below.



0 = the worst health you can imagine

100 = the best health you can imagine

My health today = _____

8. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

9. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot ↓	Yes, limited a little ↓	No, not limited at all ↓
<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
Climbing <u>several</u> flights of stairs	☐1	☐2	☐3

10. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
<u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5

11. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	↓	↓	↓	↓	↓
<u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

12. During the <u>past 4 weeks</u>, how much did your <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

13. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> . . .

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	↓	↓	↓	↓	↓
Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
Have you felt downhearted and low?	☐1	☐2	☐3	☐4	☐5

14. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

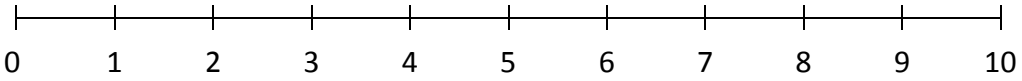
All of the time	Most of the time	Some of the time	A little of the time	None of the time
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

15. Compared to 12 months ago, how would you rate your health now?

Much better than 12 months ago	☐ 1
Somewhat better than 12 months ago	☐ 2
About the same	☐ 3
Somewhat worse than 12 months ago	☐ 4
Much worse than 12 months ago	☐ 5

16. How happy do you feel at the moment? Please put a mark on the scale below that indicates how happy you feel at the moment.

Completely unhappy ***Completely happy***



17. Please think about the impact that meningitis or septicaemia and any after effects has had on <u>your own life</u>. With this in mind, please tick the box in each row below that best describes how the condition has affected that aspect of your life.

	In this aspect of my life, the condition has had...		
	a negative impact	no impact	a positive impact
Stress and anxiety	☐ 1	☐ 2	☐ 3
Depression	☐ 1	☐ 2	☐ 3
Family and relationships	☐ 1	☐ 2	☐ 3
Social life	☐ 1	☐ 2	☐ 3
Finances	☐ 1	☐ 2	☐ 3
Work	☐ 1	☐ 2	☐ 3
Exercise	☐ 1	☐ 2	☐ 3
Physical health	☐ 1	☐ 2	☐ 3
Sleep	☐ 1	☐ 2	☐ 3

18. Has having someone close to you that has had meningitis or septicaemia changed how you view your own health?

I now view my own health more <u>positively</u>	☐ 1
There has been <u>no change</u> in how I view my own health	☐ 2
I now view my own health more <u>negatively</u>	☐ 3

19. Has having someone close to you that has had meningitis or septicaemia affected how likely you are to use healthcare services if you fall ill (for any reason)?

I am more likely to use healthcare services if I fall ill	☐ 1
There has been no change	☐ 2
I am less likely to use healthcare services if I fall ill	☐ 3

Finally, we would like to know a little more about unpaid activity and care you are involved in. For these last two questions please report *any* relevant activity (i.e. not limited solely to activities that arise from meningitis and/or septicaemia).

20. In a typical week do you spend time on the activities below in the house of the person affected? If you do, please indicate how much time you spend on these activities.

Task	Minutes per day		Hours per week
Preparing food and drink.....	_____	**OR**	_____
Cleaning the house.....	_____	**OR**	_____
Doing the laundry and ironing.....	_____	**OR**	_____
Home maintenance and gardening.....	_____	**OR**	_____

21. In a typical week do you spend any time on assisting the person affected with the activities below? If you do, please indicate how much of your time you spend on the activities.

Task	Minutes per day		Hours per week
Help with personal care..... *(e.g. dressing, washing, combing, shaving)*	_____	**OR**	_____
Help with toileting..... *(e.g. going to the toilet or changing nappies)*	_____	**OR**	_____
Therapy..... *(e.g. physio, occupational and speech therapy)*	_____	**OR**	_____
Help with eating and drinking.....	_____	**OR**	_____
Help with communication.....	_____	**OR**	_____
Help with moving around inside the house.....	_____	**OR**	_____
Help with moving around outside the house..... *(e.g. help with walking or wheelchair)*	_____	**OR**	_____
Help with outings and family visits.....	_____	**OR**	_____
Contacting and visiting health professionals.....	_____	**OR**	_____
Organising help, aids and house adaptations.....	_____	**OR**	_____
Taking care of other domestic tasks.....	_____	**OR**	_____

(e.g. finances and shopping)

Other care (please describe below)..... _____ **OR** _____

_____

22. Please use the text box below to say the single, biggest way in which you feel that meningitis or septicaemia has affected your life.

Please could you check that you have answered all the relevant questions including the consent section on page 2 and then:

- ***Return the questionnaire to us in the enclosed FREEPOST envelope to us (including a parental 'assent' form if you are aged 13-15).***

- ***If you can, please pass the second questionnaire, key facts sheet and second pre-paid envelope to a second relative or friend of the same person affected.***

Thank you very much for your valuable help in this research study.

UNIVERSITY OF BIRMINGHAM

Meningitis Research Foundation

Family impact of meningitis and septicaemia

- FOLLOW-UP QUESTIONNAIRE -

This questionnaire is part of a government-funded research study into the impact of meningitis. This is the follow-up questionnaire to conclude the study you kindly responded to in 2012.

The information you provided last year has been studied in detail. However, your further help will allow us to more accurately understand the long-term impacts of meningitis on the family.

