Establishment of the Measurement Properties and Clinical Interpretation of the Family Reported Outcome Measure (FROM-16)

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Rubina Mustafa Shah

School of Medicine Cardiff University

Cardiff UK

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To the loving memory of my best friend and mentor, my late father, Prof G M Shah, whose unrelenting faith in me inspired me to take this journey to accomplish my dream.

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SUMMARY

Chronic diseases impact the quality of life (QoL) of family members as well as patients. The Family Reported Outcome Measure (FROM-16) could be used to measure this family impact. This PhD study aims to validate FROM-16, transforming it into a robust clinical and research tool, that can also inform health economic appraisal of medical interventions.

Descriptive score bandings give meaning to QoL assessment, allowing clinicians to make better-informed decisions. The FROM-16 score banding (0-1=no effect on family members; 2-8=small effect; 9-16=moderate effect;17-25=very large effect; 26-32=extremely large effect on family members) was created using an anchor-based method and data from 4,413 family members of UK patients, recruited online.

A major obstacle to including family members' impact in health economic evaluation has been the lack of appropriate utility measures comparable to EQ-5D-3L. To address this gap, using data from 4,228 family members, FROM-16 was mapped to EQ-5D-3L to generate utility values using multinomial logistic regression and split-half validation. The algorithm now enables researchers to calculate EQ-5D health utility values from FROM-16 scores.

For FROM-16 to measure the impact of a new intervention on family members, its sensitivity to change must be demonstrated. A study including 83 NHS patients and family members confirmed that the FROM-16 was responsive to change (paired samples t-test $p < 0.05$). The data from 100 family members were used to calculate the Minimal Clinically Important Difference (MCID). This benchmark to evaluate clinically significant improvement was estimated for FROM-16 as a score change of ‘four’ points using anchor and distribution-based methods.

The FROM-16 was used in a global COVID-19 study demonstrating that family members of COVID-19 survivors (n=735) experienced a substantial QoL impact of their relative's COVID-19. This study confirmed the value of FROM-16 for use in a pandemic.

Major new aspects of FROM-16 have now been successfully validated.

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADHD	Attention Deficit and Hyperactivity Disorder
ARC	Autism Research Centre
ARDS	Acute Respiratory Distress Syndrome
AUC	Area Under Curve
CASP	Critical Appraisal Skills Programme
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
COVID-19	Coronavirus Disease 2019
CUA	Cost-Utility Analysis
DD	Developmental Disabilities
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
EQ-5D-3L	Euroqol- 5 Dimension -3 Level
ES	Effect Size
FDA	Food and Drug Administration
FROM-16	Family Reported Outcome Measure-16
GDPR	General Data Protection Regulation
GQ	Global Question
GRCQ	Global Rating of Change Question
GSQ	Global Severity Question
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
HWW	Healthwise Wales
JDR	Join Dementia Research
JISC	Joint Information Systems Committee
MAE	Mean Absolute Error
MCID	Minimal Clinically Important Difference
MERS	Middle East Respiratory Syndrome
MIC	Minimal Important Change
MID	Minimal Important Difference
mlogit	Multinomial Logistic Regression
MSE	Mean Square Error
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPOR	Non-Proportional Odds Regression
ODD	Oppositional Developmental Disorder
OLS	Ordinary Least Squares
PBM	Preference Based Measure
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PRO	Patient-Reported Outcome
PROMs	Patient-Reported Outcomes Measures
PSGs	Patient Support Groups
QALY	Quality-adjusted life year
QoL	Quality of Life
RMS	Root Mean Square Error
ROC	Receiver Operating Characteristics
SARS	Severe Acute Respiratory Syndrome
SEM	Standard Error of Measurement
SMREC	School of Medicine Research Ethics Committee
SPSS	Statistical Product and Service Solutions
SRM	Standardised Response Mean
SRTOBE	STrengthening the Reporting of OBservational studies in Epidemiology
SSDs	Social Services Departments
SURE	Specialist Unit for Review Evidence
TTO	Time Trade-Off
VBH	Value Based Healthcare
WHO	World Health Organisation

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CHAPTER 1

General Introduction

1.1 BACKGROUND

The World Health Organization (WHO) defined "health" as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948). It is this definition of health that revolutionised thinking concerning medical care and transferred healthcare attitudes from the traditional disease-centred model to a patient-centric holistic model, leading to growing interest in the concepts of well-being and quality of life (QoL) both in the clinical and research environment. Quality of life can be defined as a "person's sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to the individual" (Ferrans 1990). The notion of QoL emerged in the medical literature for the first time in the 1960s with J R Elkinton's editorial in *Annals of Internal Medicine* in which he wrote:

> What every physician wants for every one of his patients old or young, is not just the absence of death but life with a vibrant quality that we associate with a vigorous youth. This is nothing less than a humanistic biology that is concerned, not with material mechanisms alone, but with the wholeness of human life, with the spiritual quality of life that is unique to man. Just what constitutes this quality of life for a particular patient and the therapeutic pathway to it often is extremely difficult to judge and must lie with the consciousness of the physician (Elkinton 1966, p.714).

This quotation clearly indicates a shift in attitudes of physicians from disease-centric medical care towards patient-centric care, keeping a patient’s QoL at the heart of therapeutic decision-making. Furthermore, medical, and technological advancement during the 1950s and 1960s such as renal dialysis (Strauss and Glaser 1975), renal transplantation and new forms of cancer therapy meant longer life expectancy which generated increased demand for the evaluation of the '*quality'* of that increased time (Carlens et al. 1971). The sacrifices required for increased life expectancy (Graham et al.1973) and the side effects associated with some medical procedures (Bunker 1973) emphasised the need to consider QoL as an important outcome measure alongside survival (Beard 1971). Thus, the concept of QoL gradually emerged as a new common

currency of medical outcome that would allow meaningful comparison across different interventions and lead to ethical and legitimate clinical decision-making.

1.1.1 Defining Quality of Life

Although the term 'QoL' has been extensively used in medicine over the past six decades, there is currently no consensus among researchers and scholars on its definition. Table 1.1 includes multiple definitions of QoL that have been created over the last six decades mostly based on a person's evaluation of self, ranging from the simplest such as 'degree of satisfaction' (Campbell 1976; Hörnquist 1982; Emerson 1985) to the most comprehensive definitions (Gotay and Moore 1992; WHO 1995; Haas 1999; Thenmozhi 2018). One of the earliest definitions of QoL was given by Campbell et al. (1976) who defined QoL as "satisfaction of needs, and level of satisfaction that can be precisely defined as the perceived difference between aspiration and achievement". Hörnquist (1982) went beyond satisfaction by referring to the particular areas of an individual's life which are impacted: "The degree of need and satisfaction within the physical, psychological, social, activity, material, and structural area". Calman (1987) based his conceptualisation of QoL on the difference between perceived goals and actual goals. He proposed that QoL "measures the difference, at a particular period of time, between the hopes and expectations of the individual and the individual's present experience". He argued that improving QoL of an individual can only be achieved by reducing the gap between actual and perceived hopes, which could vary from person to person. The WHO (1995) defined QoL, taking into consideration cultural and societal norms that could influence the experience of QoL, as: "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Haas (1999) placed the concept of QoL in the context of the person's own environment: "QoL is a multidimensional evaluation of an individual's current life circumstances in the context of the culture and value systems in which they live and the values they hold. Quality of life is primarily a subjective sense of well-being encompassing physical, psychological, social, and spiritual dimensions. In some circumstances, objective indicators may supplement or, in the case of people unable to subjectively perceive, serve as a proxy assessment of QoL". The most recent comprehensive definition of QoL is given by Thenmozhi (2018) who included the

impact of stress and sexual function on QoL: "overall assessment of a person's well-being, which may include physical, emotional and social dimensions, as well as stress level, sexual function and self-perceived health status".

Table 1.1 Definitions of 'Quality of Life' in the literature

	Author	Definition
1.	Campbell 1976	"Satisfaction of needs", and "level of satisfaction can be precisely defined as the perceived difference between aspiration and achievement".
2.	Hörnquist 1982.	"The degree of need and satisfaction within the physical, psychological, social, activity, material, and structural area".
3.	Wenger et al. 1984	"An individual's perceptions of his or her functioning and well-being in different domains of life".
4.	Emerson 1985	"The satisfaction of an individual's values, goals and needs through the actualisation of their abilities or lifestyle".
5.	Calman 1986	"Measures the difference, at a particular period of time, between the hopes and expectations of the individual and the individual's present experience. It is concerned with the difference between perceived goals and actual goals".
6.	Ferrans 1990	"Person's sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important to the individual".
7.	Gotay and Moore1992	"A state of well-being which is a composite of two components: 1) the ability to perform everyday activities which reflects physical psychological, and social well-being and 2) patient satisfaction with levels of functioning and the control of disease and/or treatment related symptoms".
8.	WHO 1995	"Individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".
9.	Haas 1999	"QoL is a multidimensional evaluation of an individual's current life circumstances in the context of the culture and value systems in which they live and the values they hold. QoL is primarily a subjective sense of well-being encompassing physical, psychological, social, and spiritual dimensions. In some circumstances, objective indicators may supplement or, in the case of individuals unable to subjectively perceive, serve as a proxy assessment of QoL".
10.	Thenmozhi 2018	"Overall assessment of a person's well-being, which may include physical, emotional and social dimensions, as well as stress level, sexual function and self-perceived health status".

While researchers and scholars have given a wide range of definitions of QoL, some simple and others more comprehensive, all convey that QoL is a subjective concept,

using defining phrases such as "an individual's perception" and "individual's present experiences". However, individuals' experiences and perceptions can vary with their personality, attitude, values and the environment around them. Thus, it is imperative that QoL assessment should be carried out by the patient themselves as any proxy measure will not be able to reflect perceptions and experiences unique to the individual under investigation. Furthermore, with so many definitions of QoL, there is a likelihood of confusion among researchers about how one should define QoL. Post (2014) suggests that researchers should use a QoL definition that best fits the topic and objective (s) of their study. As the term 'QoL' has many meanings, researchers should precisely specify what they mean in their studies (Dijkers 2007).

1.1.2 Health-Related Quality of Life

The term 'health-related quality of life' (HRQoL) was introduced for the first time in the literature in the mid-1980s by Torrance (1987) who defined it as a subset of QoL, relating only to the domain of health. Torrance's concept of HRQoL only contains physical and emotional functioning, omitting social functioning, which he considered beyond the scope of health despite the WHO definition of health as, "a state of complete, physical, mental and social well-being". On the other hand, Ebrahim (1995) gave a more general subjective definition of HRQoL without specifying domains: "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment". Patrick and Erickson (1988) gave an objective definition of HRQoL: "the value assigned to duration of life as modified by the impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment, or policy", while Hays and Reeve (2008) included both subjective and objective concepts in his definition of HRQoL: "how well a person functions in their life and his or her perceived well-being in physical, mental, and social domains of health" (Hays and Reeve 2008). Here the term "functioning" refers to the ability of a person to carry out some pre-defined activities (Wilson and Cleary 1995; Hays and Reeve 2008) and well-being refers to the subjective feelings of that person (Hays and Reeve 2008). However, there seems to be considerable overlap between specific HRQoL and generic QoL (Wilson and Cleary 1995). Barofsky (2012) argues that 'QoL' and 'HRQoL' can be differentiated, as 'QoL' refers to the general population, while 'HRQoL' refers to persons who are medically ill. Interestingly, researchers in health are using both terms

'QoL' and ‘HRQoL’ and for the purpose of this thesis, the two terms will be used interchangeably.

The evolution of QoL definitions over the last six decades is clear evidence of a growing interest in this area among researchers, clinicians, scholars and international professional societies. The International Society for Quality-of-Life research (ISOQOL), founded in 1994, has a mission to advance the scientific study of HRQoL and other patient-centred outcomes to improve the QoL of the population (ISOQOL 2021).

1.1.3 Measurement of QoL

The measurement of QoL and HRQoL comes under the umbrella of "patient-reported outcomes" (PROs). PRO describe outcomes collected directly from the patient without interpretation by clinicians or others, such as symptoms, satisfaction, preference, activity limitations, and health status (Higgins and Green 2008; Acquadro et al. 2003; Doward and McKenna 2004; FDA 2009). Patient-reported outcome measures (PROMs) are instruments that are used to measure the PROs and are often self-report questionnaires and interviews (Johnston 2023), provided that the interviewer records only the patient's response (FDA 2009). However, in some cases, QoL can be measured using observer-reported outcomes, where the QoL measurement is made by someone other than the patient (usually a family member or clinician). These are not PROMs but are considered clinician-reported or observer-reported outcomes (Powers et al. 2017).

1.1.3.1 Operationalisation of PROs to PROMs

Providing high-quality care requires patients to provide information about their feelings, symptoms and treatment effects. A major contribution to this concept was the medical outcomes study that examined both patient and clinical outcomes as well as differences in healthcare, clinicians, and communication styles (Tarlov et al.1989). The concept was further extended into drug development research in the last two decades (Patrick et al. 2007; FDA 2009; FDA 2022), with the pharmaceutical industry recognising the importance of PROs being considered alongside biomarkers of health improvement (Willke et al. 2004). The distinction between health outcomes and

treatment effects became clearer when research into health services focused on improving the patients' health-related quality of life, especially when patients received optimal medical therapy (Willke et al. 2004). This, in turn, led to a requirement for valid and reliable PROMs. Although PROMs were initially used in pharmacological and health service research, mostly limited to England, Sweden, and certain areas of the US to improve patient clinical care, the use of PROMs has expanded beyond clinical research in recognition of its potential to transform health care, as well as improve quality and safety of the patient (Weldring and Smith 2013). Since 2009, the UK has made the use of PROMs mandatory for some surgical procedures in order to facilitate health service comparison (Black 2013), reveal the strengths and shortcomings in the delivery of healthcare, inform commissioning, and foster choice (Department of Health 2011; Darzi 2014).

Quality of life assessment is often used alongside other forms of PROs, for example, symptom assessment or the measurement of health behaviour. An individual's QoL can be assessed using validated and standardised QoL instruments, allowing the comparison of results across various health conditions and groups of patients. At the same time, the different aspects influencing a patient's QoL can be considered, such as physical, social and psychological factors. In order to account for the individual variation in responses to each of these factors, QoL instruments allow users to rate the level of impact of each factor that they experience, for example, ‘not at all’, ‘a little’ and ‘a lot’ on a Likert scale.

1.1.3.2 Quality of life instruments

Quality of life instruments may be generic or disease-specific (Hand 2016).

1.1.3.2.1 GENERIC MEASURES

Generic instruments measure the effects of a wide range of diseases or treatments on the QoL of patients or those around them. Generic instruments include health profiles, which generate scores in several different domains, and health utility measures, which generate a single HRQoL score, such as a quality-adjusted life-year (Guyatt et al. 1993). Generic instruments are particularly useful when measuring QoL in people with

comorbidities (Salaffi et al. 2005) or when evaluating multicomponent interventions (Hand 2016) or assessing QoL of communities or groups of patients (Huebner et al. 2004). Moreover, generic measures can be very useful tools to measure the impact of patients' disease on family members or carers. Research has shown that family members caring for their relative with different health conditions are impacted in similar ways (Golics et al. 2014). Thus, generic instruments allow comparison of QoL of individuals across different disease areas and identification of population-wide trends. Moreover, generic instruments can be used to measure QoL of patients suffering from specific diseases and are the only possibility for use in those areas where there are no disease-specific measures. However, as the questions are necessarily general in nature, to be relevant across many disease areas, the information gathered can be too generalised and miss some disease-specific details. Revicki and Ehreth (1997) argue that generic instruments do not provide a complete picture of a patient's QoL, especially when measuring the change in a disease state.

1.1.3.2.2 DISEASE-SPECIFIC MEASURES

Disease-specific measures are designed to assess the QoL of people with a specific disease and of those around them, and thus can detect changes in individuals' QoL and those around them following clinical interventions. While disease-specific instruments can help clinicians to understand the extent to which a patient has been affected by a disease and inform appropriate treatment decisions, they cannot be used to compare across conditions or treatment programs (Revicki and Ehreth 1997). Disease-specific measures contain items relevant to the disease in question, such as items measuring specific symptoms or the impact of the clinical features of the disease.

Thus, disease-specific instruments can provide better insights into treatment specific issues which are unique to the individual patient (Temple et al. 2009). It is, therefore, because of this characteristic of disease-specific measures that they are rendered more sensitive to change over time. In some cases, QoL studies may use both generic and disease-specific instruments to capture the different patient viewpoints or to compare the results of using each type of instrument (Klassen et al. 2000).

1.1.3.3 Importance of QoL measurement

The most important use of QoL measures is in enhancing clinical consultation, improving communication, and allowing clinicians with their patients to reach better informed clinical decisions, which in turn could lead to improved adherence to treatment (Finlay et al. 2017; Basch et al. 2018). The clinical use of QoL measures provides insights to doctors and other members of the care team about how their patients are affected while at the same time, offering patients tools to help them articulate their concerns. Although there is a growing interest in PRO data among clinicians and health system leaders, challenges in its collection, analysis, interpretation, and integration can hinder its broad application in health care. However, several established resources have been developed that provide guidance on the use of PRO in clinical practice and overcoming these challenges (Crossnohere et al. 2023; Chan et al. 2019; Basch and Snyder 2017; Santana et al. 2015).

In clinical research, the use of QoL measures provides a specific understanding of the patient's perspective in evaluating the effectiveness of medical intervention or treatment (FDA 2022; Snowdon et al. 2023). In such studies, the QoL outcomes following different treatments are compared alongside clinical outcomes to identify the intervention which works most effectively in improving the QoL of patients (Brower et al. 2021). Thus, QoL measures may inform clinical decision-making, economic analysis and healthcare resource allocations (NHS 2017; Brower et al. 2021) when data is captured in a scientifically rigorous way following CONSORT (CONSORT-PRO) and SPIRIT (SPIRIT-PRO) recommendations (Calvert et al. 2013; Calvert et al. 2018)

The need to ration healthcare resources is related to limited financial resources and the rising costs of healthcare due to the increasing costs of research and development of pharmaceuticals, expensive new technologies and the ageing population, which places a greater burden on healthcare services. Considering the increasing demand on healthcare resources, allocation of such has mainly been informed by the derivation of Quality Adjusted Life Years (QALYs – i.e., combination of the quantity and quality of life) for different medical interventions. New interventions are assessed based on the number of years, and the relative quality a given intervention adds to a particular life. One year lived in perfect health is worth one QALY unit. The cost of any medical intervention can be divided by its expected QALY increase to yield a cost per QALY

(Edgar et al.1998). In this way, different medical interventions/procedures are compared according to their cost-effectiveness. The calculation of QALYs is central to the economic evaluation of new medicines in submissions to the National Institute for Health and Care Excellence (NICE) in the UK (Tolley 2001).
Furthermore, the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) have recognised the importance of the inclusion of QoL measures/patient-reported outcomes (PRO) as effectiveness endpoints in clinical trials (EMA 2005; FDA 2009; FDA 2022) and have released guidance on the use of these measures. The EMA (2005) guidance is more general and does not include specific information regarding instrument development. On the other hand, the FDA (2009) issued formal guidance on the use of PRO measures (PROMs) and outlined recommendations for instrument development.

1.1.3.4 Measurement properties of QoL measures/PROMs

The FDA (2009) has set the minimum standards for development and validation of PRO measures to ensure suitability for their purpose, particularly when being used as part of the evidence for licensing of a new drug. These standards include reliability, validity, and sensitivity to change.
Reliability: Is the ability to yield consistent, reproducible estimates of true treatment effect, which is important as clinical trials measure change over time (FDA 2009). Reliability includes test-retest reliability and internal consistency. Test-retest reliability assesses the stability of the instrument over a short period of time, assuming that the clinical dimension under assessment has remained unchanged. However, the parameters under analysis may vary from day to day in a clinical population (Carrozzino et al. 2021). This measurement property is not considered as important in clinimetrics as other features, such as sensitivity (Fava et al. 2018). Internal consistency reliability is the extent to which items measuring the same concept correlate.
Validity: Ensures that the instrument is measuring what it is intended to measure. The FDA requirements include content and construct validity. Content validity refers to the extent to which an assessment instrument is relevant to, and representative of, the targeted construct it is designed to measure. In other words, is it fit for purpose? Construct validity assesses to what extent a PRO instrument measures the construct it

is supposed to measure. This involves demonstrating moderate to high correlations with existing measures that assess the same concept (convergent validity), and low correlations with measures that assess other distantly related concepts (divergent validity) (Rothrock et al. 2011). Another important aspect of construct validity is cross-cultural validity, the degree to which the performance of the items on a translated or culturally adapted PROM adequately reflects the performance of the items of the original version of the PROM (Mokkink et al. 2010). Another type of validity is criterion validity, which is the degree to which the scores of a PROM are an adequate reflection of a 'gold standard'.

Responsiveness: A QoL/PRO measure should also be able to identify differences in scores over time in individuals or groups who have changed with respect to the concept being measured. This is particularly important when demonstrating the effectiveness of a new drug or intervention. Responsiveness is defined by COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) as the ability of a PROM to detect change over time in the construct to be measured (Mokkink et al. 2010).

Interpretability: One of the important characteristics of measurement tools is their interpretability, the degree to which one can assign qualitative meaning that is, clinical or commonly understood descriptors to a PROM's quantitative scores or change in scores (Mokkink et al. 2010).

QoL measures should be psychometrically robust (reliable, valid and sensitive) for use in clinical research/clinical trials and clinical practice. Psychometrically robust assessment is important in evidence-based practice and good research, as this provides a way to assess the populations, interventions, or other instruments accurately. Poorly developed instruments can result in the unethical waste of resources, harmful practices, and the dissemination of false or misleading information (Swan et al. 2023). The COSMIN initiative provides guidance to clinicians and researchers in developing, researching, and selecting measurement instruments with robust psychometric properties that are appropriate for their intended use (Swan et al. 2023; Mokkink et al. 2016).

1.1.4 Family Quality of Life

Caring for a family member/partner with a health condition, particularly a chronic one, disrupts normal family life and can trigger feelings of anxiety, depression, anger, fear and helplessness. The term 'family quality of life' was first formulated by Turnbull et al. in 2000: "Conditions where the family's needs are met, and family members enjoy their life together as a family and have the chance to do things which are important to them" (Turnbull et al. 2000). Later Zuna et al. (2010) further defined the concept as a "dynamic sense of well-being of the family, collectively and subjectively defined and informed by its members, in which individual and family-level needs interact". The FQoL is collective and subjective as it indicates how family members feel about their family QoL as a group. It is 'dynamic' as it can change in response to events which affect a family such as having a child with a disability. Although these concepts of FQoL, as an integrated unifying family concept, express one aspect of FQoL, each individual within a family may be affected in a specific way which may vary from person to person. Most FQoL measurement techniques assess these individual person experiences rather than attempting to measure the much more elusive integrated family impact, which is more challenging to define and capture. Although descriptors of the concept of FQoL were developed in the early 2000s when disability researchers began to focus their attention on the development of FQoL measures, work on developing such measures had already started in 1990s in the fields of diabetes (Vandagriff et al. 1992; Spezia Faulkner and Clark 1998), oncology (Ferrell et al. 1991) dermatology (Lawson et al. 1998) and ENT (Berdeaux et al. 1998). Since 2000, there has been a steady growth in the publication of generic FQoL measures, such as the Family QoL survey (Isaacs et al. 2007; Perry and Isaacs 2015; Samuel et al. 2018), the Beach Centre QoL questionnaire (Park et al. 2003; Hoffman et al. 2006; Poston et al. 2003), the Family Dermatology Life Quality Index (Basra et al. 2007), and the Family Reported Outcome Measure, FROM-16 (Golics et al. 2014). However, most of the research on the impact of disease on FQoL has been focused within a few individual medical fields such as mental health, oncology and dermatology (Poston et al. 2003; Cohen et al. 2006; Basra and Finlay 2007; Eghlileb et al. 2009). Mora et al. (2020) argue that FQoL has mainly focused on issues related to disability and chronic illnesses in children from birth to six years of age, although the concept of FQoL could be applied much more widely to families impacted by the ill health of a family member of any age. Although

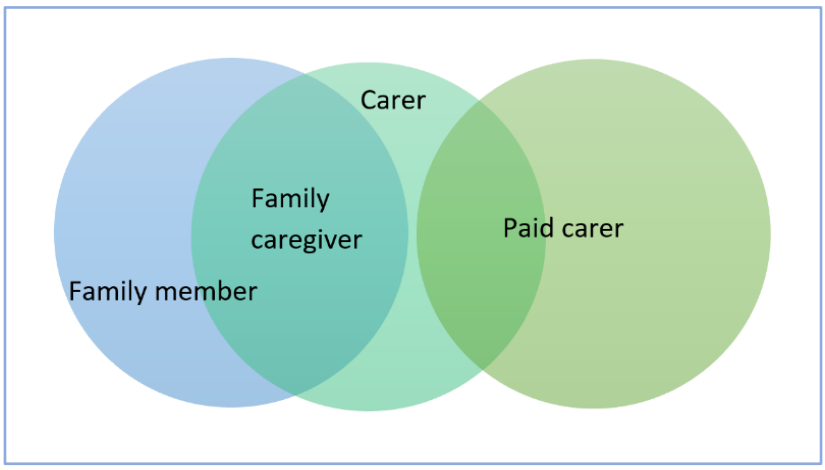
some of these FQoL measures are being used in research studies to evaluate the impact of a person's health condition on family members and partners, the clinical use of these measures to inform and focus support to improve the QoL of family caregivers is still limited.

1.1.4.1 What constitutes the family?

The traditional definition of a family is 'two parents and their children living under the same roof'. However, this definition of 'family' is inadequate and too limited to describe the reality of 'family' today. Over time what is ‘family' has evolved with changes in societal norms and relationship dynamics, resulting in the many varieties of families that we have today. This wide range of modern-day families fits into the Poston et al. (2003) definition of the concept of family as consisting of "People who think of themselves as part of the family, whether related by blood or marriage or not and who support and care for each other on a regular basis". This thesis reflects the inclusive definition given by Poston et al. (2003) as it represents the current dynamics and range of expressions of a family.

In the context of health care, the descriptors of 'carer' and 'family member' are often used interchangeably and as if they had the same meaning. However, it is important to clarify that not all carers are family members and not all family members are carers (Figure 1.1).

Figure 1.1 Venn diagram - Not all carers are family members, and not all family members are carers.



The literature review presented in this thesis has considered the impact of a patient's disease on all family members, irrespective of whether or not they are the primary carer or have any caring responsibilities at all. While the terms family members, family caregivers, carers, informal carers, and caregivers are often used interchangeably and sometimes inaccurately in the literature, this thesis will focus on family members and partners, who may or may not be unpaid carers (caregivers).

1.2 REVIEW OF THE LITERATURE

This section aims to identify the impact of chronic disease on family members of patients across a range of medical specialities informed by valid instruments. This review also presents a rapid overview of the characteristics and measurement properties of existing generic and disease-specific FQoL measures. The purpose of this review was also to find out if there have been any new generic tools for measuring family QoL since 2014 that could have replaced FROM-16 (Appendix I) and to determine whether FROM-16 is the only generic tool that could be used across all areas of medicine to measure family impact of disease. Golics and colleagues' (2013a) detailed literature review of the impact of chronic disease on a patient's family members revealed various aspects of family members' lives that are affected, including emotional, financial, family relationships, education, and work, leisure time and social activities. That review highlighted that most of the literature on the family impact of disease was restricted to a few disease areas and specialities (Golics et al. 2013a) and concluded that there was no generic instrument at that time to measure disease impact on family members of patients.

As the investigation of FQoL is a newly evolving field, with research now extending to many different areas of medicine, it is timely to update the existing knowledge base on the family impact of disease and to explore the development of the novel instruments that have been designed to measure this impact. This review builds on the areas covered by Golics et al. (2013a) but also reviews the greatly increased research activity over the last ten years.

1.2.1 Methods

1.2.1.1 Search strategy

This review followed the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines to ensure transparent and comprehensive reporting (Moher et al. 2009). Although this is not a systematic review, some systematic review principles were also relevant to this literature review, for example, “Describe the rationale for the review in the context of what is already known”, “Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated” and “Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram” (Moher et al. 2009).

A prespecified search strategy was used to identify studies published up until the 9th of May 2023 that reported burden or QoL of family members of patients with chronic diseases. The searches were carried out using six electronic databases: Medline via OVIDSP, EMBASE via OVIDSP, CINHAL via EBSCO, ASSIA via ProQuest, PsycINFO Via OVIDSP and Scopus (Table1.2). The search strategy was designed to be highly sensitive to retrieve potentially relevant studies. It involved breaking down the review question into three key concepts, family, impact, and chronic disease, and then listing alternative keywords and synonyms for each concept (Table 1. 3).

Table 1.2 Databases searched:

Database used	**Period of retrieval**
Medline via OVIDSP	1946 – 9 May 2023
EMBASE via OVIDSP	1947 - 9 May 2023
Scopus	1823 - 9 May 2023
PsycINFO Via OVIDSP	1887 - 9 May 2023
CINHAL (The Cumulative Index to Nursing & Allied Health Literature) via EBSCO	1961 - 9 May 2023
ASSIA (Applied Social Sciences Index and Abstracts) via ProQuest	1987 - 9 May 2023

Boolean operators ‘OR’ and ‘AND’ were used to combine search terms and search concepts to get focussed results. The search strategy was first used with Medline and later adapted to the other five databases (Table 1.4). A separate search was run,

replacing ‘chronic disease’ as a search term with the names of the 26 disease specialties to further enhance the search results.

Table 1.3 Search strategy design: concepts used as search keywords

Family	Disease	Impact
Family members/Father /Mothe/Partner/ Parents /Grandparent / husband/spouse/wife/ Children/siblings/carer /Caregiver/informal caregiver	Illness/ Chronic illness /chronic disease / Cardiology/Care of the elderly/Chronic Pain/Colorectal Surgery/Dental surgery/ (Dermatology or paediatric dermatology)/('Ear, nose, and throat')/Endocrinology/Paediatric endocrinology/Gastroenterology/General Practice /Genetics/Gynaecology/Haematology/Infectious diseases/Mental Health/Neurology/Oncology/ Ophthalmology/(Orthopaedics or paediatric orthopaedics)/Post-stroke/(Renal or renal transplant)/Respiratory/Rheumatology/Urology/ /Wound healing	Effect/burden/ Influence/ secondary impact/quality of life/family quality of life/ family reported outcome

Table 1.4 Search terms used in Ovid Medline (1947 to 9th May 2023) and the number of articles identified by the use of each search term.

Search terms	Results
1. (family or family member).mp.	1159337
2. (father or mother).mp.	157833
3. partner.mp.	91704
4. (parents or grandparents).mp.	239053
5. (husband or wife or spouse).mp.	27957
6. (children or siblings).mp.	1246133
7. (carer or caregiver).mp. or Caregivers/	73012
8. informal caregiver.mp.	910
9. or/1-8	2571013
10. (quality of life or family quality of life).mp.	444086
11. (impact or effect or burden or influence).mp.	6041604
12. secondary impact.mp.	122
13. family reported outcomes.mp.	17
14. ((chronic adj disease) or (chronic adj illness)).mp.	323744
15. 11 or 12 or 13	6041614
16. 9 and 10	63635
17. 14 and 15 and 16	1621
18. limit 17 to English language	**1512**

This wider search revealed 439 results which were added to the main Medline results (Table 1.5). Google Scholar was searched for any additional articles reporting the impact of disease on QoL of family members. In addition, the reference lists of key studies were also searched to ensure all relevant studies were captured. The searches were restricted to articles published in the English language

Table 1.5 Search strategy in OVID Medline (1946 to 9th May 2023) extended to include different disease areas to capture all articles about the impact of chronic disease on the family.

Search terms	Results
1. (family or family member).mp.	1159337
2. (father or mother).mp.	157833
3. partner.mp.	91704
4. (parents or grandparents).mp.	239053
5. (husband or wife or spouse).mp.	27957
6. (children or siblings).mp.	1246133
7. (carer or caregiver).mp. or caregivers/	73012
8. informal caregiver.mp.	966
9. or/1-8	2571013
10. quality of life .mp.	444086
11. (impact or effect or burden or influence).mp.	6041604
12. ((chronic adj disease) or (chronic adj illness)).mp.	323744
13. cardiology/ or cardiology.mp.	61360
14. age -related disease	5724
15. chronic pain.mp. or chronic pain/	57776
16. (colorectal or bowel disease).mp.	11236
17. dental disease.mp.	1984
18. (dermatology or paediatric dermatology).mp.	46854
19. (ear, nose, and throat).mp.	5705
20. endocrinology.mp. or endocrinology/	21310
21. gastroenterology.mp. or gastroenterology/	25760
22. general practice.mp. or general practice/	52732
23. genetic disease.mp. or genetic disease/	4068491
24. gynaecology/ or gynaecology.mp.	46598
25. haematology.mp. or haematology/	8422
26. autoimmune diseases.mp.	93257
27. mental health/ or mental health.mp.	264495
28. neurology.mp. or neurology/	46253
29. oncology.mp.	156333
30. ophthalmology.mp. or ophthalmology/	46055
31. (orthopaedic or paediatric orthopaedic).mp.	32792
32. paediatric endocrinology.mp.	1004
33. post stroke.mp.	13768
34. (renal or renal transplant).mp.	770981
35. respiratory.mp.	695795
36. rheumatology.mp. or rheumatology/	28919
37. urology/ or urology.mp.	31510
38. wound healing.mp. or wound healing/	157048
39. or/13-38	6456574
40. 9 and 11and 12	8119
41. 39 and 40	2142
42. 10 and 41	471
43. limit 42 to English language	**439**

The search was extended to identify existing generic and disease-specific FQoL measures by combining search terms such as ‘family*or caregiver’ and ‘quality of life’ with the terms scale, index, measure, instrument, assessment, surveys, questionnaires, inventory, tools, generic or disease-specific (Table 1.6). Table 1.6 shows key words/

phrases that were searched in Medline via OVIDSP, EMBASE via OVIDSP and PsycINFO. A hand search of the COSMIN database, and of the reference lists within relevant articles was carried out to ensure all generic and disease specific FQoL measures were captured. Google Scholar was searched for articles reporting development or psychometric properties of the instruments identified.

Table 1.6 Search terms employed in OVID Medline (1947 to 9th May 2023) to identify existing FQoL instruments and the number of articles identified.

Key search terms	Results
1. (family* or caregiver).mp.	1187074
2. (quality of life or QoL).mp.	445769
3. (scale or index or measure or instrument or assessment or surveys or questionnaires or inventory or tools).mp.	4856666
4. (generic or disease specific).mp.	91268
5. (development or psychometric or valid* or reliab*).mp.	4521288
6. 1 and 2	32072
7. 3 and 4	30685
8. 5 and 7	11421
9. 6 and 8	316
10. limit 9 to English language	**305**

1.2.1.2 Eligibility criteria for the review

Articles were included in the review if the source was an original paper, in the English language and measuring the impact of chronic illness or disability on patients' family members/partners using a valid QoL tool. Articles were excluded from the review if they were not in the English language, were a review article, or were not using a valid tool to measure the impact of chronic illness or disability on patients' family members/ partners. For the second part of the review, inclusion criteria included original articles in the English language discussing the development and measurement properties of family/carer QoL measures.

1.2.1.3 Data Extraction and Quality Assessments

A prespecified data extraction template was used to collect and record data from the identified studies. Data extraction was discussed and agreed with the research team. Data was extracted by one person (RS). The template included study design, country, year of publication, sample size, family member data such as gender, relationship to the patient and impact on the QoL of the family members. The scales used to measure various aspects of QoL and/or burden were also documented. A separate data extraction template was used to record the psychometric properties of existing FQoL instruments. This included the general characteristics of the QoL instrument, origin, internal consistency (Cronbach's alpha), test–retest validity, content validity, construct -convergent validity, construct-divergent/discriminant validity, criterion validity, minimal clinically important difference (MCID) and responsiveness/sensitivity to change.

1.2.1.4 Assessment of methodological quality

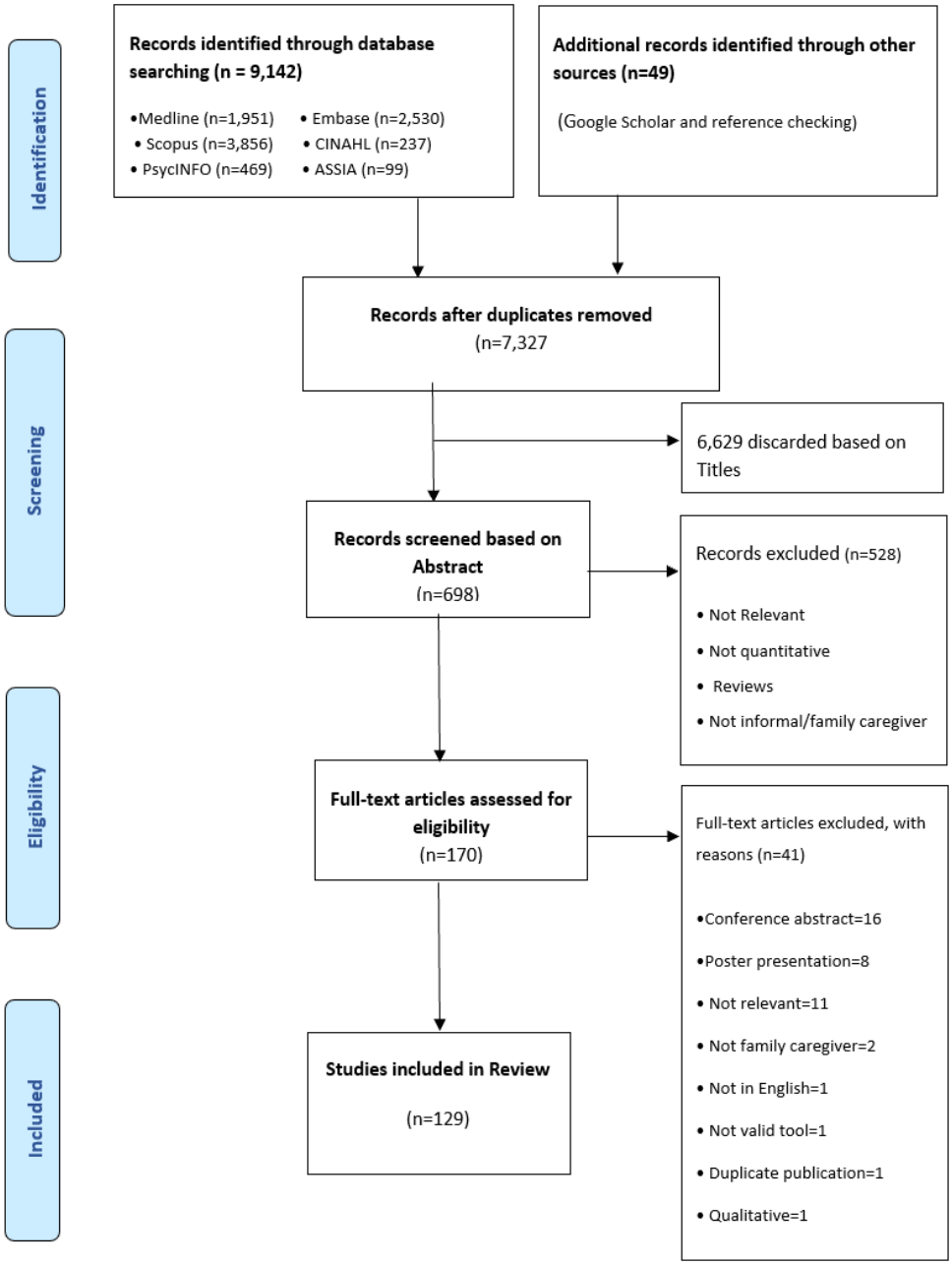
There are several different quality assessment tools available for the assessment of observational studies. These include the Critical Appraisal Skills Programme (CASP), STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), Specialist Unit for Review Evidence (SURE) Checklist and the Joana Briggs Institute Critical Appraisal tool. The CASP checklist is useful for critical appraisal of research papers, including randomised controlled trials, cohort studies and case-control studies, but does not guide evaluating cross-sectional studies (CASP 2019). The STROBE, on the other hand, is not appropriately used for assessing the quality of observational studies (Costa et al. 2011; Bastuji-Garin et al. 2013), though it was created for the reporting of observational studies to improve transparency in their reporting (von Elm et al. 2007). The SURE checklist (SURE 2018a; 2018b), although appropriate for evaluating the quality of cross-sectional studies and cohort studies, is not validated. This review used the Joanna Briggs Institute Critical Appraisal tool for evaluating the quality of cross-sectional and cohort studies, as it is validated and peer-reviewed (Moola 2017).

1.2.2 Results

1.2.2.1 A specific impact of chronic diseases on family quality of life

1.2.2.1.1 SCREENING OF THE STUDIES AND STUDY CHARACTERISTICS

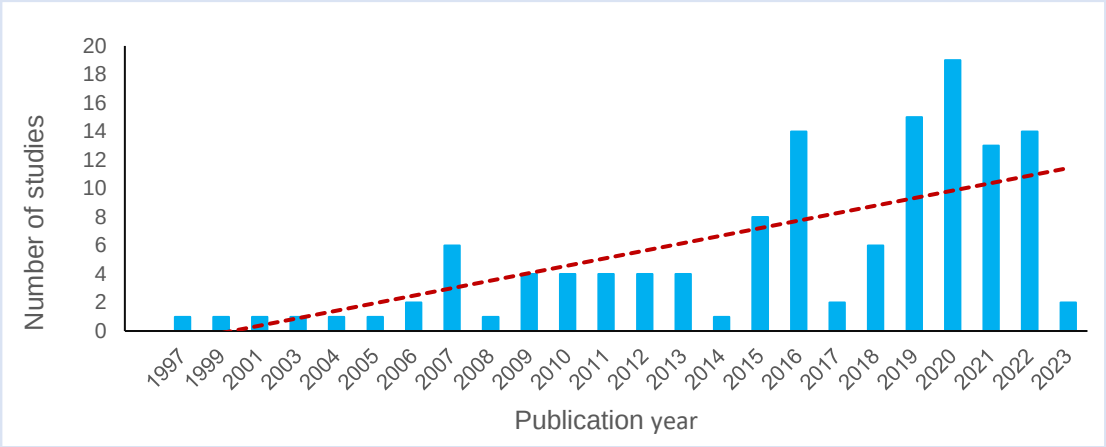
Figure 1.2 PRISMA flow diagram of study selection



Screening of studies following PRISMA guidelines was conducted solely by RS (researcher). A total of 9,191 articles were identified. After removing duplicates and irrelevant titles, 698 abstracts were screened, of which 170 underwent full-text review. Another 41 were excluded as they did not meet inclusion criteria, with 16 being conference abstracts, 11 not being relevant to this review objective, eight being poster presentations, two with caregivers not a family member (paid carer), one not in English, one a qualitative study, one being duplicate publication and one not having used a valid instrument.

A total of 129 papers met the inclusion/exclusion criteria (Figure 1.2). There were two studies published before 2000 and 127 studies published between 2000 and May 2023, indicating that interest in FQoL has grown in recent years (Figure 1.3). The 129 studies included data on 32,126 family members across 19 specialities from 39 countries (Table 1.7), the country with the greatest number of studies (17) was from the USA, followed by Turkey with ten studies (Table 17).

Figure 1.3 Growing trend in FQoL research activities in recent years



Eight studies were multi-national with data on a total of 9,363 caregivers (Chernyshov et al. 2015; Baji et al. 2019; Khair et al. 2019; Macchi et al. 2019; Mowforth et al. 2019; Suthoff et al. 2019; Balkaran et al. 2021; Klomberg et al. 2022) (Table 1.8). One hundred and twenty-two studies were cross-sectional, reporting a total of 30,648 family members, and seven studies were longitudinal prospective cohort studies involving 1,478 family members, with follow-up ranging from one month to three years (Forbes et al. 2007; McCusker et al. 200; Grant et al. 2012; Chen et al. 2020; Suthoff et al. 2019; Rensen et al. 2022; Klomberg et al. 2022).

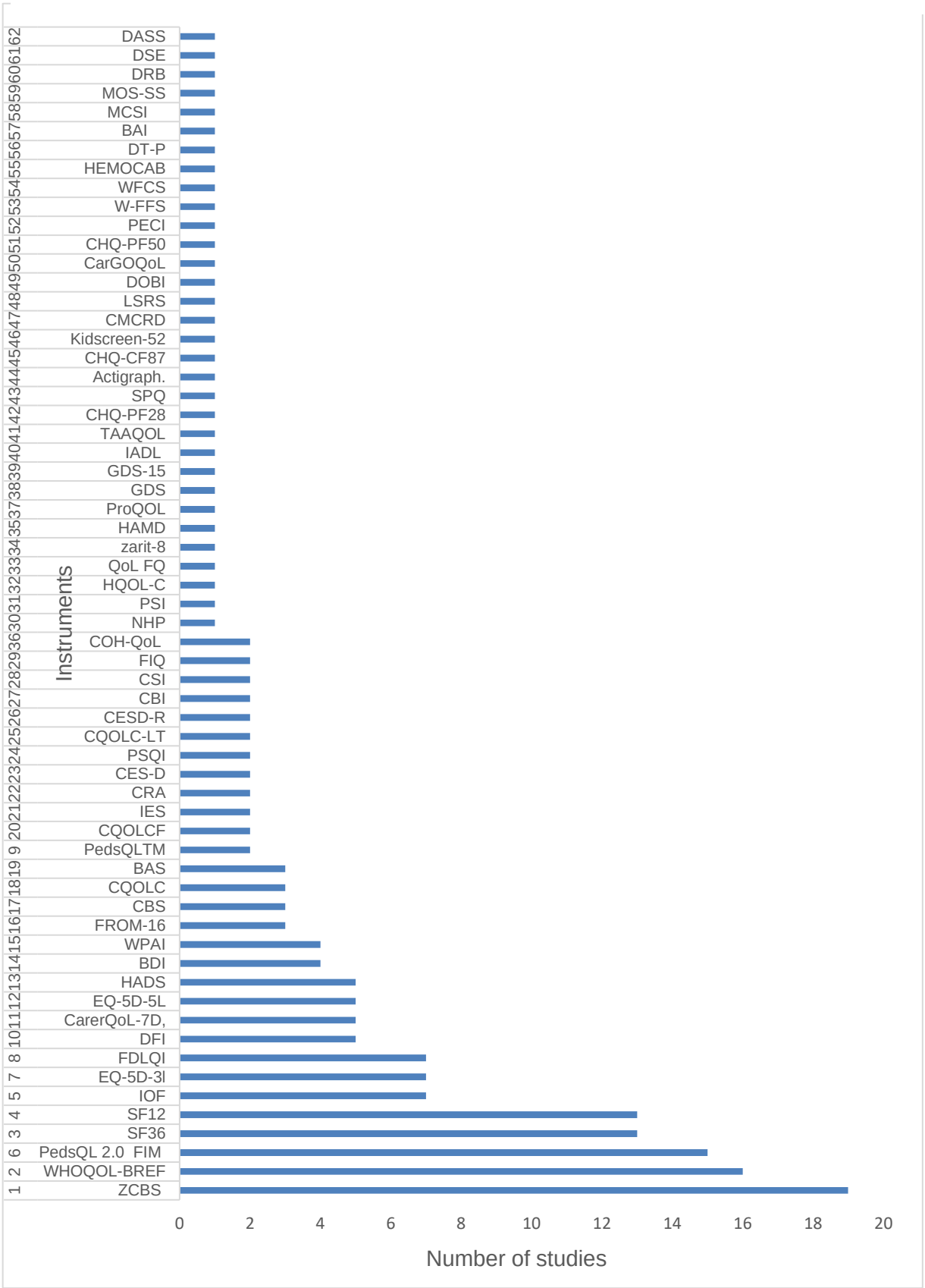
Table 1.7 Number of studies per country included in the review

	Countries	Number of studies
1	USA	17
2	Turkey	10
3	China	7
4	Canada	7
5	Netherlands	7
6	UK	7
7	Australia	6
8	Brazil	5
9	Iran	4
10	Italy	4
11	Spain	4
12	Germany	4
13	Japan	3
14	Malaysia	3
15	Singapore	3
16	KSA	3
17	India	3
18	Poland	2
19	Egypt	2
20	Korean	2
21	Portugal	2
22	Argentina	1
23	Belgium	1
24	Croatia	1
25	Czech-Rep	1
26	Greece	1
27	Israel	1
28	Jordan	1
29	Kenya	1
30	Kuwait	1
31	South Africa	1
32	Sudan	1
33	Sweden	1
34	Serbia (part of a multinational study)	1
35	Slovenia (part of a multicentre/multinational study)	1
36	Ireland (part of a multicentre/multinational study)	1
37	France (part of a European multinational study)	1
38	Hungary (part of a multicentre/multinational study)	1
39	Ukraine (part of a multicentre/multinational study)	1

Table 1.8 Multicentre and multinational studies included in the review

Countries	Number of studies
Hungary, Poland, Slovenia (Multicentre/multinational)	1
Germany, Ireland, UK, USA (Multinational)	1
Ukraine, Czech Republic, Singapore, and Italy (Multicentre/multinational)	1
Germany, Italy, Netherlands, Poland, Sweden, Turkey, UK (Multinational)	1
UK/USA (Multicentre/multinational)	1
USA/Canada (Multicentre/multinational)	1
France, Germany, Italy, Spain, and UK (European multi-national)	1
France, Israel, UK, Netherlands, Itlay, Japan, Serbia, Malaysia (Multi-national)	1

Figure 1.4 Instruments used in the reviewed studies to measure family impact of disease



ZCBS: Zarit Caregiver Burden Scale**; WHOQOL:** World Health Organization Quality of Life; **SF36**: 36-Item Short Form Survey; **SF12**:12-Item Short Form Survey; **IOF**: Impact on Family Scale**; PedsQL 2.0 FIM:** PedsQL TM 2.0 Family Impact Module; **EQ-5D-3L**: Euroqol- 5 Dimension-3 level; **FDLQI:** Family Dermatology Life Quality Index**; DFI**: Dermatitis Family Impact Questionnaire; **CarerQoL-7D**: Care-related Quality of Life instrument-7 Dimension; **EQ-5D-5L**: Euroqol- 5 Dimension-5 Level**; HADS**: Hospital Anxiety and Depression Scale; **BDI:** Beck Depression Inventory; **WPAI-SHP:** Work Productivity and Activity Impairment-Specific Health Problem V2.0; **FROM-16**: Family Reported Outcome Measure; **CBS:** Caregiver Burden Scale; **CQOLC:** Caregiver Quality of Life Index-Cancer**; BAS:** Burden Assessment Scale**; CQOLCF:** Caregiver Quality of Life Cystic Fibrosis**; IES:** Impact of Event Scale; **CRA**: Caregivers Reaction Assessment Scale; **CES-D:** Centre for Epidemiologic Studies Depression Scale; **PSQI:** Pittsburgh Sleep Quality Index**; CQOLC-LT:** Caregiver Quality of Life index-Liver Transplantation**; CESD-R:** Centre for Epidemiologic Studies Depression Scale (revised); **COH-QOL:** City of Hope Quality of Life Questionnaire**: NHP:** Nottingham Health profile questionnaire; **FIQ**: Family Impact Questionnaire; **PSI:** Parenting Stress Index Questionnaire; **HDQoL-C:** Huntington's Disease Quality of Life Battery for Carers; **QoLFQ:** QoL Family Questionnaire; **Zarit -8:** Zarit burden interview-8 item**; HAMD**: Hamilton Depression Scale; **CGSQ:** the Caregiver Strain Questionnaire. **ProQOL**: Professional Quality of Life; **GDS:** Geriatric Depression Scale; **GDS-15**: Geriatric Depression Scale-15; **IADL subscale:** Instrumental Activities of Daily Living; **TAAQOL:** TNO-AZL Questionnaire for Adult Health-Related Quality of life; **CHQ-CF28:** Child Health Questionnaire-Child Form-28; **SPQ:** Sibling Perception Questionnaire; **CHQ-CF87**: Child Health Questionnaire-Child Form 87; **KIDSCREEN-52**: KIDSCREEN-52 questionnaire; **CMCRD:** Caring for My Child with a Juvenile Rheumatic Disease; **LSRS:** Lifespan Sibling Relationship Scale; **DOBI:** Dutch Objective Burden Inventory; **CarGOQoL:** CareGiver Oncology Quality of Life Questionnaire; **PedsQLTM**: Pediatric Quality of Life Inventory TM; **CHQ-PF50:** Child Health Questionnaire-Parent Form 50; **PECI:** Parent Experience of Child Illness; **W-FFS:** Work-Family Facilitation Scale; **WFCS:** Work-Family Conflict Scale; **HEMOCAB:** Haemophilia Associated Caregiver Burden Scale**; DT-P**: Distress Thermometer for Parents; **BAI:** Becks Anxiety Inventory; **MCSI:** Modified version of Caregiver Strain Index; **CIRS-G:** Cumulative Illness Rating Scale for Geriatrics**; MOS-SS:** Medical Outcomes Study-Sleep Scale; **DRB:** Diabetes-Related Burden**; DSE:** Diabetes Self-Efficacy; **DASS:** Depression Anxiety Stress Scales**.**

Although most of the articles reviewed reported the impact of a single chronic disease on family members, fifteen papers included more than one chronic disease, to allow comparison of the impact of different chronic diseases on family members and to give a wider understanding of the impact (Gupta 2007; Shu 2009; Arora et al. 2015; Serin et al. 2016; Xie et al. 2016; Guo et al. 2018; Dinleyici et al. 2019; Luckett et al. 2019; Baji et al. 2019; Ngangana et al. 2016; Balkaran et al. 2021; Velasco et al. 2020; Morawska et al. 2022; Aljuaid et al. 2022; Ibáñez-Davó et al. 2022). The included studies used 62 different tools to measure impact of a relative's disease on a family member, with many studies having used more than one tool. The most widely used tool to measure the impact of a patient's disease on a family member was the Zarit Caregiver Burden Scale (19 studies), followed by WHOQOL (16), PedsQL 2.0 FIM (15), SF-36 (13), and SF-12 (13) (Figure 1.4).

The family members who provided care to relatives were mostly females and the most widely mentioned relationships to the patient were 'parents' and 'mothers' (Figure 1.5). In 33 articles, the descriptors 'informal caregiver' or 'caregiver' were used to describe the family members caring for their relative (Figure 1.5). Although the impact of a patient's disease on family members was explored across various areas of medicine, the most widely studied areas were neurology, followed by oncology, dermatology, endocrinology and genetic disease (Figure 1.6).

Figure 1.5 Family members' relationship to patients in the reviewed studies: 33 studies did not specify the relationship.

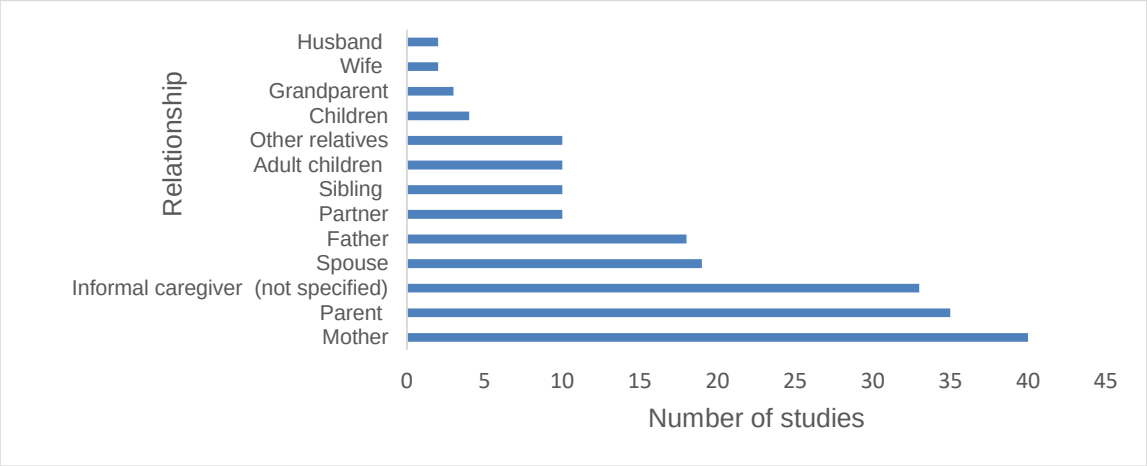
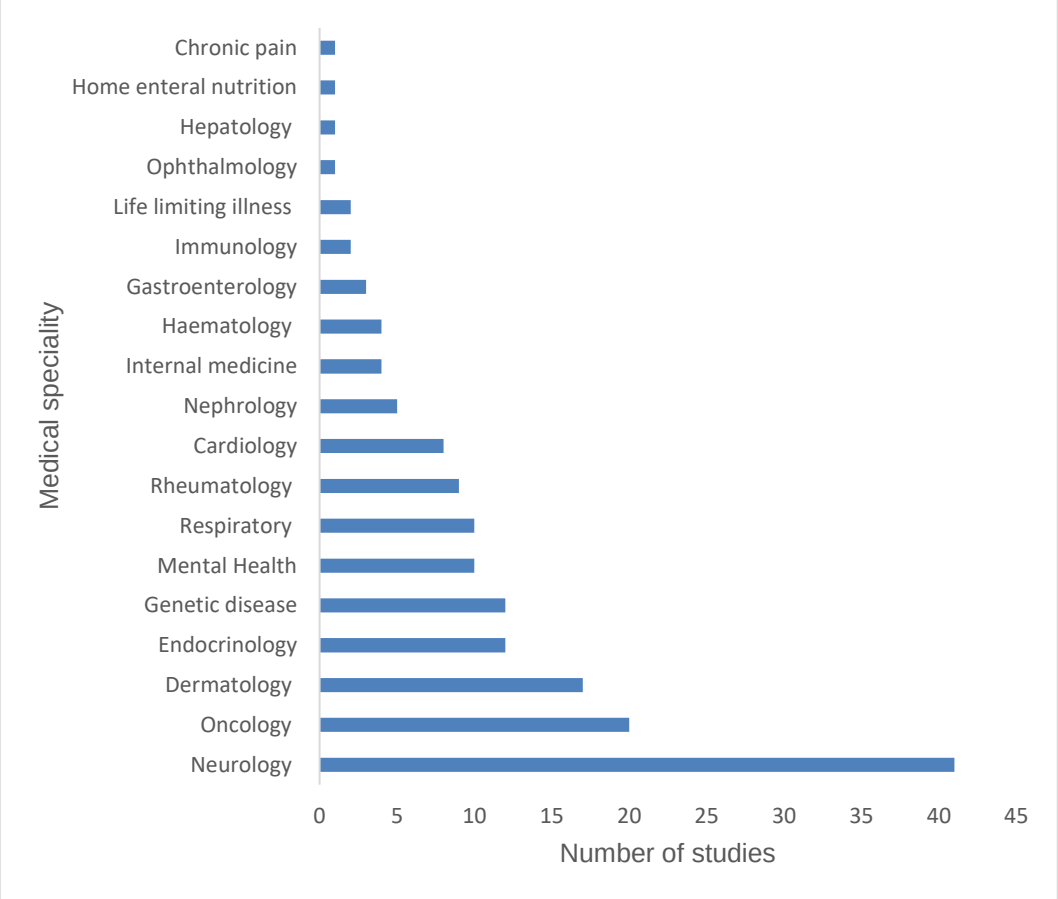


Figure 1.6 Disease specialties addressed by the reviewed studies.