More information about this follow-up questionnaire, including how your information has helped so far, can be found in the enclosed letter and information sheet.

For office use only:

Study ID

SECTION A. Questions about the person affected by meningitis or septicaemia

The questions in section A are about the person who has had meningitis or septicaemia. If you know more than one person who has had meningitis, please focus on the individual who has been affected most severely.

Please try to answer all questions, even if you provided this information last year. Some details may change, and, if not, we need to know that they have stayed the same.

1. To allow us to confirm that your answers relate to the same person, please confirm the date of birth of the person affected by meningitis or septicaemia.

☐☐/☐☐/☐☐☐☐
D D M M Y Y Y Y

The following questions will help us to understand which people are close to the person affected.

2. Do you currently share a house with the person affected?

Yes	☐0
No	☐1

3. How many people currently share your house? (Include yourself and, if relevant, the person affected).

_____ adults (18 or over)
_____ children (17 or under)

4. In general, how often do you see the person affected?

Every day	☐1
Most days	☐2
1, 2 or 3 days a week	☐3
1, 2 or 3 days a month	☐4
A few days per year	☐5
Once a year or less	☐6

5. In your opinion, does the health of the person affected have any impacts on the health or wellbeing of anyone close to them? (Please think about any people, <u>including you,</u> who may be physically or emotionally affected by their health).

How many family members? _____
How many friends? _____
How many other people? _____

6. In your opinion, how many different people does the person affected discuss important issues with? (Please include yourself, if relevant).

How many family members? _____
How many friends? _____
How many other people? _____

7. How close do you feel to this person? (Please tick one box, even if you want to indicate than you 'cannot answer').

Extremely close ☐1
Very close ☐2
Fairly close ☐3
Not close ☐4
Cannot answer ☐5

8. We are interested in the health of the <u>other</u> people you share a house with. <u>Excluding the person affected</u>, please list any other household members and their health, in general, below.

Relationship to <u>you</u>	Their health in general is…				
	Excellent ↓	Very good ↓	Good ↓	Fair ↓	Poor ↓
EXAMPLE					
Person 1…***my husband***……	☐1	☐2	☒3	☐4	☐5
Person 1 ……..	☐1	☐2	☐3	☐4	☐5
Person 2 ……..	☐1	☐2	☐3	☐4	☐5
Person 3 ……..	☐1	☐2	☐3	☐4	☐5
Person 4 ……..	☐1	☐2	☐3	☐4	☐5
Person 5 ……..	☐1	☐2	☐3	☐4	☐5
Person 6 ……..	☐1	☐2	☐3	☐4	☐5

9. The questions below relate to the health of the person affected. Under each heading please tick one box that you think best describes the person's health <u>today</u>.

MOBILITY

They have no problems in walking about	☐ 1
They have slight problems in walking about	☐ 2
They have moderate problems in walking about	☐ 3
They have severe problems in walking about	☐ 4
They are unable to walk about	☐ 5

SELF CARE

They have no problems in washing and dressing themselves	☐ 1
They have slight problems in washing and dressing themselves	☐ 2
They have moderate problems in washing and dressing themselves	☐ 3
They have severe problems in washing and dressing themselves	☐ 4
They are unable to wash and dress themselves	☐ 5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

They have no problems in doing their usual activities	☐ 1
They have slight problems in doing their usual activities	☐ 2
They have moderate problems in doing their usual activities	☐ 3
They have severe problems in doing their usual activities	☐ 4
They are unable to do their usual activities	☐ 5

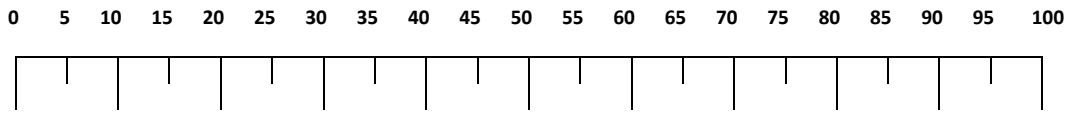
PAIN/DISCOMFORT

They have no pain or discomfort	☐ 1
They have slight pain or discomfort	☐ 2
They have moderate pain or discomfort	☐ 3
They have severe pain or discomfort	☐ 4
They have extreme pain or discomfort	☐ 5

ANXIETY/DEPRESSION

They have no anxiety or depression	☐ 1
They have slight anxiety or depression	☐ 2
They have moderate anxiety or depression	☐ 3
They have severe anxiety or depression	☐ 4
They have extreme anxiety or depression	☐ 5

10. How would you rate their health today, where 0 is the worst health you can imagine and 100 is the best health you can imagine? Please do this by drawing an X on the scale to indicate how good, or bad, their health state is today and write the number in the box below.



0 = 100 =
the worst health you can imagine the best health you can imagine

Their health today = ☐

11. Compared to 12 m ☐ would you rate their health today?

Much better than 12 months ago	☐1
Somewhat better than 12 months ago	☐2
About the same	☐3
Somewhat worse than 12 months ago	☐4
Much worse than 12 months ago	☐5

12. We would like to know whether there have been any changes in the after-effects of meningitis and/or septicaemia for this person in the last 12 months.

Please tick one box for each after-effect that has changed, and indicate whether, in the last 12 months, it has got better or worse.