1.2.2.1.2 QUALITY ASSESSMENT AND RISK OF BIAS

Twenty cross-sectional studies and three cohort study did not mention confounders or strategies to address them, while one cohort study did not mention reasons for loss of follow-ups. However, the remaining requirements were met for all of these studies, which all fulfilled the minimum criteria for quality. None of the 129 studies was rejected based on their quality or risk of bias. Overall, all studies were moderate to high quality.

1.2.2.1.3 SYNTHESIS OF FINDINGS - KEY IMPACT AREAS

This review revealed a huge impact of patients' illness on family members' QoL (Arora et al. 2015; Jirakova et al. 2012; Karg et al. 2018; Lazow et al. 2019; Mazzone et al. 2013; Pustišek et al.2016; Tadros et al. 2011; Wei et al. 2018; Macchi et al. 2019; Wu et al. 2020). In general, relatives' chronic diseases impacted family members in similar ways, with some conditions such as cancer having a bigger impact than others. The key themes identified were emotional and psychological impact; impact on other life activities including physical health; social life; leisure and daily activities; family relationships; finance; work; and positive aspects of caregiving.

1.2.2.1.3.1 Emotional and Psychological impact

The most common topic discussed in the articles reviewed was the emotional and psychological impact of having a family member with a health condition. Family members living with and caring for their relative with a chronic disease suffer from huge emotional and psychological distress with reduced QoL (Grant et al. 2012; Sharghi et al. 2006; Manee et al. 2016; Meriggi et al. 2015; Pustišek et al. 2016; Van Nimwegen et al. 2016; Ito and Tadaka 2017; Gamwell et al. 2016; Lazow et al. 2019; Macchi et al. 2019; Żychowska et al. 2020; An et al. 2021; Brittain et al. 2021; Di Cara et al. 2020; Costa et al. 2020; Pereira et al. 2020; Uhm and Kim 2020; Shah et al. 2021b; Shaw et al. 2022; Piscitello et al. 2022; Pequeno et al. 2022; Vyas et al. 2022; Tawfik et al. 2023). The aspects of psychological distress that most affected family member's QoL included worry (O'Mahony et al. 2019; Splinter et al. 2016; AlBuhairan et al. 2016; Van Nimwegen et al. 2016; Uhm and Kim 2020; Shah et al. 2021b; Brittain et al. 2021; Vyas et al. 2022; Johnson et al. 2021), feelings and emotions (Morimoto et al. 2003; Shu 2009; Żychowska et al. 2020; Roeper et al. 2022; Buoro and Nogueira 2020; Shaw et

al. 2022; Sabo et al. 2020), stress and anxiety (Serin et al. 2016; Ten Hoopen et al. 2020; Celepkolu et al. 2021), distress at the initial diagnosis (Rensen et al. 2022), grief about their relative's illness, worry about treatment side effects (Germone et al. 2022) and uncertainty about the patient's future (Lu et al. 2010; Roy et al. 2016; O'Mahony et al. 2019; Johnson et al. 2021).

1.2.2.1.3.1.1 Parenting stress

Mothers of children with chronic disease experienced high rates of stress and anxiety (Pustišek et al. 2016; Serin et al. 2016; Ten Hoopen et al. 2020) and this parenting stress was found to be correlated to the type of disability, the age of the patient, the severity of the condition and the child's gender (Sikorová and Bužgová 2016; Uhm and Kim 202; Tawfik et al. 2023; Elgamal et al. 2023). The parents of children and adolescents with disruptive behaviours such as Attention Deficit and Hyperactivity Disorder (ADHD) and developmental disabilities (DD) reported higher total stress and impaired QoL (Patel et al. 2022; Piscitello et al. 2022), than parents of children with HIV and asthma (Gupta 2007). The parents of preschool children with atopic dermatitis (AD) were more stressed, tired and exhausted than the parents of older children with AD (Chernyshov et al. 2015; Van Nimwegen et al. 2016; Tawfik et al. 2023), however, caregiver's HRQoL improved with the duration of disease (Unavane et al. 2022; Klomberg et al. 2022). Moreover, parents were impacted more when caring for girls rather than boys (Żychowska et al. 2020; Morawska et al. 2022) and if the affected areas were visible (Andrade et al. 2020) reflecting a cultural emphasis on appearance that disproportionately affects women and girls compared to men and boys. The parents of children with haemophilia experienced a high level of emotional stress when children suffered chronic pain and joint bleeds (Khair et al. 2019), indicating that disease severity had negatively impacted the psychological wellbeing and QoL of the family member (Khair and von Mackensen 2016; Lazow et al. 2019; Elgamal et al. 2023). The impact of a child's disease has been shown to affect cognitive functions in parents, who find it hard to keep their attention on a task (Kuerten et al. 2020; Johnson et al. 2021).

The increased demands caused by caring for a child due to the increased severity of a child's disease were perceived by some parents as interfering with their ability to

engage in activities such as social relationships, financial status, and work. This led to higher levels of parental stress that translated into elevated levels of psychological distress (Gamwell et al. 2016), affecting the perception of burden experienced by the mother (Calderón et al. 2011). However, this emotional distress did not result in mothers being less caring of the sick child (Ho et al. 2010).

1.2.2.1.3.1.2 Gender differences in the impact

There were some gender differences as to how caregiving impacts family members psychologically. Female caregivers experienced significantly higher rates of depression and anxiety than male caregivers, with wives being worst impacted (McCusker et al. 2007; Carod-Artal et al. 2009; Tulek et al. 2020; Koçak et al. 2022). Mothers of children with chronic disease suffered high levels of anxiety and depression (Pustišek et al. 2016; Serin et al. 2016; Ten Hoopen et al. 2020), and the impact was greater when patients suffered from severe diseases such as long-term mental health conditions (Johansson et al. 2015). This is in sharp contrast to the findings of Bonner et al. (2007), that fathers of children with cancer have higher rates of depressive symptoms than mothers, with unmarried fathers suffering more depression. Consistent with this study are the findings of Kunz et al. (2011) who reported that fathers have lower family HRQoL. Such paternal outcomes could be explained based on increased stressors arising from disease flares, such as additional medical visits and medical bills, both of which could be particularly distressing for fathers (Kunz et al. 2011). The reverse gender difference was found in the siblings of patients, with female siblings experiencing a lower QoL than male siblings (Havermans et al. 2015).

1.2.2.1.3.1.3 Nature of relationship and psychological impact

This current review has identified that the nature of the relationship has an influence on the extent of impairment of QoL of the family member. Mothers who were primary caregivers for children with chronic disease suffered most, having to undertake additional complex caring responsibilities in addition to their routine domestic work (Blanes et al. 2007). The patient's spouse, who would usually have the most intimate relationship with the patient, experienced more distress and strain than any other family member (Lu et al. 2010; Costa et al. 2020; Tulek et al. 2020; Koçak et al. 2022;

Celepkolu et al. 2021) and suffered from depression as often as the patient (Walsh et al. 1999).

It is not just the parents of a child with a disease or the partner who are impacted emotionally by their family member having a disease, but the impact is experienced by other family members such as children and siblings. Children with mothers suffering from a chronic condition experienced more symptoms of hyperactivity and inattention, especially when the mothers had psychological problems (Guo et al. 2018). The siblings of paediatric patients with chronic rheumatic diseases, kidney transplant and liver transplant experienced a worse HRQoL in relation to their perception of physical and financial well-being compared to the siblings of healthy children. These siblings considered that they did not have enough financial resources available to have a lifestyle that would give them the chance to do activities together with their peers (Velasco et al. 2020). Siblings of children with a more severe chronic condition such as coronary heart disease (CHD) or cancer reported more internalising of problems and behavioural difficulties than siblings of children with cystic fibrosis (CF) or with diabetes, with the impact being higher near the time of diagnosis (Havermans et al. 2015). The well siblings of children with life-limiting conditions experienced poorer emotional, social, and school functioning relative to published community-based norms, indicating that siblings of children with more severe conditions had significantly poorer psychosocial functioning (Jaaniste et al. 2022). This is in contrast to the finding of Yilmaz et al. (2017) that the poor emotional health of siblings of children with asthma was not related to disease severity, indicating that siblings of children with controlled asthma might also experience lower emotional wellbeing. This implies that siblings of children with chronic disease seem to be less anxious when the chronic condition follows a daily routine treatment pattern, compared to when the condition takes an uncertain and unpredictable course, leading to feelings of helplessness. However, it is of great concern when parents are unaware of the impact of their child's disease on their other children. In the study conducted by Dinleyici et al. (2019), the global impact on the QoL of healthy siblings of children with a chronic disease was significantly higher when self-reported by the children than when reported on their behalf by the parents (30.4% versus 15.1%, $p<0.05$). This suggests that siblings may be impacted psychologically and physically to a greater extent than their parents, with parents

possibly having a poor understanding of the extent of the impact on their 'healthy' children (Jaaniste et al. 2022).

1.2.2.1.3.1.4 Psychological impact of different medical conditions

Some medical conditions can put family members caring for their relative at more risk than other conditions. The caregivers of medically ill elderly patients with depression were at risk of themselves developing a mental health condition. This risk was higher for an adult child or spousal caregiver compared to other caregivers (Sewitch et al. 2004; Arora et al. 2015). The caregivers of patients with a chronic neurological condition with only minimal disability suffer from similar psychological distress, depression, anxiety, and impaired life satisfaction levels as the patient (Walsh et al. 1999; Yildirim et al. 2009; Rioux et al. 2012).

The family member's affective status (presence of anxiety and/or depression) was the most consistent factor influencing caregiver burden and perceived health (Carod-Artal et al. 2009; Khair and von Mackensen 2016; Piscitello et al. 2022; Uzuner et al. 2021). In comparison with caregivers of patients without a current diagnosis of depression, caregivers of those with major depression had a lower mental health score at follow-up (ZamZam et al. 2011; McCusker et al. 2007). However, the lower HRQoL in caregivers of dementia patients was found to be related to the different experiences that dementia caregivers have with caregiving rather than to caregivers' characteristics or mental health (Karg et al. 2018).

1.2.2.1.3.2 Impact on Physical Health

Caring for a family member with a chronic disease can have an impact on the caregiver's physical health. The physical health of a caregiver is negatively impacted by the physical burden that results from several factors, including the care recipient's functional disabilities, cognitive impairment (Khair and von Mackensen 2016; Manee et al. 2016; Lazow et al. 2019; Farajzadeh et al. 2020), behavioural problems (Ten Hoopen et al. 2020; Uzuner et al. 2021), medication management (Luckett et al. 2019), medical visits and hospitalizations (Uzuner et al. 2021), duration of care and the objective burden of the disease (Forbes et al. 2007; Duimering et al. 2020).

1.2.2.1.3.2.1 Objective burden of disease

It is reported that a high objective burden of a patient's disease is associated with poor physical health and low QoL of the caregivers (Ibáñez-Davó et al. 2022). However, caregivers of people with some chronic diseases such as glaucoma (Duimering et al. 2020) or familial Mediterranean fever reported only a moderate burden without any significant impact on QoL (Kosan et al. 2019; McDonald et al. 2020), indicating that caregiver burden is related to the severity of the patient's disease and the caregiver's perception of burden (Sikorová and Bužgová 2016). The partners of patients with heart failure perceive caregiving tasks, such as assisting with washing and bathing and moving in and around the house, as a burden (Luttik et al. 2007). This implies that greater disease severity leads to higher carer activity and greater caregiver burden leading sometimes to a deterioration in the physical health of caregivers (Forbes et al. 2007; Duimering et al. 2020; Farajzadeh et al. 2020; Boluktas 2021). The caregivers of paraplegia patients experienced lower SF-36 scores for pain and vitality, due to the high physical strain involved in caring for these patients. For example, a caregiver may spend over 11 hours per day caring for a person with spinal cord injury, in addition to carrying out housekeeping tasks and at the same time looking after other dependent family members (Blanes et al. 2007). A similar objective burden, in terms of daily total hours spent on assisting patients with basic activities of daily living and medical tasks was associated with huge physical strain impacting caregivers' health (Karg et al. 2018; Baji et al. 2019; Duimering et al. 2020; Boluktas 2021). However, impact on the health of Japanese stroke caregivers was not related to the objective burden that caregivers experienced but to their psychological dependency (Morimoto et al. 2003). Family members caring for their relative can feel overwhelmed and physically exhausted (Arafa et al. 2008; Lu et al. 2010), which may result in compassion fatigue. The study conducted by Lynch et al. (2018) indicated that it was not the total number of years of caregiving that contributed to differences in compassion fatigue, but the number of hours per week. This suggests that intensity of caring rather than duration is the key factor that influences the caregivers' health (Lynch et al. 2018).

The objective burden on the caregiver was higher if the caregiver was older and if the patient was incapable of self-care and was suffering from another chronic disease (Jafari et al. 2018). Younger family members without chronic disease, caring for elderly

people with chronic diseases maintained high levels of physical function and reported body pain less frequently (Xie et al. 2016). This indicates that impact of caregiving on physical health is related to the caregiver's age, with younger caregivers reporting better QoL (Aljuaid et al. 2022). Furthermore, caregiver burden was found to be associated with the educational levels of the caregiver: higher levels of education meant lower caregiver burden and better QoL (Sabo et al. 2020; Tulek et al. 2020; Ying et al. 2021; Aljuaid et al. 2022; Koçak et al. 2022). This could be explained by caregiver education changing parental beliefs and attitudes, and perceptions of stigma surrounding certain illnesses, thus enabling caregivers to be more innovative in managing patient illnesses, facilitating access to educational materials and support groups via social media networks, and improving caregiver–physician relationships.

1.2.2.1.3.2.2 Sleep

Sleep plays an important role in maintaining physical health and ongoing sleep deficiency can lead to poor physical health and lower QoL of caregivers. This review identified many articles describing that caregivers' physical health was impacted by poor quality of sleep (Su et al. 1997; Al Robaee and Shahzad 2010, Meltzer et al. 2015; Ridolo et al. 2015; Pustišek et al. 2016; Nozoe et al. 2016; Chen et al. 2020; McMillan et al. 2021; Rensen et al. 2022). Meltzer et al. (2015) found that parents of ventilator-assisted children experienced shorter sleep duration and greater fluctuations in sleep quality and wake times compared to parents of healthy children. The poor sleep quality resulted in higher instability in wake times with worse SF-36 scores on Physical Functioning ($p = 0.05$), Bodily Pain ($p = 0.02$), and General Health ($p = 0.01$) (Meltzer et al. 2015). In the mothers of children with Duchenne muscular dystrophy, impaired quality of sleep was related to the duration of the disease (Nozoe et al. 2016), while the sleep disturbance in the parents of children with allergies (allergic rhinitis, asthma or atopic dermatitis) and cerebral palsy were related to the sleep disruption in these children (Ridolo et al. 2015; Ying et al. 2021). The partners of patients with cancer experienced poor quality of sleep and there was a significant correlation between patients' and their partners' sleep quality and sleep latency (Chen et al. 2020). Although caregivers used medication to minimise the negative impact of sleep problems, Chen et al. (2020) argue that this could have affected their ability to respond

to the needs of the patient, indicating that many caregivers may be hesitant to use drugs to aid sleep.

1.2.2.1.3.3 Impact on Social, Leisure and Daily activities

Family members caring for a relative with a chronic condition experience a considerable impact on their social, leisure and daily activities. Many caregivers reported an impact of caregiving on their daily activities (Luttik et al. 2007; Ho et al. 2010; Haverman et al. 2014; Splinter et al. 2016; Klomberg et al. 2022; Boluktas 2021; Sabo et al. 2020) with women reporting greater disruption than men (Meriggi et al. 2015; Klomberg et al. 2022; Kuerten et al. 2020; Di Cara et al. 2020). Seventy-nine percent of the caregivers of people with degenerative cervical myelopathy (Mowforth et al. 2019) and 51% of the caregivers of children with autism spectrum disorder (Ten Hoopen et al. 2020) reported difficulties in combining caring tasks with their daily activities (Jafari et al. 2018; O'Mahony et al. 2019).

Parents of children with chronic disease explained that caring for their children reduced their time and opportunity for recreation and social activities, thereby negatively impacting their QoL (Arafa et al. 2008; Ho et al. 2010; Grant et al. 2012; Jafari et al. 2018; Tan et al. 2020; Kuerten et al. 2020; Wu et al. 2020). Caregivers reported having no time for leisure as most of them were also working or studying (Baji et al. 2019), with competing demands to fulfil their work, family, and caring obligations (Xie et al. 2016). The mothers of adolescents with chronic pain reported experiencing restriction of their social lives to a greater extent than mothers of adolescents with less severe chronic pain, and the impact was felt equally by the whole family (Hunfeld et al. 2002). This indicated that if a patient's symptoms were severe, this resulted in interference with the caregiver's involvement in social and leisure activities. The high demands of caregiving for children with developmental disabilities, especially if outwardly visible, contributed to the social isolation of the parents because of stigma and social embarrassment (Gupta 2007). Some parents of children receiving palliative care felt they had little desire to go out, indicating that the severity of their child's disease led to a loss of interest in engaging in social and leisure activities. In some cases where parents did make an effort to engage in such activities, parents had to make last-minute changes in their plans because of the child's illness (Knapp et al. 2010). The parents of children with

obsessional compulsive disorder experienced interruptions in social life, such as postponing social activities, and found themselves in arguments with other individuals when trying to fulfil the patient's needs (Suculluoglu Dikici et al. 2018).

There seems to be a cultural aspect to the impact of caregiving on social life. Japanese caregivers reported high social scores on the Zarit burden scale (Morimoto et al. 2003), even when their perception of general health was lower than that of the care recipient. This indicates that unlike Western caregivers, Japanese caregivers do not report their feelings about their social life being impacted by caregiving (Morimoto et al. 2003). Arab mothers of children with disabilities experienced reduced social interactions and lower QoL. This was said to be due to the cultural beliefs of Arab families and the stigma attached to having a child with a disability, with most mothers relying on family support, indicating a reluctance to access external support (Manee et al. 2016).

1.2.2.1.3.4 Impact on Family Relationships

Caring for a family member suffering from illness not only impacts the caregiver but also the whole family (Hunfeld et al. 2002; Tadros et al. 2011; Ammann-Schnell et al. 2021; Rensen et al. 2022; Unavane et al. 2022; Sabo et al. 2020), with caregivers having less time for other family members (Knapp et al. 2010; McDonald et al. 2020). A relative's chronic condition has an impact on the relationships between the caregiver and the patient and between the other members of the family (Fleck et al. 2015, Mowforth et al. 2019; Ten Hoopen et al. 2020). The caregivers within those families with better family functioning had a better QoL (Son et al. 2012; Sikorová and Bužgová 2016; O'Mahony et al. 2019; Ying et al. 2021; Aljuaid et al. 2022) with increased family functioning, leading to better QoL in patients (Sikorová and Bužgová 2016). Ab. Ghani et al. (2012) reported a significant positive relationship between disease severity and impact of the disease on a family. The mothers caring for children with ADHD and oppositional developmental disorder (ODD) experienced negative feelings towards their child and this impact was higher for single mothers with ADHD. These mothers believed that their child's ODD was the reason for increased conflicts between them and their partners (Fleck et al. 2015). Having more children was seen as being protective against partner conflict and maternal hostility, as siblings could assist the mother by caring for the sick child, thereby reducing parental stress and negative

feelings towards the child (Ibid). However, in some cases siblings may internalise their emotional reactions to the situation, leading to behavioural problems (Havermans et al. 2015; Ammann-Schnell et al. 2021). Adult siblings caring for their parents experienced a negative impact on their sibling relationship, with the caregiver burden being inversely related to the quality of the adult sibling relationship (Ngangana et al. 2016). This could be explained on the basis of family dynamics where some siblings may not share caring responsibilities or provide any financial assistance to support their ill parent, leading to negative feelings among siblings.

Partners of patients experienced a poor sexual life and relationship quality because of the patient's symptoms (Roy et al. 2016; Jafari et al. 2018), with a significant decrease in the partner's ability to spend quality time with the patient (Suthoff et al. 2019) leading to marital conflicts (Jafari et al. 2018). Some patients, because of their illness, tend to be negative towards their partners and often vent their frustration on their partners (Walsh et al. 1999). For many, the caregiving role, as well as their partner's illness, restricted them from having more children. Knapp et al. (2010) reported that 48 per cent of parents of children with life-limiting illnesses choose not to have more children because of their child's illness and associated caring responsibilities.

1.2.2.1.3.5 Financial Impact

Family members caring for a patient with a chronic disease often suffer from a large financial burden (Su et al. 1997; Chernyshov et al. 2015; Ab. Ghani et al. 2012, Meriggi et al. 2015; Pustišek et al. 2016; Khair and von Mackensen 2016; Jafari et al. 2018; Farzi et al. 2019; Wlodarek et al. 2020; Pereira et al. 2020; Buoro and Nogueira 2020; Al Qadire et al. 2020; Velasco et al. 2020; Kuerten et al. 2020). The family members of patients suffering from a variety of chronic skin conditions experienced increased expenditure (Chernyshov et al. 2015; Ab. Ghani et al. 2012; Pustišek et al. 2016; Farzi et al. 2019; Wlodarek et al. 2020; Żychowska et al. 2020). In the Australian study, the annual personal cost for mild, moderate, and severe atopic dermatitis was calculated at Aus$ 330, 818, and 1255 respectively, with most expenses resulting from costs of medication, dressings, and non-irritant clothing (Su et al. 1997). In the study conducted by Khair and von Mackensen (2016), 55% of parents of children with haemophilia reported economic hardship due to their child's illness. In a study of

caregivers of cancer patients, 83% of the caregivers reported that they were concerned about financial difficulties (Meriggi et al. 2015; Al Qadire et al. 2020) and 50% of the caregivers of people with degenerative cervical myelopathy experienced some financial problems (Mowforth et al. 2019). A Swedish longitudinal study revealed that 20% of parents of children who survived a childhood CNS tumour reported financial difficulties even when the children reached adulthood and after the cost of the chronic disease treatment was covered by the welfare system (Hoven et al. 2013). The caregivers reduced their working hours or quit their jobs to take up their caring responsibilities (Kuerten et al. 2020). This and the expense of hospital visits were important contributing factors to their financial difficulties (Su et al. 1997; Aung et al. 2009; Hoven et al. 2013). The family caregivers of children with autism spectrum and eating disorder belonging to low-income families reported significantly higher burden and impairment of QoL compared to caregivers from high-income families (An et al. 2021; Patel et al. 2022). This may be explained by the increased strain resulting from the costs of management of these conditions.

1.2.2.1.3.6 Impact on Work

Many studies have reported on the impact of caregiving on the caregiver's work, with higher disease burden leading to greater work impairment of the carer (Chua et al. 2016; Mowforth et al. 2019; Balkaran et al. 2021; Klomberg et al. 2022; Igarashi et al. 2020). Parents had to give up their jobs or reduce their hours at work to look after an ill family member and to manage hospital visits (Su et al.1997; Shalitin et al. 2018; Khair and von Mackensen 2016). In the study of the impact of having a child with haemophilia, 50% of parents had to change to part-time work to allow time to care for their child (Khair and von Mackensen 2016). Caregivers, mostly mothers, reported sacrificing their professional career to stay at home (Ammann-Schnell et al. 2021), changing jobs or altering their career choice to look after their sick child, with one-third of caregivers reporting a fear of consequently losing their job (Suthoff et al. 2019).

Work was seen to have a positive impact on the QoL of mothers, as it gave them temporary relief from their caring role, time to socialise with others and a lower financial burden (Suculluoglu Dikici et al. 2019; Farajzadeh et al. 2020). The mothers who took reduced hours of work or who did not work suffered lower QoL, as they spent more

time with the patients and thereby had greater exposure to the patients' symptoms (Suculluoglu Dikici et al. 2019; Kuerten et al. 2020; Roeper et al. 2022; Igarashi et al. 2020).

1.2.2.1.3.7 Positive aspect of caregiving

Despite the physical, social and psychological impact that having a relative with a disease has on family members, many caregivers have reported a positive experience of caregiving (Awadalla et al. 2006; AlBuhairan et al. 2016; Aljuaid et al. 2022; Clarijs et al. 2022; Buoro and Nogueira 2020) with older caregivers reporting more satisfaction than younger ones (Lynch et al. 2018). In the study by Meriggi et al. (2015), 93.5% of caregivers reported that they were happy with their role. Son et al. (2012) attribute an attitude of positivity in caregivers of cancer patients due to the spiritual upliftment that they experienced, which gave them a reason and purpose for living. Awadalla et al. (2006) attribute this positive impact to the associated family cohesion (Aljuaid et al. 2022), with two-thirds of caregivers finding that their patients' lives were meaningful, indicating that an attitude of hopefulness is a positive influence on coping in these families (Awadalla et al. 2006). The adult siblings caring for their parents reported that they saw caregiving as a way of giving something back to parents who cared for them when they were young (Ngangana et al. 2016). Luckett et al. (2019) found that the health status of caregivers of chronic patients was lower than that of non-caregivers. However, the difference in scores did not reach the minimal clinically important difference for either the mental or physical domains of SF12, indicating that caregivers might be satisfied in their caring roles.

1.2.2.1.4 LACK OF REPORTING

One of the interesting findings of this review was that caregivers perceive themselves in good health even though they may be experiencing a high level of burden while providing care and functioning in other roles (Lynch et al. 2018). This could be explained by the resilience of the caregiver to withstand the pressures of caring, or it could also mean that family members caring for the patient are less concerned about their own health. Caregivers may neglect their health due to the high burden of caring. This is evident from the findings of Bruce et al. (2005) that the rate of self-reporting by

carers of mental health disorders was low compared to the high levels of Mental Component Summary (MCS) scores on the SF-12. These high scores indicated serious mental health problems, with more than 25% of caregivers having scores higher than the threshold for the diagnosis of depression (Bruce et al. 2005). These results confirm the findings of Rioux et al. (2012) where family members caring for a relative receiving haemodialysis recorded low scores on the burden scale but fulfilled the criteria for depression on the Beck Depression Inventory. Rioux et al. (2012) attribute this dichotomy to the caregiver's underestimation of their overall QoL impairment or possibly to the insensitivity of the Burden scale to detect perceived burden.

1.2.2.2 Measurement properties of current family quality of life instruments

This review has identified 52 family QoL instruments measuring the impact of a patient's disease on family members using separate search strategy (Table 1.6). Most of these instruments have been developed over the last two decades, indicating the increased recognition of the importance of family QoL. Forty-six instruments are disease or speciality specific and are therefore limited to assessing the QoL of family members of that particular group of patients. The properties of these disease-specific measures are summarised in Tables 1.9 and 1.10.

The review also identified five population-specific instruments, these include the most widely used Impact on Family (IOF), the Beach Centre Family Quality of Life (BCFQoL), the PedsQL™ Family Impact Module, the Family Quality of Life survey (FQoL Survey), CareQol and one generic instrument, the Family Reported Outcome Measure FROM-16 (Table 1.11).

1.2.2.2.1 PAEDIATRIC POPULATION-SPECIFIC FAMILY QOL MEASURES

The IOF scale measures the impact of a child's chronic disease on the family caregiver. The IOF scale has a ten-minute completion time and 27 items grouped into four domains: Financial; Social; Personal strain; and Mastery (Stein and Jessop 2003). The BCFQoL scale is another FQoL instrument that measures the impact of a child's disability on family members. The BCFQoL scale has 25 items, with a fifteen-minute

completion time, grouped into five domains: family interaction, parenting, emotional well-being, and physical/material (Poston et al. 2003; Park et al. 2003; Hoffman et al. 2006). The PedsQL™ Family Impact Module, with 36 items, measures the impact of chronic paediatric health conditions on parents and the family (Varni et al. 2004). The properties of these generic measures are summarised in Tables 1.11 and 1.12.

1.2.2.2.2 ADULT POPULATION-SPECIFIC FAMILY QOL MEASURES

The two versions of CareQoL with seven items (CareQoL-7D) or with a QoL visual analogue scale (CareQoL-VAS) were developed to measure the burden of disease in the informal caregivers of long-term care recipients, with the evaluation of well-being (Brouwer et al. 2006). The instrument was created to measure the care-related QoL of informal caregivers within economic evaluation studies (Brouwer et al. 2006). This instrument is available in eight languages, including English, and has been used in cost-utility analyses of interventions aimed at informal carers across the Netherlands (Hoefman et al. 2013), and CarerQol-7D tariffs for Australia, Germany, Sweden, UK, and US have also been calculated (Hoefman et al. 2017). However, its value for use in cost-utility analysis in the UK is limited as NICE uses QALYS based on EQ-5D-3L utility values.

The Family Quality of Life (FQOL) Survey, which has also been translated into several languages, is another instrument that measures the impact of a person's intellectual and developmental disabilities on family members with caring responsibilities. The FQOL Survey, with 54 items and a one-hour completion time, focuses on nine areas: health; financial well-being; family relationships; support from others; support from services; the influence of values; careers; leisure and recreation; and community integration (Werner et al. 2009). As it is very extensive and in-depth, the detailed information recorded may help researchers understand the complexities of family members' burden. However, completing such a lengthy questionnaire could place a huge burden on an already stressed family member and makes this questionnaire impractical for routine use in clinical settings (Tanco et al. 2017).

The IOF scale, PedsQL™ Family Impact Module, the BCQoL, the CareQol and the FQOL survey are not truly generic as they are specific to particular conditions or carers. Their use in family members across all disease areas is, therefore, limited.

1.2.2.2.3 GENERIC FAMILY QUALITY OF LIFE MEASURE

The FROM-16 is the only family generic instrument that measures the impact of any disease, across all medical specialities, on the QoL of adult partners and family members of patients of any age. The FROM-16, with 16 items, focuses on the emotional, personal and social impact on the partner or family member of a person affected by a health condition. One practical feature of the FROM-16 is that it is a user-friendly and relatively simple questionnaire with a two-minute completion time, making it a practical tool for completion by family members/partners. The use of such a measure can help a clinician to understand the impact of a patient's disease on the family member, when deciding on the management options which are in the best interests of the family as well as the patient.