After effect	...**better** (or has disappeared) ↓	...**worse** (or is a new after-effect) ↓
Behavioural, psychological or emotional problems	☐	☐
Mild or moderate learning difficulties	☐	☐
Severe learning difficulties *(that would prevent attending mainstream school even with educational support)*	☐	☐
Migraines or headaches	☐	☐
Memory loss	☐	☐
Speech or language problems	☐	☐
Hearing loss in one ear	☐	☐
Hearing loss in both ears	☐	☐
Sight loss	☐	☐
Other visual impairment	☐	☐
Seizures or fits	☐	☐
Hydrocephalus (water on the brain)	☐	☐
Hypotonia (reduced muscle strength or tone)	☐	☐
Motor deficits (such as severe problems moving limbs)	☐	☐
Incontinence	☐	☐
Balance problems	☐	☐
Pain (even after taking medication)	☐	☐

Amputations.....	☐.....	☐.....
Scarring or tissue damage.....	☐.....	☐.....
Abnormal bone growth.....	☐.....	☐.....
Arthritis or severe limb or joint pain.....	☐.....	☐.....
Kidney damage.....	☐.....	☐.....
Other (please specify) _____	☐.....	☐.....

13. Has the person affected contracted meningitis or septicaemia more than once?

No	☐ 0
Yes	☐ 1

14. Other than the person affected, have you, or anyone else in your family contracted meningitis or septicaemia?

No	☐ 1
Yes, I have	☐ 2
Yes, others in my family have	☐ 3
Yes, I have and others in my family have	☐ 4

15. Over the last 12 months, has the person affected visited the GP in relation to any health problems of their own?

No	☐ 0
Yes	☐ 1

16. Over the last 12 months, has the person affected attended hospital as an outpatient or day patient or attended casualty?

No	☐ 0
Yes	☐ 1

17. Over the last 12 months, has the person affected been in hospital as an inpatient, overnight or longer?

No	☐ 0
Yes	☐ 1

18. Who do you feel has responsibility for looking after the health and wellbeing of the person affected <u>at the moment?</u> (Please answer even if the person has no current health problems and/or is an adult and tick any boxes that apply).

You do	☐
Other family members and relatives do	☐
Other people in their life do	☐
They have responsibility themselves	☐
The government and/or other organisations do	☐

Section B. Questions about you

The first four questions in section B are about any <u>care</u> you provide for the person, <u>as a result of their meningitis or septicaemia and any after-effects</u>. If you do not provide any care for the person, as a result of their meningitis or septicaemia and any after-effects, please go straight to <u>question 5</u>, otherwise please continue.

1. In a typical week, please state roughly how many hours, on average, you spend on the activities below as a result of their meningitis or septicaemia and any after effects.

Assisting the person with daily living ..... _____hours/week
(e.g. helping with personal care, going to the toilet, eating, communication, moving around, therapy)

Organisational support for the person affected..... _____hours/week
(e.g. help with outings, visits to health and care professionals, organising assistance, taking care of finances)

Extra household activity..... _____hours/week
(e.g. additional work on food preparation, cleaning, laundry, home maintenance)

Other care activity (please state what the activities are below)..... _____hours/week

_____

2. In general, do you provide care for this person every day?

Yes ☐0
No ☐1

3. Do any people, other than you, provide care for this person?

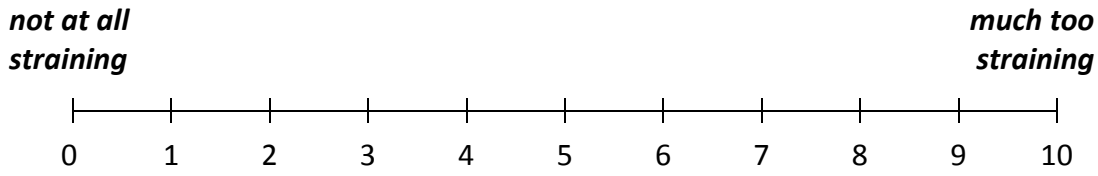
No ☐0
Yes ☐1
(if yes, please indicate roughly how many hours below)

Relatives of the person affected _____hours/week
Friends of the person affected _____hours/week
Paid carers _____hours/week

4. How much strain do you feel caring for the person affected puts you under at the moment?

Please put a mark on the scale below that indicates how how much strain you feel caring for the person affected puts you under at the moment.

On the scale below, '0' means that you feel that caring for the person at the moment puts you under no strain; '10' means that you feel that caring for the person puts you under far too much strain



PLEASE RESTART THE QUESTIONNAIRE HERE IF THE QUESTIONS ABOUT ADDITIONAL CARE WERE NOT RELEVANT TO YOU.

5. Have there been any impacts on your work, as a result of the meningitis, any after-effects of the meningitis, or any meningitis-related caring duties? (Please tick any that are applicable).