Assessment of the psychometric properties of the 52 FQOL instruments revealed that all measures except four reported internal consistency reliability, 35 reported test re-test reliability, 40 reported content validity, 47 reported construct convergent validity, 24 reported construct divergent validity and 33 instruments reported completion time. Overall, most of the instruments identified in this review demonstrated good evidence of psychometric properties, including reliability and construct validity, however, only nine reported criterion validity, 11 reported responsiveness and only one reported information on the minimal clinically important difference (MCID) which allows clinical interpretation of the scores (Tables 1.10 and 1.12). Thus, it is not known whether these instruments are sensitive to detecting changes in family members' QoL over time.

Table 1.9 Summary characteristics of family quality of life measures – Disease/Speciality specific

Name of measure / key references	Country	Disease/ Speciality	Population	Language / translation	Completion time	Origin	Domains	Number of items	Scale	Mode of administration
1. Family Dermatology Life Quality Index (FDLQI) (Basra et al. 2007; Basra et al. 2008) https://www.cardiff.ac.uk/family-dermatology-life-quality-index	UK	Speciality-specific (Dermatology)	Family members of patients with skin disease	English, Arabic, Chinese, Croatian, Czech, Dutch, Filipino, French, German, Greek, Hebrew, Hindi, Hungarian, Italian, Japanese, Lithuanian, Nepali, Persian, Polish, Portuguese, Romanian, Russian, Spanish, Swedish, Turkish, Ukrainian, and Welsh	2-3 min	Semi-structured interviews with family members or partners of patients with a variety of skin diseases.	Domains not specified- QoL impact areas covered: Emotional and physical wellbeing, relationships, social life, leisure activities, burden of care, impact on job study, housework, and expenditure.	10	4-point Likert	Self-report
2. Dermatitis Family Index (DFI) (Lawson et al. 1998); (Beattie and Lewis-Jones 2006)	UK	Disease-specific (Dermatitis)	Parents and other family members of affected children with	Arabic, Chinese, Czech, Dutch, Filipino, French, German,	2-3 min	Qualitative interviews with family members /focus groups	Domains not specified- QoL impact areas covered: Housework, food preparation and feeding, sleep, family leisure activities, time spent on shopping for	10	4-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

	https://www.cardiff.ac.uk/dermatitis-family-impact-questionnaire			Atopic Dermatitis.	Greek, Italian, Japanese, Latvian, Malay, Norwegian, Polish, Portuguese, Russian, Serbian, Spanish, Swedish, Taiwan and Thai			the family, expenditure, tiredness, emotional distress, relationships between the main carer and partner or between the main carer and other children and helping with treatment.			
3.	Parents' Index QoL Atopic Dermatitis (PiQoL) (McKenna et al. 2005; Meads et al. 2005) https://eprovide.mapi-trust.org/instruments/parents-index-of-quality-of-life-in-atopic-dermatitis	UK, Netherlands, Germany, Italy, Spain, France, USA, Switzerland	Disease-specific (Atopic Dermatitis)	Caregiver of children with Atopic Dermatitis, aged 8 years or younger.	English, Dutch, Italian, French, German and Spanish	4-5 min	Qualitative interviews with parents of children with Atopic dermatitis in the UK, Netherlands and Italy.	Domains not specified- Needs that can be influenced by a child having atopic dermatitis (e.g., need for child to have a safe and successful future, need for rest and relaxation, need for Self-respect, need for independence)	28	Dichotomous	Self-report
4.	QoL in primary caregivers of children with atopic dermatitis (QPCAD) (Kondo-Endo et al. 2009; Katsunuma et al. 2013)	Japan	Disease-specific (Atopic Dermatitis)	Primary caregivers of a child with Atopic Dermatitis.	English	1-2 min	Semi-structured interviews	Four domains- Exhaustion, Worry about atopic dermatitis, Family cooperation, and Achievement	19	5-point Likert	Self-report, mail
5.	Childhood Atopic Dermatitis Impact Scale (CADIS) (Chamlin et al.	USA	Disease-specific (Atopic Dermatitis)	Parents of children with Atopic Dermatitis, younger than	English	6 min	Focus groups with parents and experts and literature review	Five domains-three of whom refer to the impact on the family: family and social function, sleep, and emotions.	45	5-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

	2005; Chamlin et al. 2007)			six years and their families.				Three domains for CADIS Short form	15		
6.	Psoriasis Family Index (PFI) (Eghlileb et al. 2009; Basra et al. 2015) https://www.cardiff.ac.uk/psoriasis-family-index	UK	Disease-specific (Psoriasis)	Family members of Psoriasis patients	English, Italian, Polish and Turkish	2-3 min	Interviews with relatives of people with psoriasis.	Domains not specified- QoL impact areas covered: frustration, worry about the reaction of other people, worry about their future, relationships, housework due to psoriasis and to treatment, time spent on treatment, social life, sporting activities, leisure activities, type of clothes, routine shopping and sleep.	14	4-point Likert	Self-report
7.	Atopic dermatitis Burden Scale (ABS) (Méni et al. 2013)	France	Disease-specific (Dermatology)	Parents of children with Atopic Dermatitis (AD).	French, English, US, German, Italian, Spanish, Danish, Romanian and Georgian	NF	Literature review; educational workshop/ discussion groups with parents of children with AD; feedback from expert HCPs / Parent association AD	Four domains-Family life, Budget and work, Daily life and Treatment.	14	4-point Likert	Self -report
8.	Haemangioma Family Burden (HFB) questionnaire (Boccara et al. 2015)	France	Disease- specific (Dermatology)	Parents of children with Infantile haemangioma (IH).	French, US and UK English, Spanish, Italian and German	NF	Literature review, interviews with healthcare professionals (paediatricians, dermatologists, nurses) and with	Five domains- Family life, Relationship and work, Emotions/feelings, Psychological and Disease management.	20	3-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

						the parents of children that have or have had IH of varying severity				
9. FamilyPso (Mrowietz et al. 2017)	Germany	Disease-specific (Psoriasis)	Partners or family of Psoriasis patient	English	NF	Literature reviews and interviews with relatives of people with psoriasis.	Four domains-Emotional impact of the disease, impact on daily activities and work or school and treatment characteristics, and influence on leisure activities and personal relationships	15	5-point Likert	Self-report
10. Epidermolysis Bullosa Burden of Disease (EB-BoD) (Dufresne et al. 2015)	France	Disease-specific (Epidermolysis Bullosa)	Families of children with epidermolysis bullosa (EB)	French	NF	Verbatim report-based literature review and data collection from parents of patients during a one-to-one session with the same social worker	Four domains-Family life, child's life, disease and treatment, and economic and social impact	20	7-point Likert	Self-report
11. Family Burden Ichthyosis (FBI) (Dufresne et al. 2013)	France	Disease-specific (Ichthyosis)	Families of children with Ichthyosis	French	NF	Literature reviews and interviews with patients, parents and experts	Five domains-Economic aspects, Daily life, Familial and personal relationships, Work, and Psychological impact	25	4-point Likert	Self-report
12. Family burden of Incontentia pigmenti (IP) F'BoIP	France	Disease- specific (Dermatology)	Parents/ family members of children with IP condition.	French and US English	NF	Interviews with dermatologists, patient-reported outcome (PRO) experts and IP parents.	Four domains-Social life and family life, Professional life and	20	6-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

	questionnaire (Taieb et al. 2019)							renunciation, Daily life and Economic impact.			
13.	Parents' diabetes QoL Questionnaire (PDQoL) (Vandagriff et al. 1992; Faulkner and Clark 1998)	USA	Disease-specific (Diabetes Type 1)	Parents of children with type 1 diabetes	English	NF	NF	Three domains-Life satisfaction, Impact of disease, and Worries related to the disease.	42	5-point Likert	Self-report
14.	Well-being and Satisfaction of CAREgivers of children with Diabetes Questionnaire (WE-CARE) (Cappelleri et al. 2008) https://eprovide.mapi-trust.org/ WE-CARE	USA	Disease-specific (Diabetes)	Caregivers of children with Diabetes	English, Portuguese and Spanish	10-15 min	Interviews with children and caregivers/paediatricians	Four domains-Psychosocial well-being, Ease of Insulin use, Treatment satisfaction, and Acceptance of Insulin administrations	37	5-point Likert	Self-report
15.	Diabetes family impact scale (DFI-S) (Katz et al. 2015) https://fam-net.org/product/diabetes-family-impact-scale/	USA	Disease-specific (Diabetes Type 1)	Parents of children and adolescents with type 1 Diabetes	English	NF	Interviews with parents of children with diabetes and a multi-disciplinary expert panel	Four domains-School, Work, Finances and Family well-being.	14	4-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

16. Type 1 Diabetes and Life (T1DAL) (Hilliard et al. 2021)	USA	Disease-specific (Diabetes Type 1)	Parents of children and adolescents with type 1 Diabetes	English	5-10 min	Interview with parents of children with diabetes	Three to four domains depending on age band-QoL areas covered-Emotional & daily activities, Support/family relationship, Financial consideration, Interaction with HCPs, diabetes management	20-30	0-100 scale higher scores mean better HRQOL	Self-report
17. Parent Ear Nose and Throat QoL questionnaire (PAR-ENT-QoL) (Berdeaux et al. 1998) https://eprovide.mapi-trust.org/PAR-ENT-QoL	France, Italy, Germany Czech Republic, Portugal	Speciality-specific (Ear-nose-throat infection/ pharyngitis)	Parents of children with ENT infections	French, Italian, German, Czech and Portuguese	5 min	Interviews with families	Three domains-An emotional score (eight items), A daily disturbance score (six items) and a global score.	14	5-point Likert	Self-report
18. Food Allergy Quality of Life Parent Burden (FAQLQ-PB) (Cohen et al. 2004; Mendonca et al. 2020; Knibb and Stalker 2013) https://eprovide.mapi-trust.org/FAQLQ-PB	USA, UK, Brazil	Disease-specific (Food Allergy)	Parents of children with Food Allergy	English, English UK* Chinese and Brazilian*	5-7 min	Interviews /focus groups with caregivers	Two domains-Life limitations and Emotional stress	17	7-point Likert	Self-report
19. Caregiver Quality of Life Cystic Fibrosis (CQOLCF) (Boling et al. 2003) https://eprovide.mapi-trust.org/CQOLCF	USA	Disease-specific (Cystic Fibrosis)	Caregivers Patients with Cystic Fibrosis	English	7-8 min	Expert review/care staff team	Domains not specified-areas of QoL impact covered: the physical well-being, emotional well-being, social/family	35	5-point Likert	Self- report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

							well-being, and functional well-being			
20. OverActive Bladder Family Impact Measure OAB-FIM (Coyne et al. 2010) https://eprovide.mapi-trust.org/OAB-FIM	USA	Disease-specific (Overactive Bladder)	Family members of a patient with Overactive bladder	English, Spanish and Turkish	NF	Focus group with Family members of patients with Overactive bladder	Six domains-(Irritation, Activities, Travel, Concern) for all family members and Sleep, Sex for spouses and significant others	19	5-point Likert	Self -report
21. Idiopathic thrombocytopenic purpura— Parental Burden QoL questionnaire (ITP—PB) (Barnard et al. 2003)	Canada, USA	Speciality specific (Haematologic Disorder)	Parents of children with a Haematologic Disorder	English	5-7 min	Interview with parents/health professionals	Six domains-Concerns related to diagnosis/ investigation, Treatment/disease monitoring, Monitoring of child's activities, Interference with daily life, Disease outcome, and Emotional impacts.	26	5-point Likert	Self-report
22. Haemophilia Family Impact Tool (H-FIT) (Dover et al. 2021)	Canada	Disease-specific (Haemophilia)	Parents of boys with haemophilia aged <4 years	English	5-10 min	Focus groups were conducted with parents of boys with haemophilia and haemophilia health care providers	NF	16	0-100 scale Higher score least impact	Self-report
23. Huntington's disease quality-of-life battery for carers (HDQoL-C) (Aubeeluck and Buchanan 2007) https://www.nottingham.ac.uk/HDQoL-C	UK	Disease-specific (Huntington's Disease)	Family caregivers of persons with Huntington's Disease.	English, French, German, Italian, Spanish, Swedish and Norwegian	21 min	Qualitative interview/ Photovoice	Four domains- Demographic and objective information; Practical aspects of caregiving; Satisfaction with life; feelings about living with Huntington's	34	11-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

24. Huntington's disease quality-of-life battery for carers short form (HDQoL-C-SF) (Aubeeluck et al. 2009) https://studylib.net/HDQoL-C-SF-University-of-Nottingham	France, Italy	Disease-specific (Huntington's Disease)	Family caregivers of persons with Huntington's Disease.	English, French, Italian, German, Polish, Portuguese, Spanish and Swedish	NF	312 carers from France and Italy completed HDQoL-C to develop a shortened version of the HDQoL-C	Domains not specified-QoL areas covered: Satisfaction with life; feelings about living with Huntington's disease	20	11-point Likert	Self-report
25. Alzheimer's Carers Quality of Life Instrument (ACQLI), (Doward 1997)	UK France, Germany, Italy, Spain	Disease-specific (Alzheimer's)	Carers of patients with Alzheimer's disease	English	NF	NF	The single domain of carer QoL	30	Dichotomous (true/ not true	Self-report
26. Family Quality of Life in Dementia (FQOL-D) scale (Rose et al. 2021)	USA	Disease-specific (Dementia)	Carers of patients with Dementia	English	5-10 min	Interviews with Expert panel and caregivers	Four domains-Family interactions, Well-being, Disease-related support/medical care, and Caregiver support.	41	4-point Likert	Self-report
27. Care related Quality of care – Multiple Sclerosis (CAREQOL-MS) (Benito-León et al. 2010)	Spain	Disease-specific (Multiple Sclerosis)	Caregivers of patients with Multiple Sclerosis	English and Spanish	NF	Focus groups were organized with MS patients and caregivers/ MS expert	Domains not specified-QoL areas covered: Physical burden and global health; social impact; emotional impact; need of support; emotional reactions to patient's psychic status	24	5-point Likert	Self-report
28. Parkinson's Disease Questionnaire for Carers (PDQ-Carer)	UK	Disease-specific (Parkinson's Disease)	PD carers	English	NF	Carer Surveys registered with local branches of Parkinson's UK	Four domains-Social and personal activities, Anxiety and depression, Self-care, and Stress	29	5-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

(Jenkinson et al. 2012) https://eprovide.mapi-trust.org/PDQ-Carer										
29. Parkinson Disease Questionnaire for Carers Summary Index (PDQ-Carer-SI) (Morley et al. 2012)	UK	Disease-specific (Parkinson's Disease)	PD carers	English	NF	Carer Surveys registered with local branches of Parkinson's UK	Single summary index score computed using the four subscales of the PDQ-Carer	29	5-point Likert	Self-report
30. Parkinsonism Carers QoL PQoL Carers (Pillas et al. 2016) https://xip.uclb.com/product/PQoL_Carers	UK	Disease-specific (Atypical Parkinsonism)	Carers of patients with Atypical Parkinsonism	English	NF	Qualitative interviews with Atypical Parkinson (AT) carers and Consultation with AP experts	Single domain of carer QOL	26	5-point Likert	Self-report
31. Family Outcome Measure-40 (FOM-40) (Simpson and Winstanley 2012; Migliorini et al. 2019)	Australia, New Zealand, Canada, UK	Disease-specific (Traumatic Brain Injury-TBI)	Families with relative having a TBI	English	NF	Developed with social workers from 12 rehabilitation centres across Australia, New Zealand, Canada, and the UK	Seven domains-Family member coping, Family cohesion, Support demands (burden), Relative adjustment, Adequacy of service, Family member resilience, Sustainability of family support	40	4-point Likert	Self-report
32. The TBI-CareQOL measurement system (Carlozzi et al. 2019) https://www.tbicareqol.com/	USA	Disease-specific (TBI)	Families with relative having a TBI	English	6-8 min per domain	Focus groups, discussions, interviews with caregivers of person with TBI	Five caregiver-specific domains-(feelings of loss-self, feelings of loss-person with TBI, anxiety, feeling trapped, caregiver strain) and 10 PROMIS measures-(anger, anxiety, depression, emotional support, informational support, social isolation,	124 caregiver specific items plus 10 PROMIS measures 6-item short form	T-score	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

							fatigue, sleep disturbance)			
33. Caregiver Quality of life (CGQOL) (Vickrey et al. 2009)	USA	Disease-specific (Dementia)	Family caregivers of people with Dementia	English	17 min	Interviews with carers of Dementia Patients	Ten domains-Assistance with instrumental activities of daily living; Assistance with activities of daily living; Role limitations due to caregiving; Personal time; Family interaction; Demands of caregiving; Worry; Spirituality and faith; Benefits of caregiving; Caregiver feelings	80	3 and 5-point Likert	Telephone interview /Self-report
34. Dementia Quality of Life (C-DEMQOL) (Brown et al. 2019) https://kclpure.kcl.ac.uk/C-DEMQOL	UK	Disease-specific (Dementia)	Family members of people with Dementia	English	15 min	Literature reviews /qualitative interviews with family carers and support staff, /Focus groups with carers and staff	Five domains-Responsibilities and personal needs; Wellbeing; Carer role and relationships with the person with dementia; Feelings about future and Carer support	30	5-point Likert	researcher administered/ Self-report
35. Family Impact Scale-Oro-facial (FIS—OFD) (Locker et al. 2002; Thomson et al. 2013)	Canada	Disease-specific (Oro-facial Disorder)	Parents of children with Oro-facial conditions	English	5 min	Review of existing child health status and family impact questionnaires, interviews with 41 parents/ caregivers	Three domains-Parental and family activity, Parental emotions and Family conflict	14 (original) 8 (short form)	5-point Likert	Self-report
36. Quality of Life in life-Threatening Illness–Family Carer Version	Canada	Speciality-specific (Oncology)	Caregivers of cancer patients receiving	English and French	<10 min	Previous research and expert review	Domains not specified-QoL areas covered: Carer's own state, relationships, carer	16	11-point Likert	Self-report

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

	(QoLLTI–F) (Cohen et al. 2006) https://eprovide.mapi-trust.org/QoLLTI-F			palliative care				outlook, quality of care, patient condition, finances, environment			
37.	CareGiver Oncology Quality of Life questionnaire (CarGOQoL) (Minaya et al. 2012) https://eprovide.mapi-trust.org/CarGOQoL	USA	Speciality-specific (Oncology)	Caregivers of cancer patients	English and French	6 min	Qualitative interviews with informal caregivers of cancer patients	Domains not specified-QoL areas covered: Psychological wellbeing, burden, relationship with healthcare, administration and finances, coping, physical well-being, Self-esteem, leisure time, social support and private life	29	5-point Likert	Self-report
38.	Caregiver Quality of Life Index–Cancer (CQOLC) (Weitzner et al. 1999; Ehmann et al. 2020; Duan et al.2015) https://eprovide.mapi-trust.org/CQOLC	USA Germany China	Speciality-specific (Oncology)	Primary caregiver of cancer patients	English, Turkish, Korean, Chinese* and German*	10 min	A semi-structured interview with family caregivers, physicians, nurses and social/ Expert Review	Four domains-Burden, Disruptiveness, Positive adaptation, and Financial concern	35	5-point Likert	Self-report
39.	City of Hope QoL Scale–Family Version (Ferrell et al. 1991; City of Hope National Medical Center 2020) https://eprovide.mapi-trust.org/City of Hope QoL Scale - Family version	USA	Speciality-specific (Oncology)	Family caregivers of cancer patients	English and Spanish		In-depth qualitative interviews with cancer survivors over five years Pilot	Four domains-Physical, Psychological, Social, and Spiritual	37	11-point Likert	Self-report, mail

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

40. Caregiver Impact Questionnaire (CIQ Survey Otitis Media) Boruk et al. (Boruk et al. 2007)	USA	Disease-specific (Acute Otitis Media)	Parents of children with acute otitis media	English	NF	Previous research/Expert Panel/parents/ non-medical volunteer	Domains not specified– QoL areas covered: Caregiver physical functional health status (FHS) and caregiver emotional FHS,& caregiver QoL rating and sibling impact score	10	5 and 7-point Likert	Self-report
41. Acute Otitis Media QoL questionnaire (AOM) (Dubé et al. 2010)	Canada	Disease-specific (Otitis Media)	Parents and children with Otitis media	English and French	10 min	Developed based on two already validated questionnaires	Four domains-(Sleep deprivation, Change of daily and social activities, Emotional distress, Cancelling family plans and trips) and two domains assessing adverse consequences for the siblings and Caregiver overall QOL	13	4 and 5-point Likert	Telephone
42. Pediatric Asthma Caregivers' Quality of Life Questionnaire (PACQLQ) (Juniper et al. 1996 ; Minard et al. 2016) https://eprovide.mapi-trust.org/PACQLQ	Canada	Disease-specific (Asthma)	Caregivers of children with asthma.	English, Spanish, Swedish, French, Portuguese, Bulgarian, Danish, Finnish, German, Chinese, Hungarian, Hebrew, Dutch, Norwegian, Persian, Polish, Russian, Serbian, Afrikaans and Arabic	3-5 min	Unstructured interviews with parents of children with asthma, a literature review and discussion with health professionals.	Two domains-Activity limitations, Emotional function	13	7-point Likert	Self, internet, hardcopy

Table 1.9 continued (Summary characteristics of family quality of life measures – Disease/Speciality specific)

43. Influenza-like illness Quality of Life (Care-ILI-QoL) (Chow et al. 2014) https://eprovide.mapi-trust.org/Care-ILI-QoL	Australia	Speciality-specific (Respiratory and Infectious Disease)	Parents of Children with Influenza-Like Illness	English	NF	Quantitative survey, qualitative interviews with parents, and meetings with paediatricians.	Four domains-Daily Activities, Perceived Support, Social Life, and Emotions	16	7-point Likert	Self-report
44. CAREGIVERS questionnaire Juvenile Idiopathic Arthritis (JIA) (Torres-Made et al. 2020) https://figshare.com/CAREGIVERS questionnaire JIA	Mexico	Disease-specific (Juvenile idiopathic arthritis)	Caregivers of children with JIA	Spanish and English	NF	Non-systematic Literature review /semi-structured interview with primary caregivers/ multidisciplinary group input	Eight domains-Disease impact, Social impact, Economic and working impact, Family impact, Impact on caregiver-patient relationship, Impact on couple relationship, Impact on spirituality/religion / personal beliefs, Impact on social networks.	28	Mixed Likert/ dichotomous	Self -report
45. Coeliac Disease parent/ caregiver QoL questionnaire (CDPC-QOL) (Abreu Paiva et al. 2019)	Brazil	Disease-specific (Coeliac Disease)	Parents and caregivers of Children and adolescent with Coeliac Disease	Brazilian-Portuguese	6 min	Developed based on literature review, researchers' experience and reviewing other QoL questionnaires	Three domains-Emotions, Worries, and Social (10 items each)	30	5- point Likert	Self- report
46. Family Caregiver Quality of Life (FAMQOL) Scale (Nauser et al. 2011)	USA	Disease-specific (Heart Disease - Heart Failure)	Caregivers of Heart Failure patients.	English and Turkish	NF	Developed through interviews with caregivers/ experts	Four domains-Physical, psychological, Social, and Spiritual	16	5-point Likert	Self -report

NF=Not Found: *Validated version

Table 1.10 Psychometric properties of family QoL measures – Disease/Speciality specific

Name of the measure/key references	Country	Disease/speciality	Internal consistency (Cronbach's alpha)	Test-retest	Content	Construct/ convergent	Construct/ divergent/discriminant	Criterion	MID	Responsiveness/ sensitivity to change
1. Family Dermatology Life Quality Index (FDLQI) (Basra et al. 2007**;** Basra et al. 2008)	UK	Speciality-specific (Dermatology)	Yes, α=0.88	Yes, r = 0.94	Yes	Yes	NF	NF	NF	Yes
2. Dermatitis Family Index (DFI) (Beattie and Lewis-Jones, 2006; Dodington et al. 2013)	UK	Disease- specific (Dermatitis)	Yes, α=0.85 to 0.90,	Yes, (r = ·95).	Yes	Yes	NF	NF	NF	Yes
3. Parents' Index QoL Atopic Dermatitis (PiQoL) (McKenna et al. 2005; Meads et al. 2005)	UK, Netherlands, Germany, Italy, Spain, France, USA, Switzerland	Disease-specific (Atopic Dermatitis)	Yes, α=0.88 and 0.93	Yes, r>0.85	Yes	Yes	NF	NF	Yes	Yes
4. QoL in primary caregivers of children with atopic dermatitis (QPCAD) (Kondo-Endo et al. 2009; Katsunuma et al. 2013)	Japan	Disease Specific (Atopic dermatitis)	Yes,(α=0.66-0.87)	Yes, (r=0.80–0.87)	Yes	Yes	NF	NF	NF	Yes
5. Childhood Atopic Dermatitis Impact Scale (CADIS) (Chamlin et al. 2005; Chamlin et al. 2007)	USA	Disease-specific (Atopic dermatitis)	Yes, (α=0.76-0.93)	Yes, r=0.96.	Yes	Yes	Yes discriminant	NF	NF	Yes

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

6. Psoriasis Family Index (PFI) (Eghlileb et al. 2009; Basra et al. 2015)	UK	Disease-specific (Psoriasis)	Yes, α=0.86	Yes, r= 0.93	Yes	NF	NF	NF	NF	NF
7. FamilyPso (Mrowietz et al. 2017)	Germany	Dermatology	Yes, α= 0.88	NF	Yes	Yes	Yes discriminant	NF	NF	NF
8. Atopic dermatitis Burden Scale (ABS) (Méni et al. 2013)	France	Speciality-specific (Dermatology)	Yes, α=0.78	Yes, r=0.89	Yes	Yes	Yes, concurrent and discriminant	NF	NF	NF
9. Haemangioma Family Burden (HFB) questionnaire (Boccara et al. 2015)	France	Speciality-specific (Dermatology)	Yes, α= 0.93	NF	Yes	Yes	Yes, concurrent and discriminant	NF	NF	NF
10. Epidermolysis Bullosa Burden of Disease (EBBoD) (Dufresne et al. 2015)	France	Disease-specific (Epidermolysis Bullosa)	Yes, α=0.90	Yes, r=0.97.	Yes	Yes	Yes discriminant	NF	NF	NF
11. Family Burden Ichthyosis (FBI) (Dufresne et al. 2013)	France	Disease-specific (Ichthyosis)	Yes, α=0.89	NF	Yes	Yes	Yes discriminant	NF	NF	NF
12. Family burden of Incontinentia pigmenti F'BoIP questionnaire (Taieb et al. 2019)	France	Speciality-specific (Dermatology)	Yes, α=0.93	Yes, ICC = 0·85 for each domain	Yes	Yes	Yes	NF	NF	NF

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

13. Parents' Diabetes QoL Questionnaire (PDQoL) (Vandagriff et al. 1992; Faulkner and Clark 1998)	USA	Disease-specific (Diabetes Type 1)	Yes, α=0.64–0.9	NF	NF	NF	Yes discriminant	NF	NF	NF
14. (WE-CARE) (Cappelleri et al. 2008)	USA	Disease-specific (Diabetes)	Yes, α=0.84–0.95	Yes, r=0.80–0.88	Yes	Yes	Yes	Yes	NF	NF
15. Diabetes family impact scale (DFI-S) (Katz et al. 2015)	USA	Disease-specific (Diabetes Type 1)	Yes, α=0.8	NF	Yes	Yes	NF	NF	NF-	NF
16. Type 1 Diabetes and Life (T1DAL) (Hilliard et al. 2021)	USA	Disease-specific (Diabetes Type 1)	Yes, α=0.80–0.88	Yes, r=0.73–0.86	Yes	Yes	NF	Yes	NF	NF
17. Parent Ear Nose and Throat QoL questionnaire (PAR-ENT-QoL) (Berdeaux et al.1998)	France, Italy, Germany, Czech Republic, Portugal	Speciality-specific (Ear-nose-throat infection/ pharyngitis)	Yes, α=0.80–0.93	NF	Yes	Yes	Yes	NF	NF	NF
18. FAQLQ-PB (Cohen et al. 2004)	USA	Disease-specific (Food Allergy)	Yes, α=0.95	Yes, r=0.93,	Yes	Yes	Yes	Yes	NF	NF
19. Caregiver Quality of Life Cystic fibrosis (CQOLCF) (Boling et al. 2003)	USA	Disease-specific (Cystic fibrosis)	Yes, α=0.91	Yes, r = 0.862	Yes	Yes	Yes, discriminant	Yes	NF	NF

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

20. OverActive Bladder Family Impact Measure OAB-FIM (Coyne et al. 2010)	USA	Disease-specific (Overactive Bladder)	Yes, α=0.89 or greater for all sub-scales except for one 0.71.	Yes, r=0.70-0.87 ICC=0.73 to 0.87.	NF	Yes	Yes	NF	NF	NF
21. ITP-Parental burden QoL questionnaire (ITP—PB) (Barnard et al. 2003)	Canada, USA	Speciality-specific (Hematologic disorder)	NF	NF	Yes	Yes	NF	NF	NF	NF
22. Hemophilia Family Impact Tool (H-FIT) (Dover et al. 2021)	Canada	Speciality-specific (Hemophilia)	NF	NF	NF	NF	NF	NF	NF	NF
23. HDQoL-C (Aubeeluck and Buchanan 2007)	UK	Disease-specific (Huntington's disease)	Yes, only for sub-scales α=0.80, 0.84, 0.89	Yes, r=0.78, 0.86, 0.90 for subscales	Yes	Yes	NF	NF	NF	NF
24. HDQoL-C-SF (Aubeeluck et al. 2009)	France, Italy	Disease-specific (Huntington's disease)	Yes, only for sub-scales α=0.88, 0.80	NF	NF	Yes	NF	NF	NF	NF
25. ACQL (Doward 1997)	UK, France* Germany*, Italy*, Spain*	Disease-specific (Alzheimer's)	Yes, α=0.87 and 0.95	Yes, r=0.93,	Yes	Yes	NF	NF	NF	NF
26. Family Quality of Life in Dementia (FQOL-D) scale (Rose et al. 2021)	USA	Disease-specific (Dementia)	Yes, α=0.95	NF	Yes	Yes	NF	Yes	NF	NF