	In the last 12 months ↓	Prior to 12 months ago ↓
I gave up work	☐	☐
I took time off work	☐	☐
I reduced my working hours	☐	☐
I missed promotion or job opportunities	☐	☐
I took a more flexible job	☐	☐

6. Which of these activities describes what you are doing at present? (Please tick all boxes that apply).

Paid employment (30hrs+ per week)	☐
Paid employment (<30hrs per week)	☐
Voluntary work	☐
Looking after home & family	☐
Full-time carer	☐
Wholly retired from work	☐
Unemployed and available for work	☐

Self-employed ☐
Permanently sick or disabled ☐
In full-time education or training scheme ☐

7. Now we would like to know a little about your health and wellbeing. Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐1
I have slight problems in walking about ☐2
I have moderate problems in walking about ☐3
I have severe problems in walking about ☐4
I am unable to walk about ☐5

SELF CARE

I have no problems in washing and dressing myself ☐1
I have slight problems in washing and dressing myself ☐2
I have moderate problems in washing and dressing myself ☐3
I have severe problems in washing and dressing myself ☐4
I am unable to wash and dress myself ☐5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

I have no problems doing my usual activities ☐1
I have slight problems doing my usual activities ☐2
I have moderate problems doing my usual activities ☐3
I have severe problems doing my usual activities ☐4
I am unable to do my usual activities ☐5

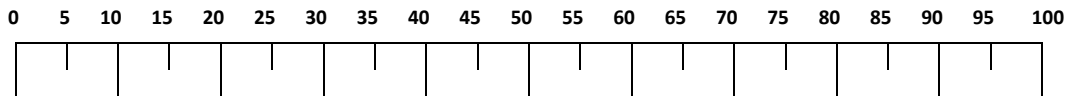
PAIN/DISCOMFORT

I have no pain or discomfort ☐1
I have slight pain or discomfort ☐2
I have moderate pain or discomfort ☐3
I have severe pain or discomfort ☐4
I have extreme pain or discomfort ☐5

ANXIETY/DEPRESSION

I have no anxiety or depression ☐1
I have slight anxiety or depression ☐2
I have moderate anxiety or depression ☐3
I have severe anxiety or depression ☐4
I have extreme anxiety or depression ☐5

8. How would you rate your health today, where 0 is the worst health you can imagine and 100 is the best health you can imagine? Please do this by drawing an X on the scale to indicate how good, or bad, your health state is today and write the number in the box below.



0 = 100 =

the worst health you can imagine

the best health you can imagine

My health today =

9. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

10. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot ↓	Yes, limited a little ↓	No, not limited at all ↓
<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
Climbing <u>several</u> flights of stairs	☐1	☐2	☐3

11. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
<u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5

12. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time ↓	Most of the time ↓	Some of the time ↓	A little of the time ↓	None of the time ↓
<u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

13. During the <u>past 4 weeks</u>, how much did your <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

14. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u> . . .

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	↓	↓	↓	↓	↓
Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
Have you felt downhearted and low?	☐1	☐2	☐3	☐4	☐5

15. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

16. Compared to 12 months ago, how would you rate your health now?

Much better than 12 months ago	☐1
Somewhat better than 12 months ago	☐2
About the same	☐3
Somewhat worse than 12 months ago	☐4
Much worse than 12 months ago	☐5

17. Over the last 12 months how many times have <u>you</u> been seen by your GP in relation to your own health? (Please tick 'none' if you have not visited the GP, rather than leaving the question blank).

None	☐1
Once or twice	☐2

3 to 6 times	☐3
7 or more times	☐4

18. Over the last 12 months, have you attended hospital as an outpatient or day patient, or attended casualty?

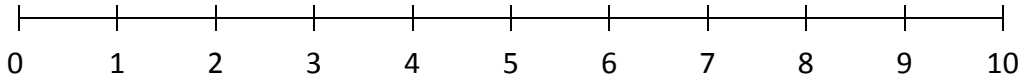
No	☐0
Yes	☐1

19. Over the last 12 months, have you been in hospital as an inpatient, overnight or longer?

No	☐0
Yes	☐1

20. How happy do you feel at the moment? Please put a mark on the scale below that indicates how happy you feel at the moment.

Completely unhappy ***Completely happy***



13. The questions in the scale below ask you about your feelings and thoughts during the last month. For each question, please indicate with a tick how often you felt or thought a certain way.

14.

15. 21. In the last month, how often have you felt that you were unable to control the important things in your life?

Never	Almost never	Sometimes	Fairly often	Very often
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

22. In the last month, how often have you felt confident about your ability to handle your personal problems?

Never	Almost never	Sometimes	Fairly often	Very often
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

23. In the last month, how often have you felt that things were going your way?

Never	Almost never	Sometimes	Fairly often	Very often
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

24. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Never	Almost never	Sometimes	Fairly often	Very often
↓	↓	↓	↓	↓
☐1	☐2	☐3	☐4	☐5

16. ABOUT YOUR OVERALL QUALITY OF LIFE

25. In this final question we are interested in what you are *able* to do in your life, and what you *actually* do in your life. For each of the five topics please place ONE tick in the first row AND ONE tick in the second row.

Being independent	...completely	...in many things	...in a few things	...in no things
	↓	↓	↓	↓
I am able to be independent…	☐1	☐2	☐3	☐4
I am independent…	☐1	☐2	☐3	☐4

Achievement and progress	...all aspects of my life	...many aspects of my life	...a few aspects of my life	...no aspects of my life
	↓	↓	↓	↓
I can achieve and progress in…	☐1	☐2	☐3	☐4
I do achieve and progress in…	☐1	☐2	☐3	☐4

Feeling settled and secure	...all areas of my life	...many areas of my life	...a few areas of my life	...no areas of my life
	↓	↓	↓	↓
I am able to feel settled and secure in…	☐1	☐2	☐3	☐4
I do feel settled and secure in…	☐1	☐2	☐3	☐4

Love, friendship and support	...a lot	...quite a lot	...a little	...not at all
	↓	↓	↓	↓
I can have love, friendship	☐1	☐2	☐3	☐4

and support…				
I do have love, friendship and support…	☐1	☐2	☐3	☐4

Enjoyment and pleasure	...a lot	...quite a lot	...a little	...not at all
	↓	↓	↓	↓
I can have enjoyment and pleasure…	☐1	☐2	☐3	☐4
I do have enjoyment and pleasure…	☐1	☐2	☐3	☐4

26. Please use the text box below to say the single, biggest way in which meningitis or septicaemia has affected your life <u>in the last 12 months.</u>

Please could you check that you have answered all the relevant questions and then:

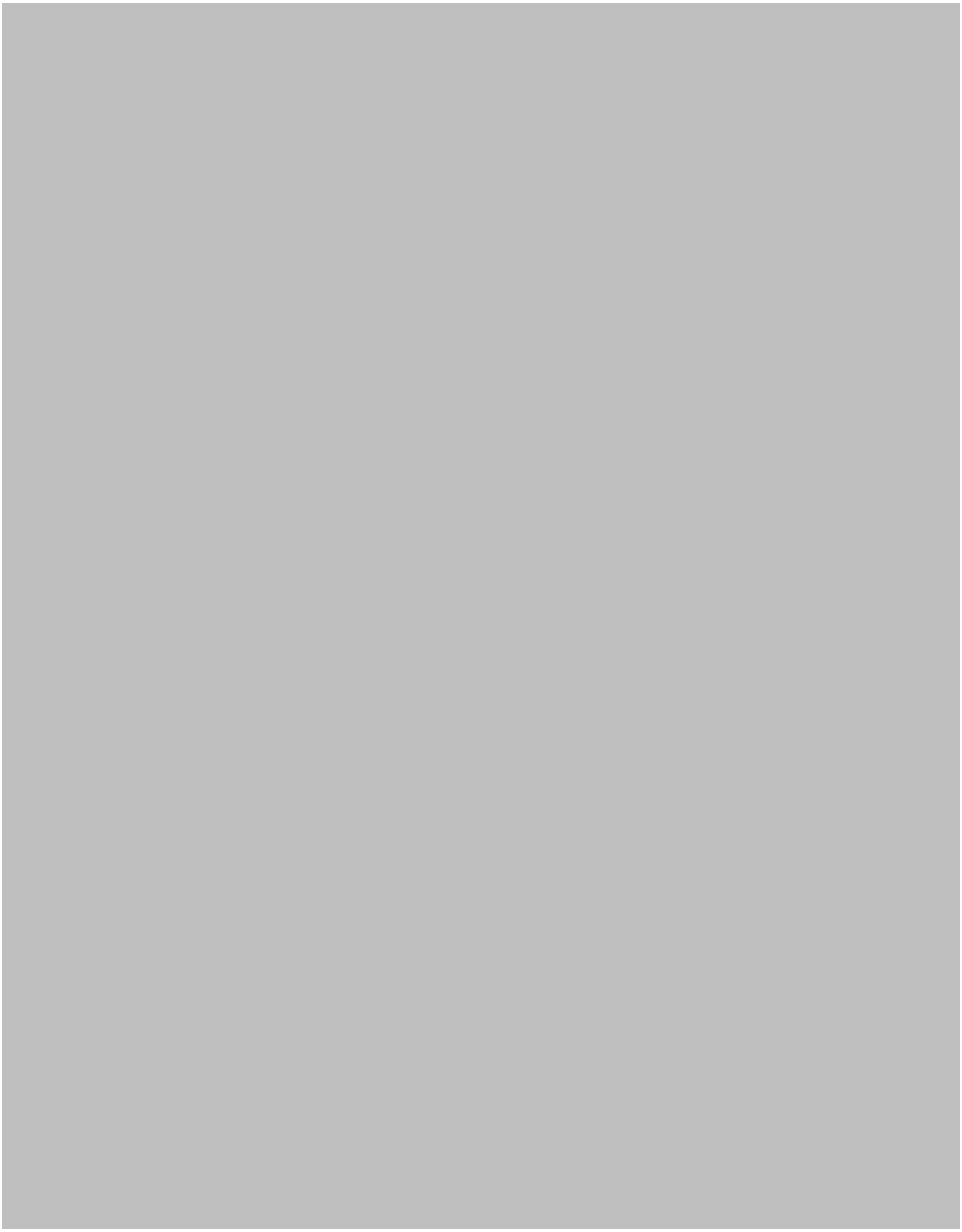
- ***Return the questionnaire to us in the enclosed FREEPOST envelope***
- ***If this questionnaire did not arrive at <u>your</u> current address, please add your address below. (We will only contact you about further voluntary research if you have indicated that you are happy for us to do so).***