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

27. CAREQOL-MS (Benito-León et al. 2010)	Spain	Disease-specific (Multiple Sclerosis)	Yes, α=0.90, 0.85, 0.81, 0.78,0.75 for sub-scales	Yes, r=0.96	Yes	Yes	NF	NF	NF	NF
28. PDQ-Carer (Jenkinson et al. 2012)	UK	Disease-specific (Parkinson's Disease)	Yes, α=0.92, 0.87, 0.86, 0.83 for Sub-scales	NF	Yes	Yes	NF	NF	NF	NF
29. PDQ-Carer-SI (Morley et al. 2012)	UK	Disease-specific (Parkinson's Disease)	Yes, α=0.94	NF	NF	Yes	NF	NF	NF	NF
30. PQoLCarers (Pillas et al. 2016)	UK	Disease-specific (Atypical Parkinsonism)	Yes, α=0.96	NF	Yes	Yes	Yes, discriminant	NF	NF	NF
31. FOM-40 (Simpson and Winstanley 2012; Migliorini et al. 2019)	UK, Australia, New Zealand, Canada	Disease-specific (TBI)	NF	NF	NF	NF	NF	NF	NF	NF
32. The TBI-CareQOL measurement system (Carlozzi et al. 2019)	USA	Disease-specific (TBI)	Yes, α ≥ .90 (0.96-0.98 across five domains)	Yes, r ≥ .9	Yes	Yes	NF	NF	NF	NF
33. CGQOL (Vickrey et al. 2009)	USA	Disease-specific (Dementia)	Yes, Subscale α=0.88, 0.93, 0.78, 0.83, 0.86, 0.86, 0.82, 0.94, 0.92, 0.89	Yes	NF	Yes	NF	NF	NF	Yes
34. C-DEMQOL (Brown et al. 2019)	UK	Disease-specific (Dementia)	Yes	Yes	Yes	Yes	Yes	NF	NF	NF

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

35. Family Impact Scale-Oro-facial disorders (FIS—OFD) (Locker et al. 2002)	Canada	Disease-specific (Oro-facial Disorder)	Yes, α= 0.83	Yes, r= 0.80	Yes	Yes	Yes, discriminant	NF	NF	NF
36. Quality of Life in Life-Threatening Illness–Family Carer Version (QoLLTI–F) (Cohen et al. 2006)	Canada	Speciality-specific (Oncology)	Yes, α=0.86	Yes, r=0.77–0.8	Yes	Yes	NF	NF	NF	NF
37. CareGiver Oncology Quality of Life questionnaire (CarGOQoL) (Minaya et al. 2012)	USA	Speciality-specific (Oncology)	Yes (0.72–0.89 except private life 0.55)	Yes, r=0.52-0.80	Yes	Yes	Yes	NF	NF	Yes
38. Caregiver Quality of Life Index–Cancer (Weitzner et al. 1999)	USA	Speciality-specific (Oncology)	Yes α=0.91	Yes, r=0.95	Yes	Yes	Yes, divergent	Yes	NF	Yes
39. City of Hope QoL Scale–Family Version (Ferrell et al. 1991; City of Hope National Medical Center 2020)	USA	Speciality-specific (Oncology)	Yes, α=0.69	Yes, r=0.89	NF	Factor analysis confirmed the 4 QoL domains as subscales for the instrument.	NF	NF	NF	NF
40. CIQ survey Otitis (Boruk et al. 2007)	English	Disease-specific (Acute Otitis Media)	Yes, α=0.88	Yes, r= 0.83,	NF	Yes	NF	NF	NF-	NF

Table 1.10 continued (Psychometric properties of family QoL measures – Disease/Speciality specific)

41. Acute Otitis Media QoL questionnaire AOM-QoL) (Dubé et al. 2010)	Canada	Disease-specific (Otitis Media)	Yes, α=0.81	NF	Yes	Yes	Yes discriminant	NF	NF-	NF
42. Pediatric Asthma Caregivers' Quality of Life Questionnaire PACQLQ (Juniper et al. 1996)	Canada	Disease-specific (Asthma)	NF	Yes, r=0.84	Yes	Yes	Yes discriminant	NF	NF	Yes
43. Influenza-like illness Quality of Life Care-ILI-QoL (Chow et al. 2014)	Australia	Speciality-specific (Respiratory and Infectious Disease)	Yes, α=0.72-0.92	NF	NF	Yes	Yes discriminant	NF	NF-	Yes
44. CAREGIVERS questionnaire JIA (Torres-Made et al. 2020)	Mexico	Disease-specific (JIA)	Yes, α=0.04-0.69	Yes	Yes	Yes	Yes, divergent	NF	NF	NF
45. CD parent/caregiver QoL questionnaire (CDPC-QOL) (Abreu Paiva et al. 2019)	Brazil	Disease-specific (Celiac Disease)	Yes, α=0.913	Yes, ICC = 0.88	Yes	NF	NF	NF	NF	NF
46. Family Caregiver Quality of Life (FAMQOL) Scale (Nauser et al. 2011)	USA	Disease-specific (Heart Disease-Heart Failure)	Yes, α=0.89	Yes, ICC=0.91	Yes	Yes	NF	yes	NF	NF

NF=Not Found: *Validated version

Table 1.11 Summary characteristics of family QoL measures - Population-specific /Generic

Name of measure/ key references	Country	Population	Language / translation	Completion time	Origin	Domains	Number of items	Scale (response options)	Mode of administration
1. PedsQL™ Family Impact Module (Varni et al. 2004, Ortega et al. 2023, Lima et al. 2023) https://eprovide.mapi-trust.org/PedsQL Family Impact Module	USA	Parents and the family members of children with Pediatric chronic health conditions	English* Spanish* and Portuguese*	NF	Developed and initially field-tested in families with medically fragile children with complex chronic medical conditions	Two domains-Parent functioning with 6 subscales measuring parents' Self-reported functioning (physical, emotional, social, cognitive, communication worry); and Family functioning with 2 subscales (daily, activities, family relationships)	36	5-point Likert	Self-report
2. Impact on-Family Scale (Stein and Riessman 1980; Stein and Jessop 2003; Williams et al. 2006; Jalil et al. 2019) https://www.apa.org/Impact on Family Scale	USA	Parents of children with chronic illness	English and Spanish	10 min	Family members interview	Four domains-Financial, Social, Personal strain and Mastery	27 (update to 15 items	4-point Likert	Self-report, interviewer administered
3. Beach centre Family Quality of life (Poston et al. 2003; Park et al. 2003; Hoffman et al. 2006) **https://beachcenter.lsi.ku.edu**	USA	Family members of children with disability	English, Spanish, French and Chinese	15 min	Interview with family members/ focus group	Five domains-Family interaction, Parenting, Emotional Well-being, Physical/ Material Well-being	25	5-point Likert	Self-report
4. Care related Quality of Life (CareQoL) (Brouwer et al.	Netherlands	Informal caregivers of Long-term Care recipients	English, Dutch German Norwegian Swedish, Italian,	NF	Based on EQ-5D and evaluation of caregiver burden scales	Seven general quality of life question domains-five negative and two positive dimensions of providing informal care and	7 and VAS	3-point Likert	Self-report

Table 1.11 Continued (Summary characteristics of family QoL measures - Population-specific /Generic

	2006; Baji et al. 2021) https://www.imta.nl/questionnaires/carergol.			Spanish, Portuguese and Hungarian*			VAS scale.			
5.	Family Quality of life survey-2006 (Isaacs et al. 2007; Perry and Isaacs 2015; Samuel et al. 2018) https://www.surreyplace.ca/FQOLS-2006	Canada	Family members of people with intellectual and developmental disabilities	English, Bosnian, Chinese, Dutch, Farsi, Flemish, French, German, Italian, Japanese, Malaysian, Polish, Romanian, Slovene, Spanish and Telugu	60 min	Expert opinion and previous research	Nine domains-Health, Financial well-being, Family relationships, Support from others, Support from services, Influence of values, Careers, Leisure and recreation, and Community integration	54	5-point Likert	self-report. Interviewer administered
6.	Family Reported Outcome Measure (FROM-16) (Golics et al. 2014; Chantarasap et al. 2019; Elsner et al. 2021; Oh and Shin 2021; Wojcik et al. 2020) https://www.cardiff.ac.uk/family-reported-outcome-measure. https://eprovide.mapi-trust.org/family-reported-outcome-measure	UK	Family members of people with any health condition	English, Welsh Thai, Polish, Korean*, Arabic, Hebrew, Swedish, Norwegian, Slovak, Turkish, Spanish, Czech, Bulgarian, Italian, Greek, Chinese Danish, Dutch, Thai*, French, Russian, Finnish, Portuguese, Hungarian and German*	2 min	Qualitative interviews with family members of patients with chronic disease, Focus group and Expert panel	Two domains-Emotional (six items), Personal and social life (10 items)	16	3-point Likert	Self-report

NF=Not Found;*Validated version

Table 1.12 Psychometric properties of family QoL measures- Population-specific /Generic

Name of the measure/ key references	Country	Internal consistency (Cronbach's alpha)	Test–retest	Content	Construct / convergent	Construct / divergent / discriminant	Criterion	MID	Responsiveness/ sensitivity to change
1. PedsQL™ family impact module (Varni et al. 2004) (Scarpelli et al. 2008)	USA	Yes, α=0.97	Yes, r= 0.81 to 0.96	NF	Yes	NF	NF	NF	NF
2. Impact on-Family Scale (15-item) (Stein and Riessman 1980; Stein and Jessop, 2003; Jalil et al. 2019)	USA	Yes, α=0.73	Yes, r=0.9	Yes	Yes	NF	NF	NF	NF
3. Beach centre Family Quality of life (Poston et al. 2003; Park et al. 2003; Hoffman et al. 2006; Waschl et al. 2019; Rivard et al. 2017)	USA	Yes, α=0.88-0.94	Yes, for subscale of importance r=0.41-0.82, for satisfaction subscale, r=0.60-0.77	Yes	Yes	Yes, divergent and discriminant	NF	NF	Yes (French version)
4. CareQoL-7D (Brouwer et al. 2006; Hoefman et al. 2013; McCaffrey et al. 2020; McLoughlin et al. 2020; Voormolen et al. 2021)	Netherlands	Yes, α =0.65	Yes, Carer 7D r=0.55-0.94 and Carer VAS, r=0.86	NF	Yes	Yes, discriminant	NF	NF	Yes, but not ascertained
5. Family Quality of life survey 2006 (Isaacs et al. 2007; Perry and Isaacs 2015; Samuel et al. 2018)	Canada	Yes, α=0.55–0.78	NF	Yes	Yes	NF	Yes	NF	NF

Table 1.12 Continued (Psychometric properties of family QoL measures- Population-specific /Generic)

6.	Family Reported Outcome Measure (FROM-16) (Golics et al. 2014)	UK	Yes, α=0.91	Yes, r=0.93	Yes	Yes	NF	Yes	Yes† in this PhD study	Yes† in this PhD study

NF=Not Found;*Validated version; † Not counted in this review as they didn't exist at the beginning of this study.

1.2.3 Discussion

This objective review of literature informed by PROM-based assessment involving 129 studies has indicated that there is a huge unrecognised secondary burden of disease. The review demonstrated that family members caring for a relative with a chronic condition are impacted in similar ways in terms of physical, social and psychological well-being. However, most of the research was focused on a few individual medical fields, such as neurology, oncology and dermatology. These findings are consistent with the previous review carried out by Golics et al. (2013a).

One of the key strengths of this current review is that its findings are based on studies that have used validated instruments to measure the impact of a patient's health condition on family members. Researchers have used a wide range of tools to measure this impact ranging from generic tools such as EQ-5D and disease-specific measures such as FDLQI, to burden tools such as the Zarit burden inventory. However, in most cases, researchers used additional tools such as HAAD and PSQI to assess depression and impact on sleep. Although this has provided in-depth insights into the impact of a person's health condition, the heterogeneity of the instruments across studies prevents the comparison of the impact of a person's health condition on family members across disease areas. Such comparison is important in identifying the most vulnerable family members and directing them to the right kind of support services. This is critical as a physically and psychosocially unhealthy family member would understandably be less able to discharge their caregiving duties, thus having a negative impact on the patients' health (Sewitch et al. 2004). Furthermore, the use of multiple tools by researchers to measure impact also suggests that researchers did not find any generic population tools or generic burden tools adequate to measure impact on family members across the whole of medicine, indicating a strong need for a generic family-specific tool that includes all aspects of impact on family members, and can be used across all diseases. This implies that FROM-16, which has been created based on qualitative research on family members of patients across 26 medical specialities, could fill this gap as a generic family-reported outcome measure.

The majority of the studies reviewed were cross-sectional, with only seven studies being longitudinal. A better understanding of the impact of a patient's disease on family

members will come from following family members caring for a relative over a period of time. Future research should focus on longitudinal studies to build a solid understanding of the long-term family impact of the disease. This is important as a chronic disease may influence major life-changing decisions, thus, understanding long-term impacts may help clinicians in developing better management plans for patients and family members (Bhatti et al. 2011). In addition, the majority of family members caring for relatives in the studies reviewed were females and mostly mothers. There is a dearth of research on the impact of caregiving on fathers, although this review has highlighted two studies where fathers were impacted more than mothers. The fact that fathers are mostly unavailable at the point of contact with healthcare workers shows that the impact on fathers is forgotten or difficult to obtain. Future research should study the impact of children's diseases on fathers to help identify any unmet need.

An appraisal of existing FQoL instruments identified a recent plethora of FQoL measures indicating the growing recognition of the importance of FQoL. Appraisal of the psychometric properties of these tools has revealed that only a few instruments have published responsiveness and only one had MCID information, however, evidence of responsiveness is essential for an instrument to be useful for clinical monitoring or as an outcome measure in assessment of the value of interventions. Information concerning MCID is important for clinicians to be able to interpret changes in scores over time. While it is important in the assessment of an intervention to determine change over time, "statistically significant" change in scores might not always be clinically relevant (Wright 1996; Wright et al. 2012; Batterham and Hopkins 2006). Therefore, the interpretation of HRQoL score data should be based on clinically significant change, as indicated by the MCID, the smallest change in scores that the subject (in this case, a family member) finds beneficial. As only a few instruments have published responsiveness and MCID information, it might be thought that such psychometric properties have not been considered to be important by other researchers assessing the family impact of disease, in researcher's view, incorrectly. However, most of the instruments reviewed were developed in recent years, and perhaps new studies planned or underway may describe further psychometric properties. Only a psychometrically robust instrument will be able to measure the impact of family caregiving in a reliable way. Therefore, future studies should engage in further psychometric testing of existing measures.

Furthermore, all instruments identified in this review were created in developed countries such as the USA and the UK, highlighting a need for cross-cultural validation in developing countries (Camfield 2012). This is important as some aspects of the impact of caregiving, such as finance, may not be so important in some countries, especially those covered by a national health service. However, finance can be a critical factor in the QoL of family members of a patient in developing countries (Chow et al. 2013), and indeed also at the poorer end of the socio-economic spectrum in richer countries.

The review of the literature presented in this chapter has some limitations. Firstly, it did not employ a systematic review technique because of time constraints and resources available. However, the current review followed a rigorous methodology and fulfilled 19 of the 27 relevant PRISMA checklist items (Moher et al. 2009). Secondly, the review only included studies in the English language, thus limiting understanding of the impact of a patient's disease on family members in different cultures.

Even though the review was updated at the end of this PhD project in May 2023, there is a possibility that some studies or study information might have been missed as only one person, RS (researcher), conducted data extraction and screening. Although PRISMA guidelines were observed, this review was not claimed to be a systematic literature review. Therefore, it was not required to have two independent reviewers conducting the review and extraction. Another limitation of this review is that it did not include the lived experience of the patient's family members. A more in-depth appreciation of the lived experience of family members could have been achieved through a qualitative synthesis or meta-ethnography. However, such qualitative reviews are a requirement for instrument development, which was not a focus of this study.

The overview of measurement properties of existing family QoL instruments presented in this Chapter was not intended to follow a full COSMIN style process in which the quality of both the studies (risk of bias) and their psychometric properties are evaluated (Prinsen et al. 2018). This review was conducted solely by the researcher (RS), and a COSMIN style review requires that quality assessment be done by two reviewers independently and that consensus among the reviewers is reached, if necessary, with the help of a third reviewer (Prinsen et al. 2018). However, following such criteria would be a requirement of carrying out a systematic literature review,

which was not the intention of the literature review presented in this thesis. Although fully following COSMIN guidelines could have enhanced the value of this review, time constraints and resource availability (such as time and availability of a second independent reviewer) for this PhD did not allow this approach, as the main focus of the PhD was on validating several aspects of FROM-16.

In conclusion, this review found that family members caring for their sick relative experience a huge, but similar impact on their physical, social and psychological well-being across different disease areas. To address this and for it to influence practice and support family members impacted by their relative's disease, there is a need for a generic family QoL measure which offers acceptable practicality and flexibility to researchers and clinicians who need to administer it. This review has identified FROM-16 as the only generic family-friendly instrument that can be used across all disease areas to measure the family impact of a person with a disease. However, to support the use of FROM-16 in clinical settings across all disciplines of medicine, in the assessment of the cost-effectiveness of medical intervention, in clinical trials and in research, there is a need for further examination of its psychometric properties.

1.3 CRITICAL ANALYSIS OF FROM-16

1.3.1 Development of FROM-16

FROM-16 was developed following a literature review and semi-structured interviews with 133 family members across 26 medical specialities, exploring in depth the impact of a relative's health condition on family members (Golics et al. 2013a; Golics et al. 2013b). A preliminary 31-item questionnaire, with 5-point Likert scale response options for each item, developed from the content of the interviews with family members, was reduced to a 16-item questionnaire, with a three-point Likert scale, using Rasch model and factor analysis with data from a separate cohort of 240 family members. This resulted in a very strong foundation of FROM-16 as a tool for the measurement of the QoL impact on family members caused by having a person in the family with a health condition. As the items in FROM-16 were developed directly from the experiences of affected family members, they are likely to represent a much more accurate reflection of the impact on family members compared to other population-specific generic family

QoL measures that were developed from information in the literature rather than from direct qualitative research. Examples of such measures are the Family Strain Questionnaire (Ferrario et al. 2004) and the Family Quality of Life Survey (Issacs et al. 2007).

Content validity for 31 items of the FROM-16 was assessed by expert panels involving clinicians and family members using qualitative and quantitative data (Golics 2013). The acceptability of items by those people who will ultimately use the measure can only be assessed by qualitative data from the target population (Patrick et al. 2011). This means that the item reduction of the FROM was executed to the highest standards, involving mathematical modelling alongside the human voice of the content validity panels. However, re-validation of content validity through the process of cognitive debriefing might be required if new concepts that are not covered by the FROM-16 emerge for specific diseases. Although the extensive and excessive interviewing beyond saturation across 26 disease specialities that was carried out by Golics et al. (2014) make this unlikely with respect to disease areas, it may be required as the definition of 'family' continues to evolve in ever changing societies. The modern definition of family used in both this thesis and Catherine Golics's thesis (Golics 2013) includes friends as family members; therefore, in the future, content validity for 'friends as family members' through the process of cognitive debriefing might be required.

Face validity of FROM-16 was established during its initial validation, demonstrating that FROM-16 items are relevant to the target population (Golics et al. 2014). The establishment of face validity is important when developing assessment tools and is particularly crucial when developing assessments for specific populations, such as for family members/partners of patients (Allen et al. 2023). Moreover, establishing reliability (and/or reproducibility) and construct validity are equally important (Terwee et al. 2018), and new questionnaires should be tested for such properties (McKenna et al. 2019). It has been demonstrated during its development that FROM-16 has high internal consistency (n=120, Cronbach's α= 0.91), high reproducibility (n=51, ICC=0.93) and good construct validity through correlation with WHOQOL-BREF total (n=119, $r=-0.55$, $p<0.001$) (Golics et al. 2014).

1.3.2 Evaluation of FROM-16

The FROM-16 was created to measure the QoL impact of a person's health condition on family members and partners and assesses the impact on family members either living with or caring for a patient. This is important as partner/family members living with a person with a health condition may be impacted emotionally and psychosocially even when they are not directly involved in caring for their relative. Therefore, FROM-16 measures the often hidden impact on family members and is valid for use in family members/partners who are not carers or who do not see themselves as carers.
The FROM-16 is shorter than some existing population-specific/generic family QoL measures, such as the Impact-on-Family Scale (Stein and Riessman 1980), the Beach Center Family Quality of Life Scale (Hoffman et al. 2006), the Family Quality of Life Survey (Issacs et al. 2007) and the Family Strain Questionnaire (Ferrario et al. 2004) and has a shorter completion time. Although CareQoL-7D is a short questionnaire, it is not comprehensive enough to include all aspects of the family impact of a disease. For example, CareQol-7D does not include the much-reported impact on sleep of family members (Dahiya et al. 2013; Tanimukai et al. 2014) or the impact on the sex-life of spouses/partners (Richards et al. 2011; Yoo et al. 2018).

Furthermore, from a visual perspective, FROM-16 appears short and concise, containing all information (the title, instructions, items, response options and scoring of the measure) on one A4 page, making it appealing and acceptable to family members and clinicians. This is likely to lead to better response rates than for more lengthy questionnaires.

The use of plain language in communications aimed at patients or their family members/partners is an important consideration that can facilitate patient participation and accurate PROM completion (Papadakos et al. 2019). FROM-16, with a Flesch readability score of 64.7(Golics 2013), can be easily understood by 13-15-year-olds, which means that it is easier to read than many PROMs, such as the EQ-5D-5L that has a Flesch readability score of 61.3 (Hill et al. 2016). The 16 items of FROM-16 have a mean length of 5.6 words (range=3-12), demonstrating their conciseness and readability. The simplicity and brevity of the items allow for ease of translation and enhanced translation accuracy, and furthermore, the simple response options reduce ambiguity during translation, facilitating the use of FROM-16 internationally.

A short recall period improves the accuracy of the response data, optimising validity by minimising the negative effects of inaccurate recollection of increasing or decreasing trends in symptoms over the course of the recall period. FROM-16 has a recall period of "at the moment", allowing the measure to be used accurately in family members of patients whose illnesses fluctuate frequently and whose symptoms occur less frequently, improving the measure's generalisability.

1.4 STRENGTHS AND WEAKNESSES OF FROM-16

The FROM-16 has several strengths. The FROM-16 has been designed to measure the impact on any adult family member of any patient with any disease. This is a major advantage over existing population-specific generic measures that all have some restriction precluding general use: the IOF scale measures the impact of a paediatric chronic condition on the family caregiver (Sein and Jessop 2003), the Family QoL Survey measures the impact of adult family members caring for a person with intellectual and developmental disabilities (Werner et al. 2009), and the CareQol-7D measures the caregiver impact of long-term conditions (Brouwer et al. 2006). This places FROM-16 in a unique position, possessing a wider scope as a generic tool for use in research, allowing comparison across populations and disease areas to inform resource allocation and in routine practice to identify and support family members.

FROM-16 is user-friendly, with a completion time of two minutes, making it suitable for use in clinical settings and research. However, this brevity of the FROM-16 does not compromise its comprehensiveness as it includes a wide range of family QoL aspects impacted by having a family member with an extensive number of health conditions with its determinants arrived directly from target population in 26 medical specialities.

Another strength of FROM-16 is that it asks focused questions regarding the impact of a relative's health condition on family members/partners, meaning there are no interpretation difficulties due to double-barrelled or ambiguous questions, compared to other generic measures such as the EQ-5D (van Leeuwen et al. 2015), resulting in spontaneity of responses.

The translation of PROMs into a variety of languages and cross-cultural validation are important requirements to allow for international implementation (Epstein et al. 2015).

Validated translation methodology ensures that the items and responses for translated PROMs have the same meaning as the original language version (Mokkink et al. 2010), but the extra process of cross-cultural validation ensures that the questions and responses are appropriate for and, where necessary, adapted to the target culture that is ensuring cultural, semantic, experiential and conceptual adaptation (Teig et al. 2023). Many of the disease-specific and all generic/population-specific family/carer measures have undergone cross-cultural validation (Tables 1.9 and 1.11). Since its development in 2014, FROM-16 has undergone a number of cross-cultural validations and is currently available in more than 25 languages (https://www.cardiff.ac.uk/family-reported-outcome-measure; https://eprovide.mapi-trust.org/family-reported-outcome-measure), reflecting growing international interest in the instrument.

Although a person's health condition may physically, socially, and psychologically impact family members, FROM-16 was not designed to directly assess physical impact. However, it does include items such as the effect of 'having a family member with a health condition on sleep' and 'time for self' that can impact a person's physical health. Furthermore, in the process of FROM-16 development, 'tiredness' (as mentioned as the impact on physical health in CareQoL-7D) was removed from FROM-16 during item reduction as it was found to be dependent on the item "effect on sleep". This implies that FROM-16 includes items that respond to aspects of the physical health of family members/partners.

Unlike other carer instruments (Brouwer et al. 2006), the FROM-16 does not measure any potential positive outcomes that a family member may experience from caring for their relative. Although during the development of FROM-16, some family members identified some positive effects relating to "emotional impact" and "family relationships" (Golics 2013), these points were not addressed in the design of the FROM-16. This was because one of the purposes of developing FROM-16 was to identify the negative impact of caring for or living with a person with a health condition to support healthcare workers in routine practice to identify problems and hence focus on how to improve the lives of those affected. Ware et al. (1995) argue all items must measure the same negative trait and be scored in the same direction for an instrument to be used in disease assessment. The FROM-16 specifically measures the negative impact of caring for or living with a person with a health condition to identify and support impacted family members in routine practice. However, if the aim of researchers or

clinicians is to measure the overall experience of living with a relative with a health condition, FROM-16 should be used in conjunction with other techniques, such as semi-structured interviews, to avoid over-representation of negative aspects of caring.

The usefulness of a PROM is determined by the instrument's psychometric properties, including evidence for reliability, validity, and responsiveness. FROM-16 does not yet have evidence of responsiveness, measurement error or MCID and may benefit from further validation of these psychometric properties, increasing its usability across research and clinical practice. Interpretability is another important property of PROMs that enhances their use in clinical practice (Singh and Finlay 2020). The COSMIN (The **CO**nsensus-based **S**tandards for the selection of health **M**easurement **In**strument) describes interpretability as: "the degree to which one can assign qualitative meaning, that is, clinical or commonly understood connotation to an instrument's quantitative scores or change in scores" (Mokkink et al. 2016). The FROM-16 does not have established score interpretability. Although score interpretability is highly desirable if a tool is to be used for clinical practice, none of the family QoL tools have score-meaning descriptors. Mapping of non-preference-based measures to preference-based measures (PBM), such as EQ-5D, may be considered to be another form of interpretability. This type of interpretability is important if data collected using the respective instrument is to be utlised for health economic evaluation. None of the family QoL measures, including FROM-16, have been mapped to EQ-5D.

1.5 STUDY RATIONALE

Although a higher score of FROM-16 indicates a greater impact on family members' QoL, descriptive banding gives meaning to absolute scores. The utility of QoL instruments could be maximised if a clinical meaning is assigned to the scores (Roger et al. 2012). For example, the score banding of the Dermatology Life Quality Index (DLQI) was clinically useful to dermatologists and has facilitated the integration of the DLQI into national guidelines in over 45 countries (Hongbo et al. 2005; Singh and Finlay 2020). This is important as, in the absence of such interpretation, scores are just arbitrary numbers, leaving clinicians to guess the magnitude of the effect or importance of score change in response to treatment. The development of score banding of FROM-16 would transform FROM-16 from being primarily a research tool to being of

practical benefit to clinicians across all medical specialities enabling them to interpret scores and score changes and thus allowing better-informed decision-making for patients and families.

While the use of score descriptor bands is the first important step for the interpretation of scores, this does not provide information on MCID (Delong & Chen 2012). The MCID can be defined as the smallest change in a measurement instrument score that patients (in this case, family members) perceive to be beneficial. This “smallest change” may be within a single score band descriptor or extend over two bands. The score descriptor bands give information about the current interpretation of a score, but the MCID is used to interpret change in a score. Hence the establishment of the MICD for FROM-16 will make it a more robust measure with an improved precision for assessment of family QoL as well as an additional endpoint for clinical trials.

The QoL of family members is greatly impacted by their relative’s health condition (Gallagher and Mechanic 1996; Pinquart and Sörensen 2003; Brouwer 2006; Schulz and Beach 1999; Bobinac et al. 2011; Golics et al. 2013a; Golics et al. 2013b; Shah et al. 2021a). Therefore, any new treatment or intervention that improves a patient’s QoL may also improve a family member's QoL. However, at the moment, usually only the patient’s QoL is considered in the health economic evaluation of a new medical intervention. Although the inclusion of family member/informal carer QoL in health economics and the development of ways to calculate it is encouraged by the National Institute for Health and Care Excellence (NICE), the lack of suitable utility measures is a significant barrier (Basarir et al. 2019). NICE uses Quality-Adjusted Life Years (QALYs) to compare various treatments when making health economic decisions. QALYs take into account the impact of treatment on length of life (in years) and HRQoL (utility values). The beauty of QALYs lies in that, using a single measure, interventions can be compared across a range of clinical areas in terms of efficacy and cost-effectiveness. An assessment that uses QALYs as an outcome is referred to as a cost-utility analysis (CUA). In order to generate QALYs, health utilities (or HRQoL weights) are needed, and the NICE’s preferred utility measure is the European Quality of Life-5 Dimensions three-Level (EQ-5D-3L) (Whitehead and Ali 2010). The utility values range from 0–1, where 0 indicates death and 1 indicates full health. Anything less than ‘0’

indicates a health state worse than death. The QALY can be calculated using the following formula:

QALYs= Years of Life x Utility Value = #QALYs

The incremental cost per QALY reveals how many extra QALYs the new medicine delivers and how much more it costs than the current treatment. This information allows NICE to make a judgement about its value for money.