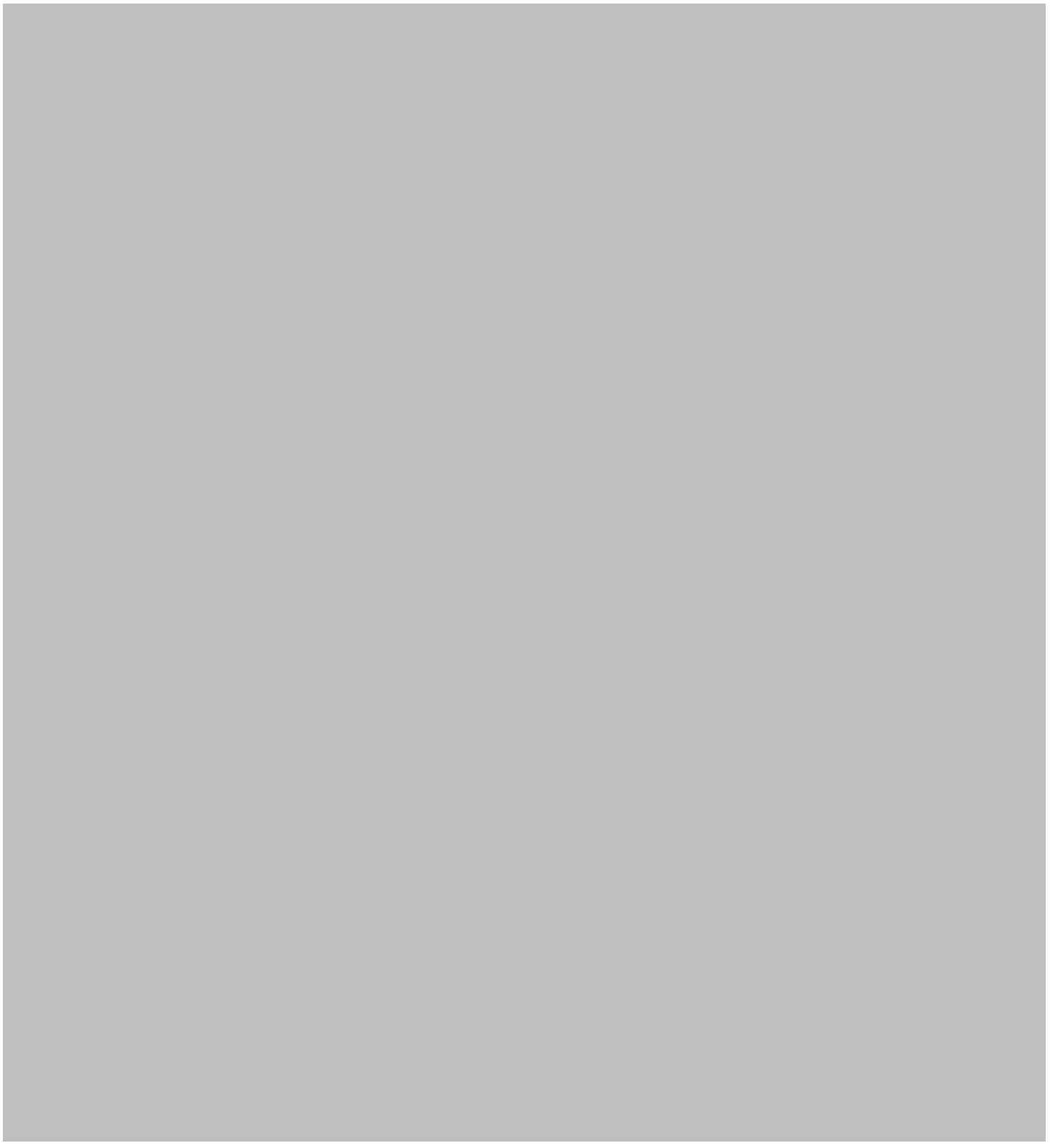
Postal address ……
……
……
Email address ……

- ***The findings of this research will be reported in the Microscope Newsletter and at: http://www.meningitis.org/family-impact. If you would also like to receive a copy of the findings in the post, please tick this box.*** ☐

Thank you very much for your valuable help in this research study.

Appendix 5.1. Ethical approval for the COPD family impact study





Appendix 5.2. Family impact of COPD questionnaires

UNIVERSITY OF BIRMINGHAM

Family impact of mild lung disease

This questionnaire is part of a research study into the impact of treatment for a specific type of mild lung disease (chronic obstructive pulmonary disease). If you share a house with a person enrolled in the (COPD) trial we would be very grateful if you could complete the questionnaire.

This research will help us to understand whether treatment for lung conditions have an impact on other people close to the patient. This information will be useful for those making decisions about funding care for people with lung conditions.

More information about the study can be found in the enclosed letter and information sheet.

The questionnaire should take about 10 or 15 minutes to complete.

For office use only:

Study ID

Your consent to take part in the study

Before completing this survey please read the information sheet and complete the sections below.

PART 1: CONSENT

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 13th May 2014 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

I understand that the data collected during the study may be looked at by individuals from the University of Birmingham or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

3. I agree to take part in the above study. ☐

Signature…… Date……..

Name (please print)……

PART 2: CONTACT DETAILS

Could you put your contact details below so we can contact you directly with the follow-up questionnaire.

Postal address ……
……
……

Email address ……

Telephone number .....

PART 3: OTHER STUDIES

Would you be willing to be contacted by the University of Birmingham about other voluntary research studies in the future?

Yes	☐ 0
No	☐ 1

Thank you for taking the time to participate in this research. We are very grateful.

WE WOULD LIKE TO START BY ASKING A FEW QUESTIONS ABOUT <u>YOURSELF</u>. ALL PERSONAL DETAILS WILL BE TREATED IN CONFIDENCE.

1. Are you female or male?

Female	☐ 0
Male	☐ 1

2. How old are you? _____ years old

3. What is your relationship to the patient? You are...

their husband, wife or partner	☐ 1
their child	☐ 2
their parent	☐ 3
their brother or sister	☐ 4
other (please state below)	☐ 5

_____

<u>SMOKING</u>

4. Do you smoke a cigarette, cigar or pipe regularly? *(by regularly we mean at least 1 cigarette/day or 7 cigarettes/ week for at least 6 months)*

Yes		☐ 0
No	(please go to q. 8)	☐ 1

5. How much do you usually smoke each day now?

Filter cigarettes per day	_____	per day
Non-filter/ hand-rolled cigarettes	_____	per day
Cigars	_____	per day
Pipe tobacco	_____	g / day

6. Would you like to give up smoking altogether?

Yes ☐ 0 No ☐ 1

7. Have you ever tried to give up smoking?

Yes ☐ 0 No ☐ 1

PHYSICAL ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

8. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities → ***Skip to question 10***

9. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

10. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? **Do not include walking**.

_____ **days per week**

☐ No moderate physical activities → ***Skip to question 12***

11. How much time did you usually spend doing moderate physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

Think about the time you spent **walking** in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

12. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

_____ days per week

☐ No walking → *Skip to question 14*

13. How much time did you usually spend walking on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

14. During the last 7 days, how much time did you spend sitting on a week day?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

HEALTH AND HEATHCARE

15. How many times have you consulted the following health care personnel regarding your health during the past **3 months**?

GP	_____ times
Practice nurse	_____ times
Pharmacist	_____ times

16. Has a doctor EVER told you that you had any of the following conditions? Please tick all that apply

	Yes	No	
Cancer (Please state type)	☐	☐	_____
Diabetes	☐	☐	
High blood pressure	☐	☐	
Coronary heart disease/Angina/Heart Attack	☐	☐	
Heart failure	☐	☐	
Stroke/mini-stroke	☐	☐	
Chronic Obstructive Pulmonary Disease / chronic bronchitis / emphysema	☐	☐	
Asthma	☐	☐	
Tuberculosis	☐	☐	
Osteoarthritis	☐	☐	
Rheumatoid arthritis	☐	☐	
Osteoporosis	☐	☐	
Depression	☐	☐	
Other condition (Please specify)	☐	☐	

_____

_____

QUALITY OF LIFE

17. Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐1
I have slight problems in walking about ☐2
I have moderate problems in walking about ☐3
I have severe problems in walking about ☐4
I am unable to walk about ☐5

SELF CARE

I have no problems in washing and dressing myself ☐1
I have slight problems in washing and dressing myself ☐2
I have moderate problems in washing and dressing myself ☐3
I have severe problems in washing and dressing myself ☐4
I am unable to wash and dress myself ☐5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

I have no problems doing my usual activities ☐1
I have slight problems doing my usual activities ☐2
I have moderate problems doing my usual activities ☐3
I have severe problems doing my usual activities ☐4
I am unable to do my usual activities ☐5

PAIN/DISCOMFORT

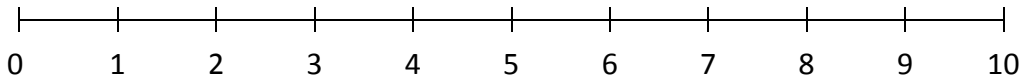
I have no pain or discomfort ☐1
I have slight pain or discomfort ☐2
I have moderate pain or discomfort ☐3
I have severe pain or discomfort ☐4
I have extreme pain or discomfort ☐5

ANXIETY/DEPRESSION

I have no anxiety or depression ☐1
I have slight anxiety or depression ☐2
I have moderate anxiety or depression ☐3
I have severe anxiety or depression ☐4
I have extreme anxiety or depression ☐5

18. How happy do you feel at the moment? Please put a mark on the scale below that indicates how happy you feel at the moment.

Completely unhappy *Completely happy*



17. The questions in the scale below ask you about your feelings and thoughts during the last month. For each question, please indicate with a tick how often you felt or thought a certain way.

18. 19. In the last month, how often have you felt that you were unable to control the important things in your life?

Never ☐1 Almost never ☐2 Sometimes ☐3 Fairly often ☐4 Very often ☐5

20. In the last month, how often have you felt confident about your ability to handle your personal problems?

Never ☐1 Almost never ☐2 Sometimes ☐3 Fairly often ☐4 Very often ☐5

21. In the last month, how often have you felt that things were going your way?

Never ☐1 Almost never ☐2 Sometimes ☐3 Fairly often ☐4 Very often ☐5

22. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Never ☐1 Almost never ☐2 Sometimes ☐3 Fairly often ☐4 Very often ☐5

23. Please use the text box below to say the single, biggest way in which you feel that your household member's lung condition has affected your life.

Please could you check that you have answered all the relevant questions including the consent section on page 2 and then return the questionnaire to us in the enclosed FREEPOST envelope to us .

Thank you very much for your valuable help in this research study.