Although the main beneficiaries of QALYs from a healthcare intervention are usually 'patients', the QALY changes will also impact those around the patients if their health is dependent on the patient's health state. This means that interventions that change a patient's health may also change the health of their family member/informal carer (Al-Janabi et al. 2011b). Therefore, most economists support the inclusion of family member/informal carer QALYs in health economic evaluation; however, measurement of carer utility has been challenging (Basarir et al. 2019).

An example of how QALYs are calculated and how they can be used in decision-making in health economic evaluation is given in the following text box:

QALYs and Cost per QALY calculation – How does it work?

For example, let us assume a person has a medical condition and is currently receiving medicine X.

If he continues to receive medicine **X**, he will live for 10 years with a utility level of 0.5.

If he receives a new medicine, medicine **Y**, for the same condition, he will live for 12 years, and his utility level will increase to 0.7.

The new medicine, medicine **Y**, is compared with medicine **X** in terms of QALYs gained as follows:

- medicine X: QALY=5 (10 years x 0.5)
- medicine Y: QALY=8.4 (12 years x 0.7)

This means the new medicine **Y** results in 3.4 additional QALYs when compared with medicine **X.** Medicine **Y** costs £10,000 more than medicine **X**.

To calculate the cost per QALY gained, the difference in treatment cost is divided by the number of QALYs gained.

The cost per QALY is, therefore £10,000/3.4=£2,941. Therefore, the use of medicine **Y** would result in an extra cost of £2,941 per QALY.

As £2,941 per QALY is much lower than the threshold of between £20,000 and £30,000 per QALY set by NICE, medicine **Y** would be favoured over medicine **X.**

Even though the EQ-5D has been used to assess carer utility, it was created with the patient in mind and may not provide an adequate assessment of family member/informal carer QoL (Davidson et al. 2008; Bell et al. 2001).
While the CarerQoL (Hoefman et al. 2017) and Carer Experience Scale (CES) (Al-Janabi et al. 2011a) have been valued using choice-based methods, these presently cannot be used to estimate utility weights (on a scale where 1=full health and 0=dead) (Al-Janabi et al. 2011b). Therefore, there is a need to map family-specific QoL measures such as the Family Reported Outcome Measure (FROM-16) to EQ-5D. Mapping of FROM-16 scores to EQ-5D utility values will address this research gap allowing the calculation of family member QALYs and, consequently, the inclusion of family member's QoL across multiple disease areas in health economic evaluation.
One of the important psychometric properties of any measure is its sensitivity to change and its ability to detect change over time (Lohr 2002). Sensitivity to change, also known as responsiveness, is the ability of an instrument to detect meaningful changes in a person's QoL over time. It is essential to formally demonstrate that FROM-16 is appropriately sensitive to change. Without such evidence, FROM-16 could not be confidently used in clinical trials and health economic evaluation to measure change over time. NICE has recommended that future research should explore how family/carer health-related quality of life (HRQoL) changes over time, including when the patient's health improves or worsens or if the patient dies (Pennington & Wong 2019). Therefore, demonstrating the sensitivity of FROM-16 to change will meet the research gap highlighted by the NICE decision unit in the 2019 NICE technology appraisal (Pennington & Wong 2019). It is hoped that further validation of FROM-16 will encourage clinicians to use FROM-16 alongside Patient-Reported Outcome Measures (PROMs) to inform treatment choices that are in the best interests of the patient and the patient's partner or family members.
This thesis describes further validation of FROM-16 using quantitative methods, contributing to making FROM-16 a robust tool for clinical and research practice.

1.6 AIM OF THE STUDY

To validate the FROM-16 for its robustness as a family QoL instrument to be used across all disease specialities.

1.6.1 Objectives

1. To develop FROM-16 score descriptor interpretation bands using the anchor-based technique. Study1, Chapter 2.

2. To map FROM-16 scores to EQ-5D-3L utility values to allow the use of FROM-16 in health economic evaluation. Study 2, Chapter 3.

3. To assess the responsiveness of FROM-16 to change over time and responsiveness of FROM-16 to patient's QoL by ascertaining whether the mean scores of FROM-16 in family members are changed over time (i.e., improved or deteriorated QoL) in parallel with the patient's QoL scores based on the intervention's hypothesised outcomes. Study 3, Chapter 4.

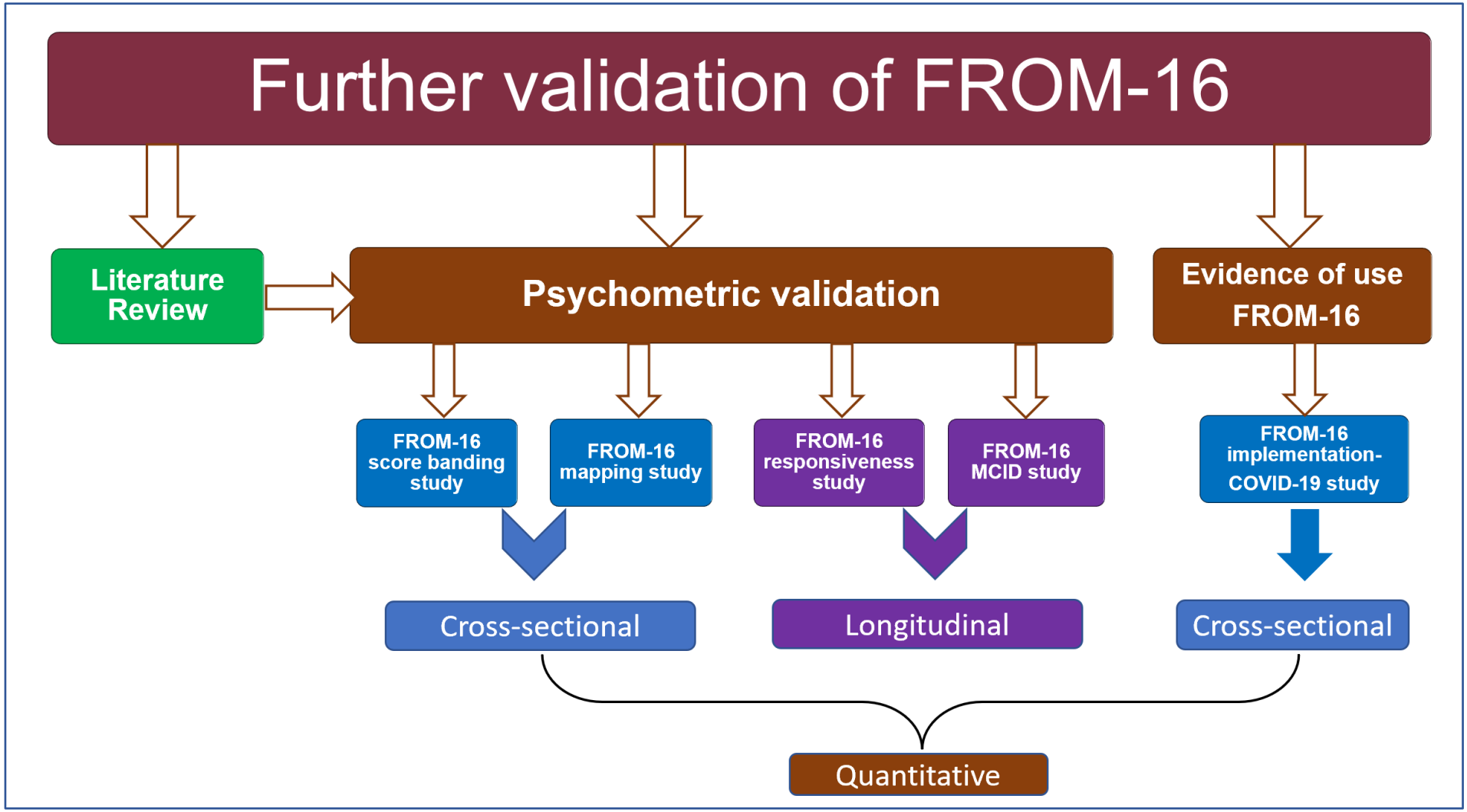
4. To estimate the minimal clinically important difference (MCID) for FROM-16. Study 4, Chapter 5.

5. To demonstrate the value of using FROM-16 during the COVID-19 pandemic. Study 5, Chapter 6.

1.7 FLOW CHART–DESCRIBING STRUCTURE OF THE THESIS AND THE STUDIES EMPLOYED

For the purpose of clarity and to demonstrate the depth and breadth of the studies undertaken for this thesis, the studies are presented graphically in a flow chart, in the hope that it gives the readers an initial appreciation of the progression and extent of the work presented in this thesis (Figure 1.7).

Figure 1.7 Flow Chart Describing structure of the thesis and the studies employed



CHAPTER 2

Development of FROM-16 Score-Meaning Bands Using an Anchor-Based Approach

2.1 INTRODUCTION

FROM-16 displays adequate reliability and validity, key performance properties needed for any outcome measure (Golics 2013). However, some important instrument properties have not yet been formally studied for FROM-16. For example, data on how a clinician would translate a FROM-16 score into clinically meaningful information are unavailable- a measurement property termed interpretability. This measurement property is highly desirable if FROM-16 is to be used in routine clinical practice. Research has shown that the utility of QoL questionnaires can be maximised if a clinical meaning is assigned to the questionnaire scores (Rogers et al. 2012). Descriptive score banding, therefore, gives vital meanings to absolute scores. The ability to interpret questionnaire scores is essential if the questionnaire is to be of value in clinical decision-making or in monitoring clinical change. Developing score bands for FROM-16 would create cut-off points, making it easier for clinicians to identify at-risk and high-risk family members and direct them to the appropriate support services. FROM-16 score banding would transform it from being primarily a research tool into being a practical tool for clinicians worldwide across all medical specialties. Therefore, the study described in this Chapter aims to develop score descriptor bands for the FROM-16 using the anchor-based approach.

2.2 METHODS

The data for this study (development of FROM-16 score banding) and for study 2 (mapping of FROM-16 scores to EQ-5D-3L utility values, described in Chapter 3) were collected at the same time online addressing FROM-16 score interpretation. Some of the data collected was used within both studies.

2.2.1 Study Design

This was an online cross-sectional study conducted between April and November 2021 involving family members/partners of patients with a wide range of health conditions recruited through UK-based patient support groups (PSGs).

2.2.2 Ethical Considerations

During the design of this PhD programme, particular attention was paid to the ethical considerations surrounding all studies. The ethical issues considered and addressed included gaining ethical approval, respecting COVID-19 restrictions, minimising Face to Face (F2F) contacts, conforming to the General Data Protection Regulation (GDPR) compliant survey platform, gaining informed consent, ensuring voluntary participation and maintaining anonymity and confidentiality.

Ethical approval was sought for the four PhD studies (FROM-16 score banding, FROM-16 mapping, FROM-16 responsiveness and FROM-16 MCID) (Appendix II) from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) and granted on 23 October 2020 (REC reference: 20/EE/0242) (Appendix III). According to this approval, the data for FROM-16 score banding and FROM-16 mapping studies were to be collected at the same time through a postal study of NHS patients and their relatives within Cardiff and Vale University Health Board across the 26 medical specialities that had been included in the initial development of FROM-16 (Golics et al. 2014). However, due to the pandemic and with COVID-19 restrictions still in place in January 2021, the researcher's plan to seek engagement with consultants and doctors for these studies was not possible. Consequently, alternate ways of recruitment were discussed with the research team, and it was decided to conduct these studies online, recruiting participants through UK-based patient support groups (PSGs) and associations instead of carrying out a postal survey of family members of patients within the NHS. Therefore, additional ethics approval was sought to conduct an online study (Appendix IV) from the Cardiff University School of Medicine Research Ethics Committee, and approval was granted on 22 March 2021; SREC reference: 21/19 (Appendix V).

The online study was conducted using the Joint Information Systems Committee (Jisc) survey platform. The Jisc Surveys (formerly Bristol Online Survey - BOS) is a General Data Protection Regulation (GDPR) compliant platform for academic surveys operated via https://admin.onlinesurveys.ac.uk (Jisc 2021) established on 1st April 1993.

Approval was also sought from Euroqol for the use of the electronic version of the EQ-5D-3L health status questionnaire in the PhD studies (Appendix VI). Permission was

sought from CAN STOCK PHOTO INC, and royalty was paid for a picture of “family” used to promote the study to patient support groups (Appendix VII).
The participants were provided with information about the study in an approved Participant Information Sheet embedded in the survey, and electronic informed consent was sought from the participants. The participants had a choice either to participate or not to participate in the study.
The FROM-16 interpretation study was anonymous, and no identifiable information was recorded, and all computer files with survey data are password-protected. Only the investigator has access to this data. To comply with the regulations concerning the safe keeping of records of studies of humans, the anonymised data generated from all of the studies will be kept securely for 15 years in accordance with Cardiff University's data retention policy.
Patients and public involvement and engagement (PPIE) is a research practice recommended by ethics committees (Smith et al. 2005; NHS 2011). This study involved two patients and one family Member as “Research Partners”.

2.2.3 Inclusion and Exclusion Criteria.

2.2.3.1 Inclusion criteria for patients

- UK patients with any health condition that are members of UK patient groups/associations
- Able to give informed consent
- Able to read and understand English
- Have the mental capacity to give electronic, informed "written" consent and complete the questionnaires using an electronic device**.**

2.2.3.2 Inclusion criteria for family members

- UK partners and family members (aged 18 years or older) of the patients with any health condition registered with UK-based patient groups or associations
- Able to give informed consent
- Able to read and understand English
- Have the mental capacity to give electronic informed "written" consent and complete the questionnaires using an electronic device**.**

2.2.3.3 Exclusion criteria for patients and family members

- Family members aged under 18 years
- Not living in the UK
- Unable to read and understand English
- Unable to give electronic written informed consent or operate an electronic device to answer the survey
- Paid carers (formal carers)
- Family members of deceased patients
- Patients and family members not living in the UK.

2.2.4 Selection of Medical Specialities

The participants for FROM-16 score banding and mapping studies were recruited with the help of various local and national patient groups, forums, charities, and associations. The criteria for the selection of these groups were based on the 26 disease specialities that were included in the original creation of the FROM-16 questionnaire. This was important in order to make study results generalisable across all areas of medicine. A list of patient support groups for various disease areas was created using the National Health Service (NHS) A to Z website (https://www.nhs.uk/conditions/). This website lists all health conditions and associated support groups in the UK. A further Google search was undertaken to identify carer associations and patient research platforms to ensure that family members and partners of patients with a diverse range of severities and diseases were included. The full list of patient support groups and research platforms that were approached for participant recruitment is given in Appendix VIII.

2.2.5 Sampling

The study used nonprobability convenience sampling. The sample size for this study was based on considerations of the sample size of similar studies carried out by the Cardiff dermatology research team in the past (Hongbo et al. 2005; Ali et al. 2017). However, consideration of sample size also depends on other factors such as the study objective, the nature of the population and the method used for analysing the data (Daniel 2012). As the focus of the FROM-16 score banding study was family members

of patients across all specialities with varying disease severities from “no effect” on their QoL to “extremely large effect” on their QoL, it was important to have a large enough sample size to represent all severities. Similarly, for the FROM-16 mapping study (discussed in Chapter 3), the use of the split-half cross-validation method necessitated that the sample size should be twice the actual sample size. A sample size of 4,400 was considered appropriate for these studies. However, to reduce inherent selection bias,106 patient support groups were approached to ensure family members of patients across all specialities and with all severities were included.

2.2.6 Survey Design

The online study was carried out using the Jisc survey platform (Jisc. Online surveys. Jisc, 2021), which is General Data Protection Regulation (GDPR) compliant. The online study questionnaire was available in two formats:

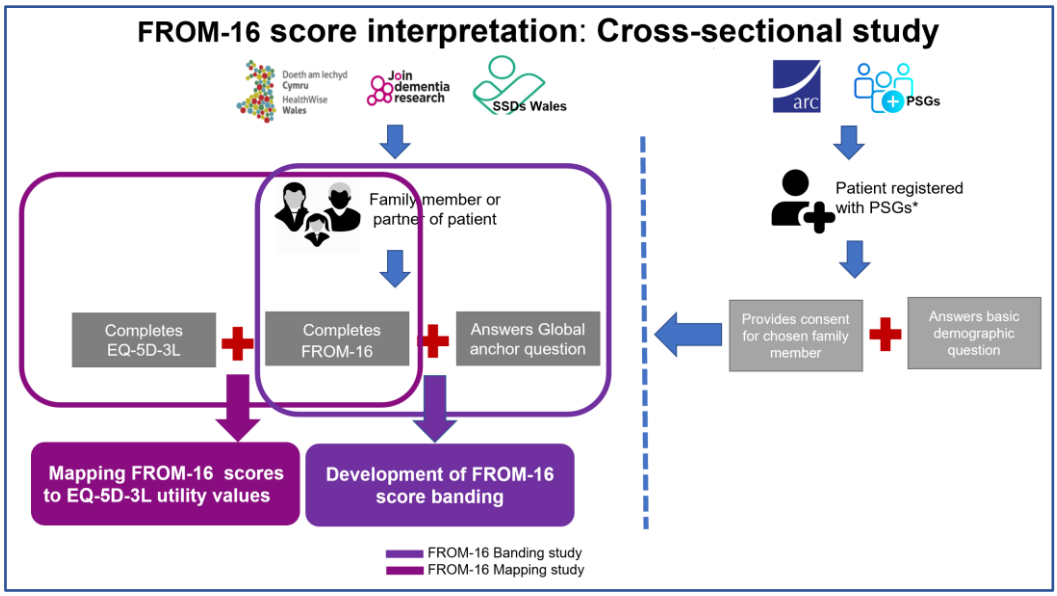
- *Patient and family member study questionnaire*: This questionnaire was directed to patients registered with various PSGs who then provided consent to involve their family members in the study.
- *Family member-only study questionnaire:* This questionnaire was directed to the family members of patients who were unable to provide consent either because of the severity of their health condition or because they were aged under 18 years. The family member-only questionnaire was also used for participant recruitment through Health Wise Wales (HWW), Joint Dementia Research (JDR) and Social Services Departments (SSDs).

The questionnaire had two sections. Section one was completed by the patient. The patients' role was limited to completing some basic information about themselves including gender, age, occupation, health condition, country of residence and choosing and allowing their family member/partner to take part in the study**.** The designated family member/partner had the choice to participate or not in the study. In the 'family member only' questionnaire, patient demographic information was completed by the family member.

Section two was completed by the family member/partner, who provided some basic demographic information (age, gender, occupation and relationship to the patient) and answered FROM-16, EQ-5D-3L and a Global Question (GQ). The participants were

provided with information about the study in a Participant Information Sheet embedded in the survey, and electronic informed consent was sought from the participants.

Figure 2.1 Flow diagram: FROM-16 score interpretation study



**Patients registered with 58 Patient Support Groups (PSGs)*

For this study (FROM-16 score banding), family members/partners of patients completed the FROM-16 (Appendix I) and global anchor, GQ (Figure 2.1). The single item global question (GQ) asked family members/ partners:

"How much is your life being affected by your family member's or partner's health condition at the moment? Please tick one of the following:"

0	1	2	3	4
No effect on my life	Small effect on my life	Moderate effect on my life	Very large effect on my life	Extremely large effect on my life

2.2.7 Participant Recruitment

The participants were recruited through UK-based patient support groups (PSGs) and associations. Of the 106 PSGs invited to contribute, 58 (55%) participated in the study (Appendix VIII). The main reason given by PSGs for their declining to participate included lack of capacity to assess and support such requests during the COVID-19 pandemic, recruitment support only available for their funded projects and the study objective not being relevant to their current organisational priorities. The recruitment

process varied across patient support groups and involved the researcher (RS) completing recruitment applications, preparing poster blurbs/adverts specific to each PSG and participating in online carer meetings to explain the study and to answer questions. Examples of these burbs and posters are given in Appendix IX. After three months of recruiting through PSGs, it was realised that in order to achieve the target response of 4,400 participants, there was a need to explore other possibilities for participant recruitment. Therefore, recruitment was extended to three research support platforms (Healthwise Wales (Hurt et al. 2019), Autism Research Centre-Cambridge University database, Join Dementia Research [JDR]) and Social Service Departments (SSDs) in Wales. The PSGs and associations distributed the survey using various channels, including posting a survey link on their support group Blogs, Facebook page and Twitter, mentioning the survey in their newsletter and emailing a link to members. Patient and family member participation in the study was voluntary. No incentive was given to participants for participation in the study; however, it was agreed with PSGs that the lay summary (Appendix X) of the results of the studies would be shared with the participating PSGs once the study results were published.

2.2.8 Patient and Public Involvement and Engagement - PPIE

Two patients and one family member/partner were involved as study research partners, and they were involved in the study from the start of our research planning discussions. These partners identified patient support groups for recruitment and reviewed the study protocol, study questionnaire, ethics application, recruitment application to patient support groups and patient/family member material (participant information sheets, study lay summary for PSGs, study promotional material-blurbs/posters). The patient and family member research partners also tested the final version of an online survey. All research partners attended research meetings every three months to review progress. However, email communication was maintained with all research partners throughout the study to review study documents and seek advice. One patient research partner (SJN) participated in all weekly supervisory research meetings and contributed to all study discussions, such as how to achieve the study objective of recruiting 4400 family members/partners during the pandemic, reviewing recruitment results and providing guidance on how recruitment can be extended to other groups such as the multiple sclerosis (MS) register, social services departments in Wales and research

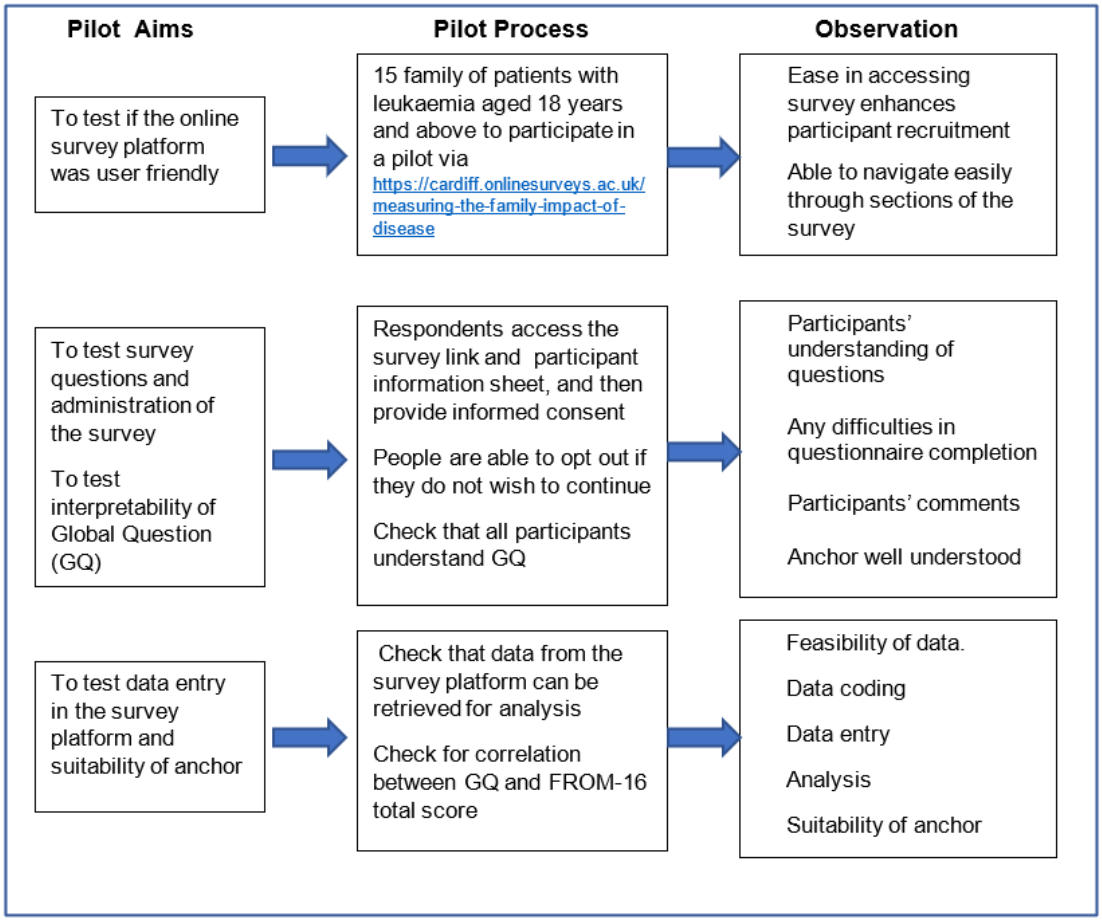
support platforms. SJN provided one-to-one guidance to the investigators on writing lay research reports.

The PPIE strategy for this study also included fifteen leukaemia patients (aged 18 years and above) from the patient support group, the Acute Leukaemia Advocates Network (ALAN) and their family members/ partners. These patients participated in a pilot aimed at testing an online study questionnaire to check if it was respondent-friendly and easy to understand and navigate. The feedback and insights from these patients were used to improve the survey. Further details about this pilot are discussed in this chapter under "pilot study".

2.2.9 Pilot Study

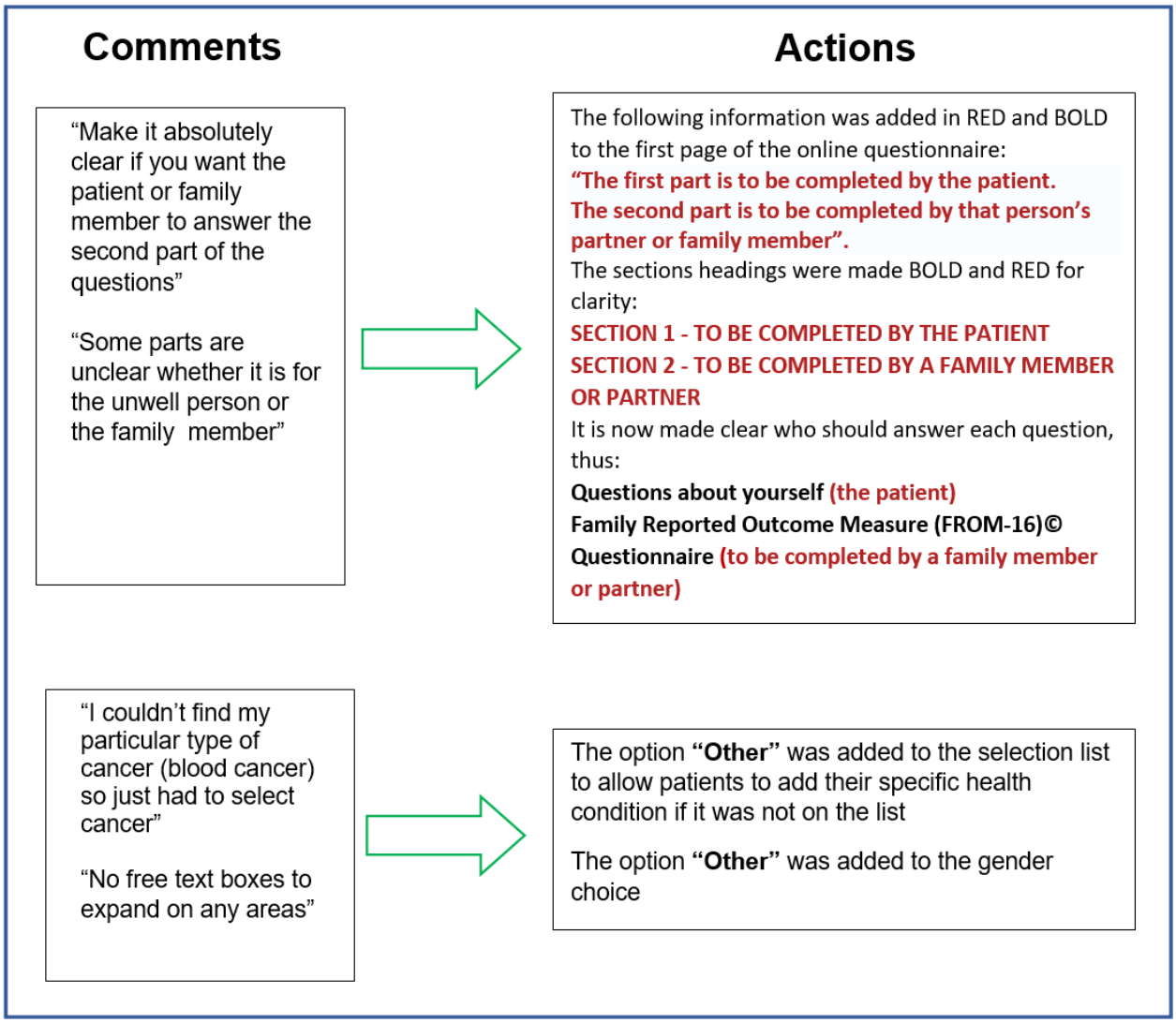
Before starting the main study, a pilot study was carried out with 15 patients registered with Acute Leukaemia Advocates Network (ALAN) and their family members/partners to test whether there was any difficulty or ambiguity in the wording of the anchor-based

Figure 2.2 Flow chart of the pilot study



question as well as the other survey questions (Figure 2.2). None of the participants reported any difficulties in understanding the anchor, although there were a few suggestions about the general format of the questions. The study questions were revised based on collective feedback (Figure 2.3).

Figure 2.3 Changes made in a pilot study following the feedback



2.2.10 Score Interpretation

Score interpretation of QoL instruments can be carried out using either the distribution-based method or anchor-based methods (Lydick and Epstein, 1993, Deyo and Patrick, 1995).

2.2.10.1 Distribution- and anchor-based approach

Score interpretation of QoL instruments can be carried out using either the distribution-based method or anchor-based methods (Lydick and Epstein, 1993; Deyo and Patrick, 1995). In the distribution-based technique, interpretations are based on the statistical distributions of scores in a given population, such as standard deviation or standard error of measurements (Crosby et al. 2003; Guyatt et al. 2002). Here magnitude of impact that patients report is compared to the normative population (sample of unaffected persons) (Nijsten et al. 2009).

On the other hand, in the anchor-based method, interpretations are made when the scores are compared or anchored with some theoretically related external measures (Chren 2010). The anchor-based method is based on patients' ratings (in this study, patients' family members' ratings) and is therefore thought to provide the best estimate of an individual's perspective (Rogers et al. 2012).

This study used an anchor-based approach since it is the most appropriate for creating descriptive bands (Hongbo et al. 2005) and has been used for score banding of various QoL and patient reported outcome measures (Hongbo et al. 2005; Leshem et al. 2015; Charman et al. 2013; Aawar et al. 2016; Gupta et al. 2019). An anchor method has two requirements. The first is that the anchor must be interpretable, and this requirement was met as the GQ was clearly understood by family members of leukaemia patients in the pilot study. Second, there must be a reasonable degree of association between the target instrument and the anchor, and both the pilot data (r_s=0.75, p=0.001) and this study results demonstrated a strong correlation between the FROM-16 total score and the GQ. The single item GQ was used as an anchor to assess the meaningfulness of total FROM-16 scores by being mapped against the multidimensional total FROM-16 scores (Golics et al. 2014; Hyland and Sodergren 1996).

2.2.11 Data Processing and Statistical Analysis

Data processing included determining frequencies for categorical variables such as gender, occupation, medical specialities, the relationship of family members to the patient, and place of residence in the UK. A gender and age comparisons were made using the Mann–Whitney U test, which compared the hypothesis of no difference in the

mean of the ranks. Regarding the FROM-16 scoring, if one item was left unanswered, this was scored 0, and the scores would be summed and expressed as usual out of a maximum of 32. The questionnaire was not scored if two or more questions were left unanswered (https://www.cardiff.ac.uk/family-reported-outcome-measure). This policy was used across all PhD studies. The correlation between FROM-16 scores and anchor (GQ scores) was assessed using Spearman's rank correlation coefficient (r_s) for appropriateness, a correlation of at least 0.3 with the FROM-16 total score was considered adequate (Revicki et al. 2008). The analysis of cut-offs for FROM-16 scores using anchor-based method was carried out using descriptive analysis and receiver operating characteristic (ROC) curve analysis.

Most studies have used descriptive analysis as the basis on which to devise score banding for QoL and patient reported outcome measures. These include in dermatology the DLQI (Hongbo et al. 2005), Eczema Area and Severity Index (Leshem et al. 2015), Patient-Oriented Eczema Measure (Charman et al. 2013) and as well as in other areas such as in nephrology, the Renal Quality of Life profile (Aawar et al. 2016). Some studies have explored both descriptive and ROC analysis for devising score bands such as, in dermatology, the Vitiligo Impact Scale-22 (Gupta et al. 2019) and the Hyperhidrosis Quality of Life Index (HidroQoL) (Donhauser et al. 2023), while one study used only ROC analysis to propose clinically meaningful cut-off scores for the Skin Cancer Quality of Life questionnaire (SCQoL) (Vinding et al. 2014). This study used both descriptive and ROC analysis to devise score bands for FROM-16. Although both methods can be used to find cut-off scores for a HRQoL measure, the descriptive method provides a visual display of score cut-offs between an anchor and target HRQoL questionnaire, and one can easily spot best alignment and cut-off scores. On the other hand, precision of cut-off scores using ROC can be determined by visual inspection of area under curve (AUC). The area under the ROC curve (AUC) should be larger than or equal to 0.70 for the analyses to be considered robust.
Statistical Product and Service Solutions version 27 (SPSS V.27) was employed for carrying out all statistical analyses except ROC analysis, which was conducted using SAS (Statistical Analysis Software version 9.4).

2.2.11.1 Descriptive analysis, score sorting and formation of score bands

The study used a simple descriptive statistical analysis by sorting the FROM-16 scores and calculating summary statistics of anchor scores (i.e., mean, mode, median) for each FROM-16 score. The mean (rounded off to the nearest whole number), mode, and median of the GQ scores for each FROM-16 total score were used to devise separate sets of bands of the FROM-16 scores. Numerical cut-off points were considered based on FROM-16 scores that corresponded to a one-step increase in mean, median, and/or mode on the anchor.

Using a bar graph plot of the sorted FROM-16 scores (x-axis) by the anchor score (y-axis), a graphical examination was performed to identify FROM-16 scores on the boundary of a step change on anchor. This approach tends to lead to several possible cut-offs. In the case of an overlap between some of the possible discrete categories where a number of FROM-16 scores could have fitted into one of two categories, cut-offs of the FROM-16 score for both possibilities were considered. and the K coefficient of agreement (weighted Kappa– for ordinal level of measurement) was calculated for each set.

For those family members/partners whose GQ score disagreed in a major way (by two or more bands) with that predicted from the devised FROM-16 banding score, sub-score comparisons were made with those family members whose GQ scores agreed with the FROM-16 banding.

2.2.11.2 ROC analysis

ROC was used as another method to determine the optimum FROM-16 cut-off scores between successive GQ bands (Prinsen et al. 2010). The optimum cut-off is the point on the ROC curve where the sensitivity and specificity are maximised, and the AUC values are ≥ 0.7; the point on the curve with minimum distance from the left-upper corner of the unit square; and the point where the Youden's index is maximum (Habibzadeh et al. 2016). There are different methods to identify the optimal cut-off value for the ROC curve, which include minimum P value approach (min P), Youden index (J), minimum Euclidean distance, Concordance Probability Method (CZ) and Index of Union (IU) (Unal 2017). The Youden Index, the most widely used method to

detect cut-off points and the 'minimum Euclidean distance measure' were used to determine the optimal balance between sensitivity (true positive rate) and specificity (true negative rate) in the estimation of the FROM-16 cut-off scores. Cut-off scores were rounded to zero decimal places. The level of agreement for each FROM-16 band with GQ was calculated using the weighted kappa-coefficient ($w\kappa$), which is specifically used for ordinal scale level of measurement and which takes into account the magnitude of disagreement between different categories (Gupta et al. 2019).

The advantage of using the descriptive statistic method for banding is that it is simple. Secondly, the bar graph provides a visual display of possible banding options, making it easier for even lay people to understand the most suitable cut-offs. The advantage of using ROC analysis is that sensitivity and specificity values contribute to the validity of the test while determining the cut-off score.

2.3 RESULTS

2.3.1 Sociodemographic Characteristics of the Study Participants

A total of 4,469 family members/partners of people with health conditions completed the FROM-16 questionnaire and GQ question. Fifty-six responses were discarded as the respondents were not relevant as they were not family members of people living with a health condition. They included paid carers, family members of deceased patients, and those who were not clearly a family member as their response to the relationship question was 'self'. The final analysis included responses from 4,413 adult family members (male=1533, 34.7%; female=2858, 64.8%; not specified=16, 0.4%; other=6, 0.14%) of people with over 200 health conditions (male=1994, 45.2%; female=2400, 54.4%; not specified=12, 0.3%; other=7, 0.16%) across 27 medical specialities in the UK (England=43%; Wales=52%; Scotland=4% and Northern Ireland=1%) (Table 2.1). The mean age of family members/partners was 57 years (SD=14.3; range=18-95y), and that of patients was 61 (SD=20.3; range=2-100y). The family members were mostly spouse/partner (60%), followed by son/daughter (22%) and parent (12%). Forty-one per cent of the family members/partners were retired, 39% were in paid jobs, and 8% were in part-time jobs. Of the people with health conditions, 58% were retired, 20% were in paid jobs, and 4% were in part-time jobs (Table 2.1).

Table 2.1 Demographic characteristics of the study participants (n=4,413)

Variables	Categories	N (%) or N (SD)
Patient		
Gender	Male	1994 (45.2%)
	Female	2400 (54.4%)
	Prefer not to say	12 (0.3%)
	Other	7(0.2%)
Age (years)	Mean (SD)	61.5(20.3)
	Median	66
	Range (IQR)	2-100 (26)
Occupation	In paid work	881 (20%)
	Part-time job	165 (3.7%)
	Unemployed	324 (7.3%)
	In unpaid work	22 (0.5%)
	Education/training	100 (2.3%)
	Homemaker	151(3.4%)
	Retired	2557(57.9%)
	Rather not say	68 (1.5%)
	Not applicable	145 (3.3%)
Medical specialities	Audiology	19 (0.4%)
	Cardiology	241 (5.5%)
	Chronic Pain	7 (0.2%)
	Critical Care	1 (0.02%)
	Dermatology	138 (3.1%)
	Endocrinology	271 (6.1)
	Gastroenterology	153 (3.5)
	Genetic/ Rare disease	44 (1%)
	Gynaecology	38 (0.9%)
	Haematology	183 (4.1%)
	Hepatology	11 (0.2%)
	Immunology	13 (0.3%)
	Infectious diseases	10 (0.2%)
	Movement disorder	10 (0.2%)
	Nephrology	58 (1.3%)
	Neurology	1620 (36.7%)
	Oncology	251 (5.7%)
	Ophthalmology	89 (2%)
	Orthopaedics	24 (0.5%)
	Otolaryngology	6 (0.1%)
	Rehabilitation medicine	30 (0.7%)
	Paediatrics	145 (3.3%)
	Psychiatry	325 (7.4%)
	Respiratory medicine	267 (6.1%)
	Rheumatology	310 (7%)
	Urology	21 (0.5%)
	Wound Healing	2 (0.05%)
	Multiple health conditions	95 (2.2%)
	Not stated	31 (0.7%)

Place of residence in the UK	England	1895 (42.9%)
	Northern Ireland	48 (1.1%)
	Scotland	185 (4.2%)
	Wales	2285 (51.8%)
Family members		
Gender	Male	1533 (34.7%)
	Female	2858 (64.8%)
	Prefer not to say	16 (0.4%)
	Other	6 (0.1%)
Age (years)	Mean (SD)	57 (14.3)
	Median	60
	Range (IQR)	18-95 (20)
Occupation	In paid work	1728 (39.2%)
	Part-time job	368 (8.3%)
	Unemployed	118 (2.7%)
	In unpaid work	52 (1.2%)
	Education/training	74 (1.7%)
	Homemaker	211 (4.8%)
	Retired	1808 (41%)
	Rather not say	54 (1.2%)
Relationship to the person affected with a health condition	Spouse/Partner	2631 (59.6%)
	Son/Daughter	973 (22%)
	Parent	523 (11.9%)
	Other*	286 (6.5%)
FROM-16 Score	Mean (SD)	15.02 (8.08)
	Range	0-32
GQ score	Mean (SD)	2.32 (1.08)
	Range	0-4
Correlation: FROM-16 and GQ score	r_s (p-value)	r_s =0.79 (p=0.001)

(Brother/Sister, Father/Mother-in-law, Grandparent, Uncle/Aunt, Grandson/Granddaughter, Brother/Sister-in-law, Nephew/Niece, Cousin, friend)

The overall mean FROM-16 score was 15.02 (SD=8.08; range 0-32), and the mean GQ score was 2.32 (SD=1.08; range 0–4). There was a strong correlation between FROM-16 scores and GQ scores (Spearman rank correlation coefficient, rs=0.79, p=0.001), a prerequisite for using the anchor-based method (Table 2.1).

The mean FROM-16 score for females (16.13; SD=8.04) was higher than that for males (12.92; SD=7.70; p=0.01), as was the mean GQ score (female=2.46, SD=1.06; male=2.04, SD=1.03; p=0.01) (Table 2.2).

The mean FROM-16 score for age group 1 (under 60 years) was higher than that for age group 2 (over 60 years) (p=0.001), however, there was no significant difference between the mean GQ score for the two age groups (p=0.391) (Table 2.2).

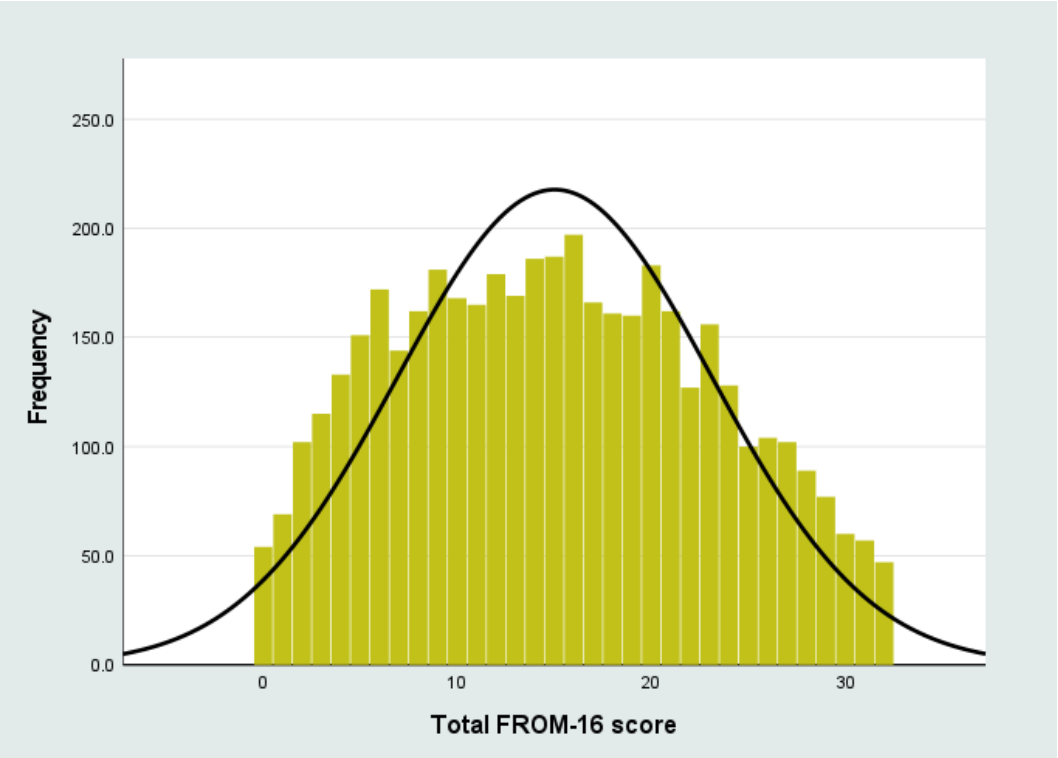
Table 2.2 Comparisons† of FROM-16 and GQ scores for gender and age groups

Measure	Gender		p value**	Age (years)†		p value**
	Male (n=1533) Mean score	Female (n=2858) Mean score		Group 1 (18-59 yrs) (n=2190) Mean score	Group 2 (60-95 yrs) (n=2223) Mean score	
Total FROM-16 score	12.92	16.13	0.001	15.53	14.53	0.001
GQ score	2.04	2.46	0.001	2.3	2.33	0.391

*†Mann Whitney U test. **p values were calculated using mean rank scores, but mean scores are presented here for ease of understanding. Similar values were obtained using t-test. †Age group cut off based on above and below median age.*

Figure 2.4 shows the distribution of FROM-16 total scores indicating scores are normally distributed; however, the Shapiro–Wilk test indicated non-normal distribution (p= <0.001). Nonetheless, the Shapiro–Wilk test is more appropriate for small samples; for large sample sizes, the normality is better assessed using histograms (Mishra et al. 2019) (Figure 2.4).

Figure 2.4 Distribution of FROM-16 total scores



2.3.2 FROM-16 Score Banding

For each score of the FROM-16 from 0 to 32, the number of family members with that score and their corresponding GQ mode, mean and median score is shown in Table 2.3 and Figure 2.5.

Table 2.3 Number of family members with each FROM-16 score and details of the corresponding GQ summary scores (mean, mode, and median) (n=4,413)

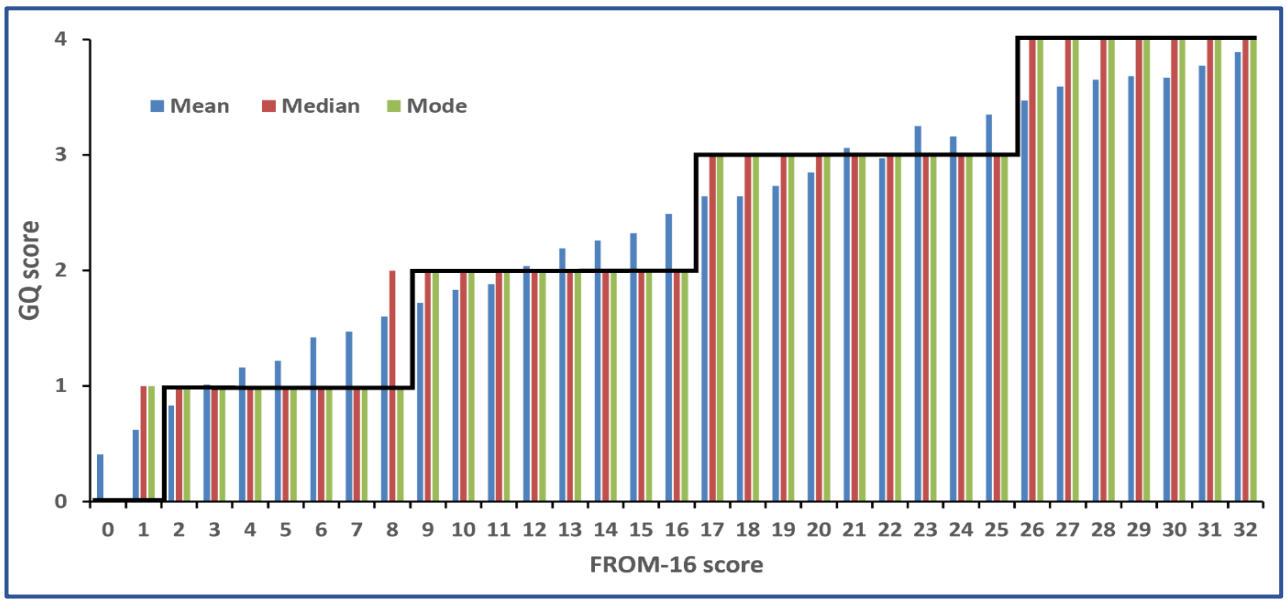
FROM-16 score	GQ score								Family member totals
	0	1	2	3	4	Mean	Median	Mode	
0	34	18	2			0	0	0	54
1	27	41	1			1	1	1	69
2	28	65	7	2		1	1	1	102
3	12	90	13			1	1	1	115
4	15	84	32	2		1	1	1	133
5	10	101	37	3		1	1	1	151
6	3	99	65	5		1	1	1	172
7	5	73	60	5	1	1	1	1	144
8	1	79	65	17		2	2	1	162
9	5	60	98	17	1	2	2	2	181
10	2	49	93	23	1	2	2	2	168
11	3	49	83	25	5	2	2	2	165
12	1	38	98	37	5	2	2	2	179
13	1	24	93	44	7	2	2	2	169
14		19	109	49	9	2	2	2	186
15		16	103	61	7	2	2	2	187
16		13	88	82	14	2	2	2	197
17		5	70	71	20	3	3	3	166
18		4	64	79	14	3	3	3	161
19		3	55	85	17	3	3	3	160
20		4	46	107	26	3	3	3	183
21			35	83	44	3	3	3	162
22			34	63	30	3	3	3	127
23			17	83	56	3	3	3	156
24		1	16	73	38	3	3	3	128
25	1		6	49	44	3	3	3	100
26	1		9	33	61	3	4	4	104
27			1	40	61	4	4	4	102
28			2	27	60	4	4	4	89
29			2	21	54	4	4	4	77
30			1	18	41	4	4	4	60
31			1	11	45	4	4	4	57
32				5	42	4	4	4	47
Family member totals	149	935	1406	1220	703				4413

Global Question (GQ) score: 0=No effect on QoL of family members; 1=Small effect; 2=Moderate effect; 3=Very large effect; 4=Extremely large effect on QoL of family members.

These were used as the basis for grouping the FROM-16 scores together into a set of five discrete bands so that each band would correspond to a single GQ score.

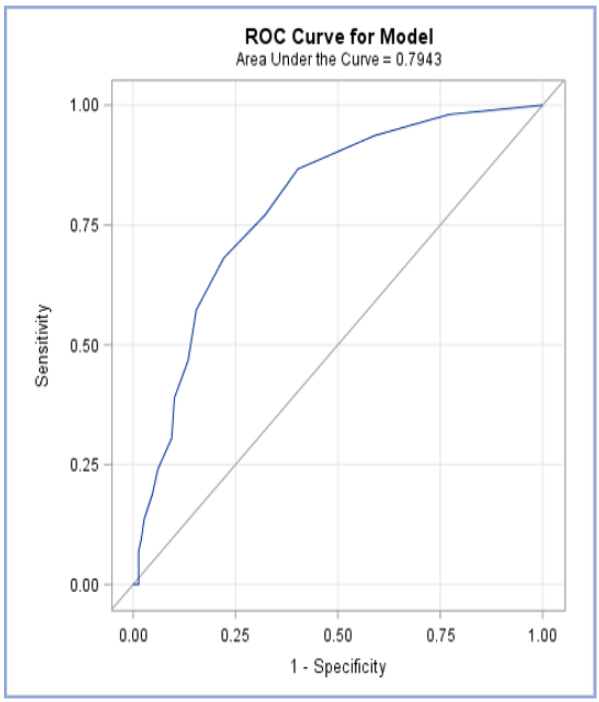
There were a few FROM-16 scores that could have possibly been included in either of the two adjacent bands. For example, a FROM-16 score of 1 could be assigned to either the GQ band 0 or the GQ band 1. Similarly, FROM-16 scores of 7 and 8 could be included in either the GQ band 1 or the GQ band 2. Subsequently, separate sets of bands were therefore produced with different groupings of FROM-16 scores, and the weighted kappa (w$\boldsymbol{k}$) coefficient of agreement was calculated for each set of bands (Table 2.3). The Kappa coefficient is a measure of the level of agreement beyond that which could be expected by chance. The maximum level of agreement is a Kappa of 1.0, and values of 0.41–0.60 are considered a moderate strength of agreement (Altman 1991).

Figure 2.5 Relationship between the Family Reported Outcome Measure (FROM-16) score and the mean, mode, and median of the Global Question (GQ) score

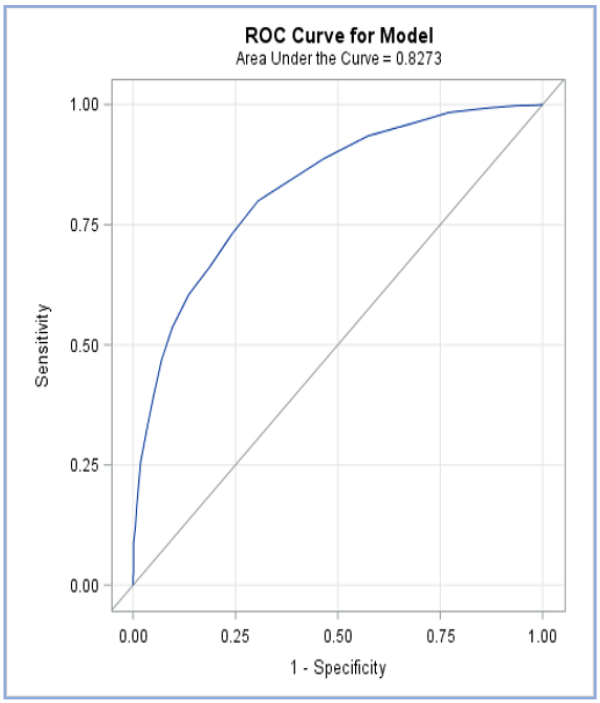


Based on the receiver operating characteristic (ROC) area under the curve (AUC) analysis, FROM-16 cut-off scores between GQ bands 0–1, 1–2, 2–3 and 3– 4 were ≥ 4 (sensitivity 86.7%, specificity 59.7%, AUC 79.4%), ≥ 8 (sensitivity 79.9%, specificity 69.5, AUC 82.7%), ≥ 16 (sensitivity 76.2%, specificity 68.2%, AUC 79.3%) and ≥ 23 (sensitivity 71.4%, specificity 70.5%, AUC 77.6%), respectively (w$\boldsymbol{k}$ =0.574) (Figure 2.6).

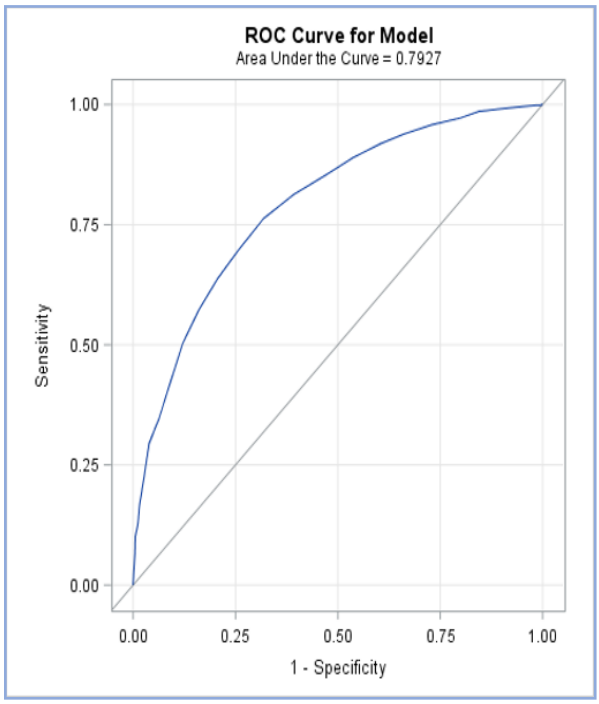
Figure 2.6 Receiver operating characteristic (ROC) curves for the FROM-16 cut-off scores between GQ bands 0-1 (a), 1-2 (b), 2-3 (c), 3-4 (d)



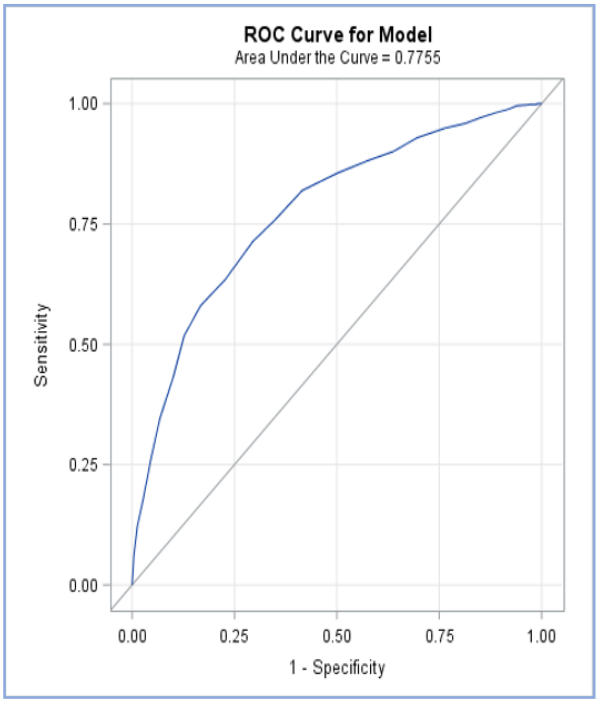
(a)



(b)



(c)



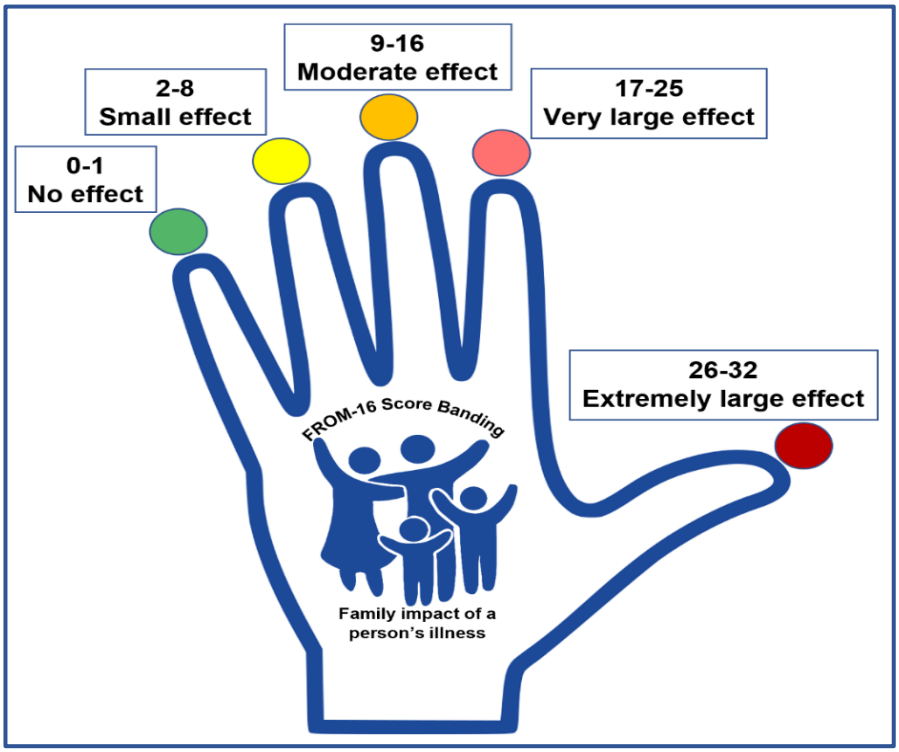
(d)

Table 2.4 Weighted Kappa Coefficients of agreement for separate possible sets of bands of the FROM-16 scores (chosen banding set highlighted in blue)

Banding Set	**Assignment of FROM-16 scores into bands**					Weighted Kappa (w$\boldsymbol{k}$) coefficient of agreement
	Band 0	**Band 1**	**Band 2**	**Band 3**	**Band 4**	
Set A	0	1-7	8-16	17-25	26-32	0.588
Set B	0	1-8	9-16	17-25	26-32	0.594
Set C	0–1	2–7	8–16	17–25	26–32	0.590
Set D	0–1	2–8	9–16	17–25	26–32	0.596
Set E	0-2	3-7	8-16	17-25	26-32	0.588
Set F	0-2	3-8	9-16	17-25	26-32	0.595
ROC AUC	0-4	5-9	10-16	17-23	24-32	0.574

The banding set proposed for FROM-16 is 0–1, 2–8, 9–16, 17–25, 26–32 based on the highest value of the weighted Kappa (w$\boldsymbol{k}$=0.596) (Figure 2.7).