UNIVERSITY OF BIRMINGHAM

Family impact of mild lung disease

- FOLLOW-UP QUESTIONNAIRE -

This questionnaire is part of a research study into the impact of treatment for a specific type of mild lung disease (chronic obstructive pulmonary disease).

This is the follow-up questionnaire to conclude the study you kindly responded to in 2014. Your further help will allow us to understand the impact, if any, that self-management for lung disease has on the family.

We are very grateful for your support for this study.

The questionnaire should take about 10 or 15 minutes to complete.

For office use only:
Study ID

YOU

So that we know that it is the same person responding as last year, please confirm your age and relationship to the trial participant (patient) below.

1. How old are you? _____ years old

2. What is your relationship to the patient? You are...

their husband, wife or partner ☐1
their child ☐2
their parent ☐3
their brother or sister ☐4
other (please state below) ☐5
_____

SMOKING

3. Do you smoke a cigarette, cigar or pipe regularly? *(by regularly we mean at least 1 cigarette/day or 7 cigarettes/ week for at least 6 months)*

Yes ☐0
No (please go to question 6) ☐1

4. How much do you usually smoke each day now?

Filter cigarettes per day	_____	per day
Non-filter/ hand-rolled cigarettes	_____	per day
Cigars	_____	per day
Pipe tobacco	_____	g / day

5. Would you like to give up smoking altogether?

Yes ☐0 No ☐1

6. Have you tried to give up smoking over the last 12 months?

Yes ☐0 No ☐1

PHYSICAL ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

7. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ **days per week**

☐ No vigorous physical activities → ***Skip to question 9***

8. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

9. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? **Do not include walking**.

_____ **days per week**

☐ No moderate physical activities → ***Skip to question 11***

10. How much time did you usually spend doing moderate physical activities on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

Think about the time you spent **walking** in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

11. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

_____ days per week

☐ No walking → *Skip to question 13*

12. How much time did you usually spend walking on one of those days?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

13. During the last 7 days, how much time did you spend sitting on a week day?

_____ hours per day

_____ minutes per day

☐ Don't know/Not sure

HEALTH AND HEALTHCARE

14. How many times have you consulted the following health care personnel regarding your health during the past 3 months?

GP	_____ times
Practice nurse	_____ times
Pharmacist	_____ times

15. Has a doctor EVER told you that you had any of the following conditions? Please tick all that apply

	Yes	No	
Cancer (Please state type)	☐	☐	_____
Diabetes	☐	☐	
High blood pressure	☐	☐	
Coronary heart disease/Angina/Heart Attack	☐	☐	
Heart failure	☐	☐	
Stroke/mini-stroke	☐	☐	
Chronic Obstructive Pulmonary Disease / chronic bronchitis / emphysema	☐	☐	
Asthma	☐	☐	
Tuberculosis	☐	☐	
Osteoarthritis	☐	☐	
Rheumatoid arthritis	☐	☐	
Osteoporosis	☐	☐	
Depression	☐	☐	
Other condition (Please specify)	☐	☐	

_____

_____

QUALITY OF LIFE

16. Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐1
I have slight problems in walking about ☐2
I have moderate problems in walking about ☐3
I have severe problems in walking about ☐4
I am unable to walk about ☐5

SELF CARE

I have no problems in washing and dressing myself ☐1
I have slight problems in washing and dressing myself ☐2
I have moderate problems in washing and dressing myself ☐3
I have severe problems in washing and dressing myself ☐4
I am unable to wash and dress myself ☐5

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure)

I have no problems doing my usual activities ☐1
I have slight problems doing my usual activities ☐2
I have moderate problems doing my usual activities ☐3
I have severe problems doing my usual activities ☐4
I am unable to do my usual activities ☐5

PAIN/DISCOMFORT

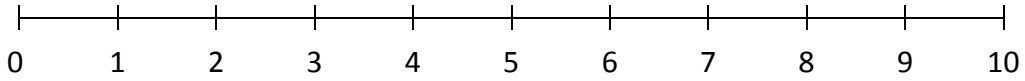
I have no pain or discomfort ☐1
I have slight pain or discomfort ☐2
I have moderate pain or discomfort ☐3
I have severe pain or discomfort ☐4
I have extreme pain or discomfort ☐5

ANXIETY/DEPRESSION

I have no anxiety or depression ☐1
I have slight anxiety or depression ☐2
I have moderate anxiety or depression ☐3
I have severe anxiety or depression ☐4
I have extreme anxiety or depression ☐5

17. How happy do you feel at the moment? Please put a mark on the scale below that indicates how happy you feel at the moment.

Completely unhappy *Completely happy*



2. The questions in the scale below ask you about your feelings and thoughts during the last month. For each question, please indicate with a tick how often you felt or thought a certain way.

3. 18. In the last month, how often have you felt that you were unable to control the important things in your life?

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21. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Never ☐1 Almost never ☐2 Sometimes ☐3 Fairly often ☐4 Very often ☐5

22. How has your family member's health care for mild lung disease affected your own health or your lifestyle behaviours over the past 12 months?

Thank you for completing this questionnaire. We are very grateful for your time.

Please could you check that you have answered all the relevant questions and then return the questionnaire to us in the enclosed FREEPOST envelope to us .

Thank you very much for your valuable help in this research study.