Figure 2.7 Proposed FROM-16 score banding



Note: The effect mentioned is the level of adverse effect on the quality of life of a patient's partner or family member

The FROM-16 total scores for males and females were compared to respective summary GQ scores to check if there is a need for separate FROM-16 score bands for males and females (Figures 2.8 to 2.9).

Figure 2.8 Possible FROM-16 score banding for male family members

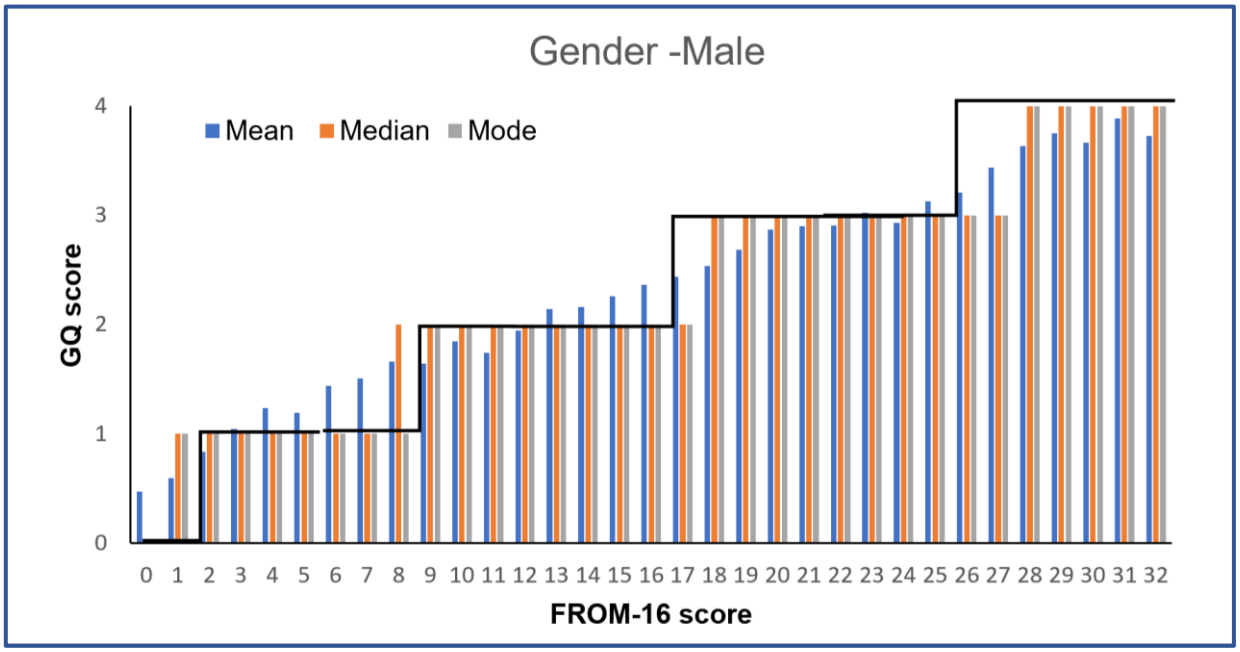


Figure 2.9 Possible FROM-16 score banding for female family members

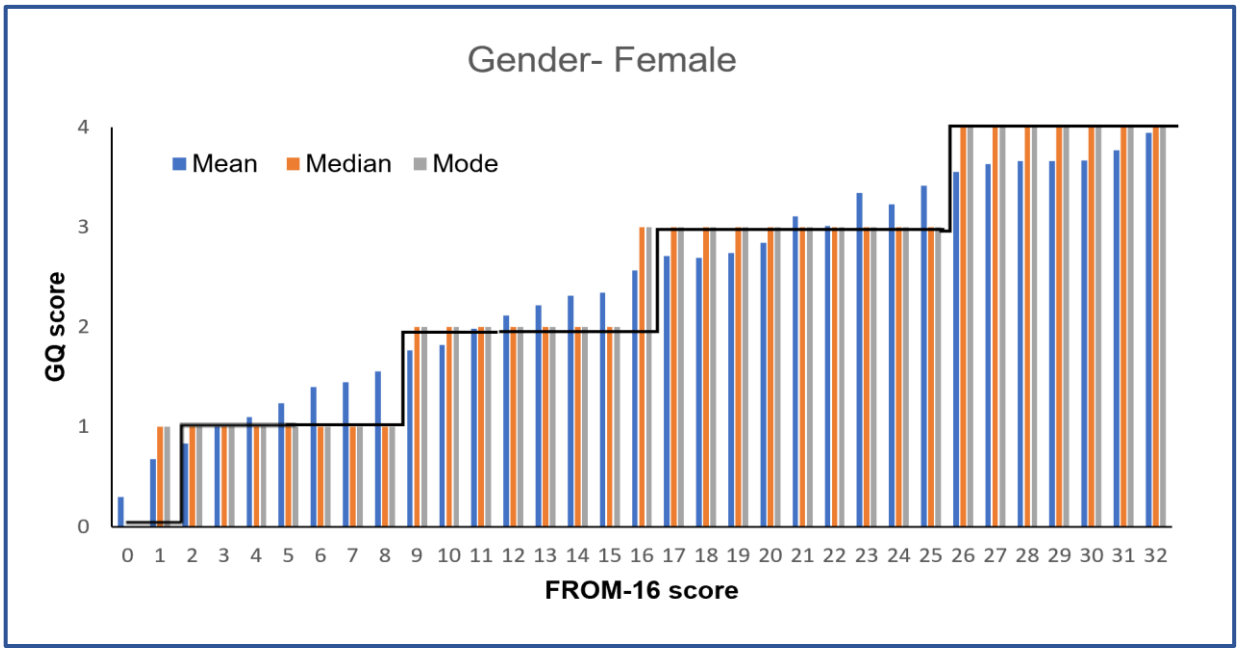


Table 2.5 Possible FROM-16 scores into bands based on gender

Gender	FROM-16 score bands				
	Band 0	**Band 1**	**Band 2**	**Band 3**	**Band 4**
Male	0	1-7	8-17	18-26	27-32
	0	1-8	9-16	17-25	26-32
	0	1-8	9-17	18-27	28-32
	0–1	2–7	8–17	18–26	27–32
	0–1	**2–8**	**9–16**	**17–25**	**26–32**
	0–1	2–8	9–17	18–27	28–32
Female	0	1-8	9-15	16-25	26-32
	0	1-8	9-15	16-25	26-32
	0	1-8	9-16	17-25	26-32
	0–1	2–7	8–15	16–25	26–32
	0–1	2–8	9–15	16–25	26–32
	0–1	**2–8**	**9–16**	**17–25**	**26–32**

Table 2.5 shows possible banding options for male and female genders, indicating that there was no striking difference between the two genders; rather, both included an option (highlighted orange) matching the proposed banding for FROM-16. Similarly, a separate banding analysis was carried out with age groups above and below 60 years.

Figure 2.10 Possible FROM-16 score bands for the age group below 60 years

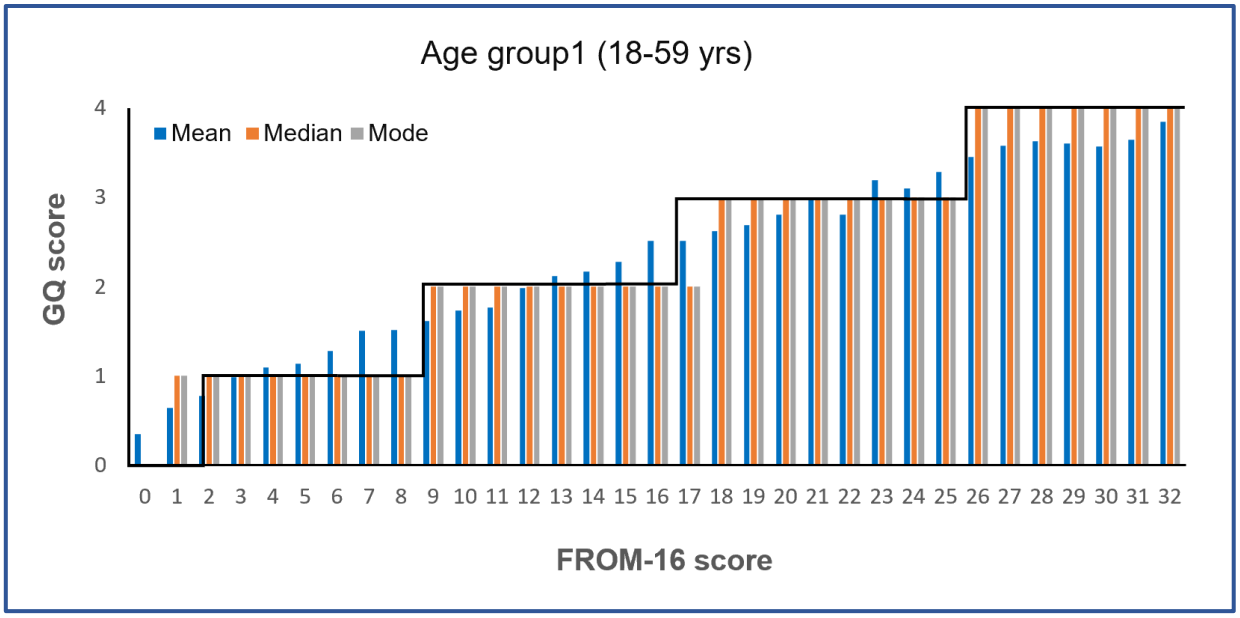
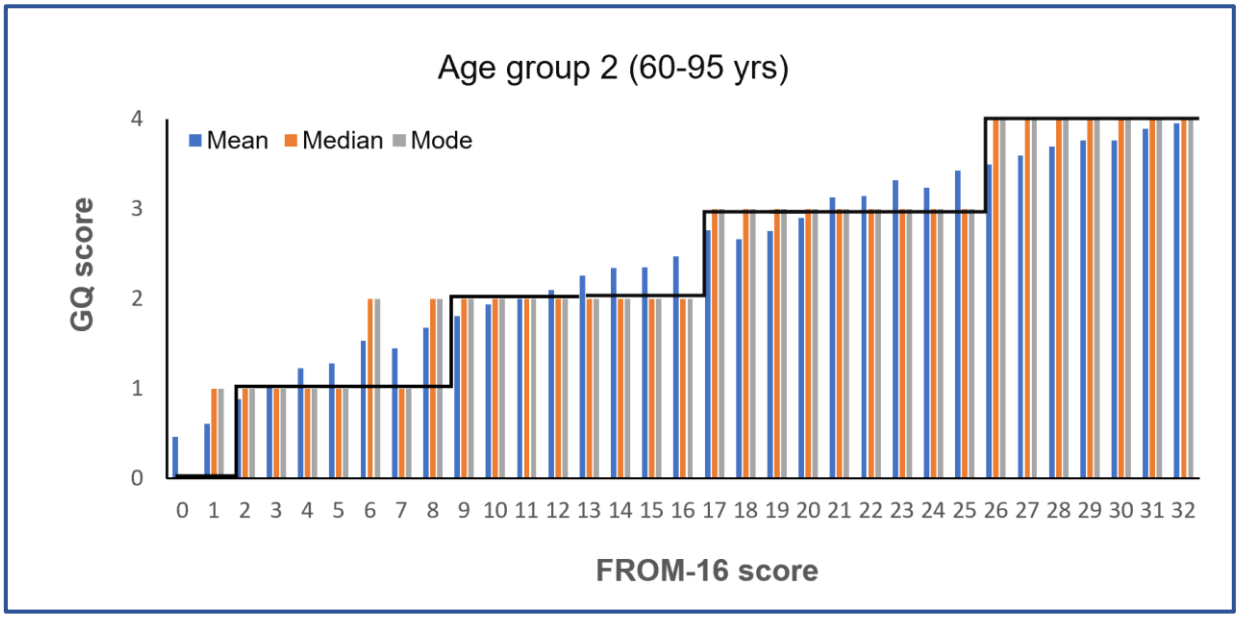


Figure 2.11 Possible FROM-16 score bands for the age group above 60 years



As is evident from Figures 2.10 and 2.11 the distribution of score bands for both age groups include the proposed banding for FROM-16.

2.3.3 Sub-Score Analysis

There was a total of 87 family members (high - Extreme Value Group -"EVG") whose actual GQ score was two or more points higher than the FROM-16 bands would have predicted from their FROM-16 score (Tables 2.6 and 2.7).

Table 2.6 Proposed banding of the FROM-16 with the distribution of GQ scores for the bands 0-1, 2-8, 9-16, 17-25, 26-32; wk coefficient of agreement=0.596

Set D	FROM-16 score band	GQ score					Family member Totals (%)
		0	1	2	3	4	
Band 0	0-1	61	59	3			123 (3%)
Band 1	2-8	74	591	279	34	1	979 (22%)
Band 2	9-16	12	268	765	338	49	1432 (32%)
Band 3	17-25	1	17	343	693	289	1343 (30%)
Band 4	26-32	1		16	155	364	536 (12%)
Family member Totals (%)		149 (3%)	935 (21%)	1406 (32%)	1220 (28%)	703 (16%)	4413

FROM-16, Family Reported Outcome Measure; GQ: Global question.
GQ score: 0=No effect; 1=Small effect; 2=Moderate effect; 3=Very large effect; 4=Extremely large effect.

Table 2.7 The frequency distribution of the sub-scores of each individual FROM-16 item

FROM-16 Question and Sub-score		FROM-16 bands										
		Band 0 (0-1)		Band 1 (2-8)		Band 2 (9-16)			Band 3 (17-25)		Band 4 (26-32)	
		NVG n=61	high EVG n=3	NVG n=591	high EVG n=35	NVG n=765	high EVG n=49	low EVG n=12	NVG n=693	low EVG n=18	NVG n=364	low EVG n=17
Q1	0	42	2	74	2	17	4	0	3	0	1	0
	1	19	1	464	19	412	19	9	151	3	21	3
	2	0	0	53	14	336	26	3	539	15	342	14
Q2	0	61	3	505	29	356	25	5	148	4	11	1
	1	0	0	81	5	348	16	5	378	13	144	11
	2	0	0	5	1	61	8	2	167	1	209	5
Q3	0	58	3	240	11	75	4	1	15	0	1	1
	1	3	0	306	13	426	20	8	259	10	29	5
	2	0	0	45	11	264	25	3	419	8	334	11
Q4	0	61	3	299	12	77	8	2	11	1	1	1
	1	0	0	252	17	449	23	5	233	9	40	0
	2	0	0	40	6	239	18	5	449	8	323	16
Q5	0	60	3	467	28	292	24	7	86	2	13	1
	1	1	0	108	5	330	18	2	305	7	85	5
	2	0	0	16	2	143	7	3	304	9	266	11
Q6	0	60	3	450	20	160	9	8	22	0	2	0
	1	1	0	134	14	504	28	3	284	12	27	5
	2	0	0	7	1	101	12	1	387	6	335	12
Q7	0	61	3	533	30	313	16	9	52	3	0	2
	1	0	0	57	3	420	20	3	367	11	37	5
	2	0	0	1	2	32	13	0	274	4	327	10
Q8	0	61	3	557	31	565	32	7	232	12	27	4
	1	0	0	34	4	175	11	5	293	3	74	7
	2	0	0	0	0	25	6	0	168	3	263	6
Q9	0	60	3	482	32	566	38	9	243	5	19	0
	1	1	0	103	3	175	9	3	352	10	109	10
	2	0	0	6	0	24	2	0	98	3	236	7
Q10	0	61	3	322	14	106	8	6	12	2	0	0
	1	0	0	261	19	527	23	4	232	11	18	0
	2	0	0	8	2	132	18	2	449	5	346	17
Q11	0	61	3	437	24	239	10	5	47	2	2	0
	1	0	0	144	8	363	15	6	191	5	11	0
	2	0	0	10	3	163	24	1	455	11	251	17
Q12	0	59	3	402	29	385	24	3	194	6	43	0
	1	2	0	144	3	187	9	8	182	2	46	1
	2	0	0	45	3	193	16	1	317	10	275	16
Q13	0	61	3	567	33	511	37	8	243	6	45	0
	1	0	0	24	2	238	10	4	338	11	46	4
	2	0	0	0	0	16	2	0	112	1	273	13
Q14	0	61	3	521	33	369	32	10	128	4	7	0
	1	0	0	68	1	346	16	2	399	8	65	5
	2	0	0	2	1	50	1	1	166	6	292	12
Q15	0	61	3	468	25	345	22	8	121	3	15	0
	1	0	0	109	9	367	19	3	340	10	52	1
	2	0	0	14	1	53	8	2	232	5	297	16
Q16	0	61	3	412	21	204	13	4	37	0	0	0
	1	0	0	173	12	464	20	7	289	8	22	0
	2	0	0	6	2	97	16	1	367	10	342	17
Mean total FROM-16		**0.44**	**0.33**	**4.60**	**5.31**	**10.01**	**9.76**	**8.50**	**13.70**	**13.22**	**15.21**	**15.41**

NVG, Normal Value Group; EVG, Extreme Value Group; Data describe the subjects whose GQ score falls exactly in the proposed band allocation, NVG and the subjects whose GQ score is at least two points above (high EVG) or below the FROM band (low EVG).

In contrast, there were only 47 patients (the "low EVG") whose actual GQ score was two or more points lower than the FROM-16 band would have predicted. All the patients whose GQ scores were two or more points away from the banding allocation were compared with those patients whose GQ scores agreed with the FROM-16 banding (Normal Value Group - "NVG") by carrying out a sub-score analysis of the 16 individual questions on the FROM-16 (Table 2.7). The sub-score comparison was carried out within each FROM-16 band. There was a higher proportion of 'maximum' sub-scores (sub-scores of 2 = “A lot”) in the high EVG compared to the NVG (8.8% vs 2.7% for band 1; and 25.8% vs 15.8% for band 2) (Table 2.8). The opposite was true for EVG with low scores compared to the NVG (13% vs 15.8% for band 2; 36.5% vs 44.2% for band 3; and 73.5 % vs 80.9% for band 4), indicating a lower proportion of maximum sub-scores (A lot) in low EVG than NVG (Table 2.8).

Table 2.8 Proportion of 'sub-score 2' (A lot) in Normal Value Group (NVG) and Extreme Value Group (EVG)

FROM-16 questions and sub-score 2		**FROM-16 bands**										
		Band 0 (0-1)		**Band 1** (2-8)		**Band 2** (9-16)			**Band 3** (17-25)		**Band 4** (26-32)	
		NVG n=61	**high EVG** n=3	**NVG** n=591	**high EVG** n=35	**NVG** n=765	**high EVG** n=49	**low EVG** n=12	**NVG** n=693	**low EVG** n=18	**NVG** n=364	**low EVG** n=17
Q1	2	0	0	53	14	336	26	3	539	15	342	14
Q2	2	0	0	5	1	61	8	2	167	1	209	5
Q3	2	0	0	45	11	264	25	3	419	8	334	11
Q4	2	0	0	40	6	239	18	5	449	8	323	16
Q5	2	0	0	16	2	143	7	3	304	9	266	11
Q6	2	0	0	7	1	101	12	1	387	6	335	12
Q7	2	0	0	1	2	32	13	0	274	4	327	10
Q8	2	0	0	0	0	25	6	0	168	3	263	6
Q9	2	0	0	6	0	24	2	0	98	3	236	7
Q10	2	0	0	8	2	132	18	2	449	5	346	17
Q11	2	0	0	10	3	163	24	1	455	11	251	17
Q12	2	0	0	45	3	193	16	1	317	10	275	16
Q13	2	0	0	0	0	16	2	0	112	1	273	13
Q14	2	0	0	2	1	50	1	1	166	6	292	12
Q15	2	0	0	14	1	53	8	2	232	5	297	16
Q16	2	0	0	6	2	97	16	1	367	10	342	17
Percentage of ‘sub-score 2’ (A lot)		0	0	**2.7**	**8.8**	**15.8**	**25.8**	**13.0**	**44.2**	**36.5**	**80.9**	**73.5**

2.3.4 Sub-Group Analysis

A sub-group analysis based on gender and age showed that the proposed FROM-16 score bands and GQ score bands were highly comparable, indicating further validity of the proposed banding (Table 2.9 and 2.10).

Table 2.9 Sub-group analysis of proposed banding based on Gender

Gender			Banding GQ					Total (%)
			No Effect	Small Effect	Moderate Effect	Very Large Effect	Extremely Large Effect	
Female	Set D	Band 0	27	25	2	0	0	54 (2%)
		Band 1	42	327	150	15	0	534 (19%)
		Band 2	2	146	468	229	32	877 (31%)
		Band 3	0	11	225	506	232	974 (34%)
		Band 4	0	0	11	117	291	419 (15%)
	Total (%)		71 (2%)	509 (18%)	856 (30%)	867 (30%)	555 (19%)	2858
Male	Set D	Band 0	32	33	1	0	0	66 (4%)
		Band 1	31	263	127	19	1	441 (29%)
		Band 2	10	121	296	108	17	552 (36%)
		Band 3	1	6	115	184	56	362 (24%)
		Band 4	1	0	5	37	69	112 (7%)
	Total (%)		75 (5%)	423 (28%)	544 (35%)	348 (23%)	143 (9%)	1533

Table 2.10 Sub-group analysis of proposed banding based on Age

Age Group			Banding GQ					Total (%)
			No Effect	Small Effect	Moderate Effect	Very Large Effect	Extremely Large Effect	
Group 1	Set D	Band 0	28	25	1	0	0	54 (2%)
(18-59)		Band 1	37	290	112	10	0	449 (21%)
		Band 2	7	149	371	143	20	690 (32%)
		Band 3	1	11	203	355	133	703 (32%)
		Band 4	1		10	96	187	294(13%)
	Total (%)		74 (3%)	475 (22%)	697 (32%)	604 (28%)	340 (15%)	2190
Group 2	Set D	Band 0	33	34	2	0	0	69 (3%)
(60-95)		Band 1	37	301	167	24	1	530 (24%)
		Band 2	5	119	394	195	29	742 (32%)
		Band 3	0	6	140	338	156	640 (29%)
		Band 4	0	0	6	59	177	242 (11%)
	Total (%)		75 (3%)	460 (21%)	709 (32%)	616 (28%)	363 (16%)	2223

Table 2.9 shows more females than males in the ‘extremely large effect’ category and more males than females in the 'no effect' category, indicating that females are impacted more by their relative's health condition (Table 2.9).
The Table 2.10 shows more people from group 1 (18-59 years) than group 2 (60-95 years) in ‘very large effect’ and ‘extremely large effect’ categories, indicating younger family members experienced more impact from their relative's health condition (Table 2.10).

2.4 DISCUSSION

There has been great interest in measuring family quality of life (FQoL) in recent years. Several instruments have been developed to assess the impact of a person's health condition/disability on family members/partners in order to understand this secondary and often unrecognised burden of disease (Shah et al. 2021b). Although the reliability and validity of several FQoL instruments have been established, they are not yet accepted in clinical practice. The assessment of the meaningfulness of the scores of an instrument and the practicality of its use in a clinical setting are the most important characteristics that enhance the value of an instrument once conventional psychometric requirements are met in particular content and face validity. Prinsen et al. (2018) argue that content and face validity are the most important measurement properties as they ensure that the items of the PROM are relevant, comprehensive, and comprehensible with respect to the construct of interest and study population. These properties, which ensure a strong psychometric foundation of an instrument, are vital for score interpretation to be meaningful and relevant.

The FROM-16 is the only generic user-friendly FQoL instrument: it has a 2–3 minute completion time, making it a practical tool for use in a clinical setting to measure the family impact of a person with a disease. However, to support the use of FROM-16 across all disciplines of medicine, there is a need for the scores to be meaningful and be easily interpreted in the context of the individual patient to support holistic clinical decision-making. Such information will assist clinicians in identifying at-risk and high-risk family members and providing or directing them to appropriate support services.

Therefore, the purpose of this study was to establish score bands for FROM-16, making overall scores more meaningful while complementing the information that can be gained by examining the detailed sub-scores of FROM-16.

Multiple FROM-16 band sets were devised as a result of the mapping of GQ summary scores to the total FROM-16 score and ROC AUC analysis. The band set with the best agreement with GQ based on weighted Kappa was selected. The weighted kappa-coefficients of various banding sets of FROM-16 scores ranged from 0.574 to 0.596, implying a moderate strength of agreement between the banding sets and GQ.

The banding set proposed for FROM-16 (0–1, 2–8, 9–16, 17–25, 26–32) is robust, pragmatic as well as easy to remember, making it suitable for routine use in clinical settings. Furthermore, it is also easy to remember that once a FROM-16 score goes above the halfway point of 16, this suggests a person's health condition is having a "very large effect" on their family member's QoL. This will mean that clinicians can now identify at a quick glance previously hidden secondary burden and direct impacted family members to the right kind of support.

Although there was substantial agreement between the family members' global rating of overall impact and predicted FROM-16 banding, 3% of the family members' FROM-16 scores fell outside the proposed banding by two points (Table 2.6). The anonymous nature of the study does not allow us to make a more detailed analysis of factors that contributed to these outliers. A few family members recorded a high GQ score, but a low FROM-16 score. A possible explanation for this anomaly could be that family members might have been overwhelmed by (only) one or more FROM-16 items that impacted their life negatively, resulting in high GQ scores but low FROM-16 scores. There is support for this from the sub-score comparison of individual FROM-16 items of family members, which showed that family members who had higher GQ scores than their FROM-16 scores when responding were more likely to mark FROM-16 items with an extreme value (“a lot”) (Table 2.7).

Men and women may perceive QoL differently (Harlow et al. 2000; Wijnhoven et al. 2003). In this study, although there was a significant difference in total FROM-16 mean scores and GQ scores between the genders and a significant difference in total FROM-16 mean scores between two age groups (18-59 and 60-95 years), the difference was not obvious in the banding. Therefore, separate banding based on gender and age was

not considered appropriate and anyway could have led to potential confusion in practice.

The sub-group analysis of proposed banding based on gender revealed a higher percentage of females in the "very large effect" and "extremely large effect" categories, indicating that females are impacted more by their relative's health condition than males. Also, the sub-group analysis based on age showed a higher percentage of family members from the lower age group (under 60 years) in "very large effect" and extremely large effect" groups than older respondents, however, their GQ scores were similar. This could be explained on the basis that 47.5% of family members caring for their relatives were in paid employment and possibly overburdened by work, family duties and caring. As FROM-16 items allowed family members to express this impact, this may have contributed to mean FROM-16 scores being higher for family members aged under 60 years than for over 60 years.

Although the descriptive analysis was used as a primary method to find cut-off values for total FROM-16 score using an anchor-based method, ROC analysis was employed as a secondary method to identify the most optimal score cut-offs defining FROM-16 score categories (score bands) representing different levels of QoL impairment in family members. The descriptive analysis method for banding was chosen because of its simplicity. The bar graph between FROM-16 total scores and GQ scores is very informative as it visually displays possible banding options, making it easier for even a lay person to understand the most suitable cut-offs. However, ROC analysis, on the other hand, was chosen because sensitivity and specificity values contribute to the validity of the test while determining the cut-off score. Sensitivity represents the probability of correct detection of positive cases (i.e., the extent to which family members that should belong to a particular band or category are included in that band). On the other hand, specificity reports the probability of correct identification of negative cases (i.e., the extent to which family members that should not belong to a particular band or category are excluded from that band), thus offering values related to the correctness of the classification of family members. However, in this study, ROC analysis appeared to be less helpful in guiding FROM-16 banding. The value of the weighted Kappa was the lowest for ROC banding, indicating lower alignment with anchor categories. This is consistent with the findings of another study where ROC analysis did not result in an ideal banding set (Gupta et al. 2019). Nevertheless, the

FROM-16 score ≥17 indicated a large impact on family members across all banding sets, including ROC banding.

This study has several strengths. One of the key strengths is the large sample size involving family members/partners of people with over 200 different health conditions. Another strength is the heterogeneous population involving family members of people with health conditions across England, Northern Ireland, Scotland and Wales. Both add to the generalisability of the findings; however, this study did not seek to revalidate these results across other countries.

2.5 CONCLUSIONS

This study provides the first data regarding the interpretability of the FROM-16 scores, using an anchor-based approach, making it the only family QoL measure with validated score bands. These score-meaning bands can now be applied in retrospect to previously published FROM-16 data and prospectively in future research studies.

2.6 SUMMARY

- Family members and partners of patients across 27 medical specialities were recruited in the cross-sectional study through 58 patient support groups, three research support platforms (HWW, JDR, ARC), and Welsh Social Services Departments.

- The family members/partners completed a FROM-16 questionnaire and a 5-point Likert scale global question to rate the overall impact of their relative's heath condition question (GQ) on their QoL.

- Data analysis used an anchor-based approach to create FROM-16 score banding, which involved comparing FROM-16 score to GQ summary scores (mean median and mode). Mean, median and mode were used to group the

FROM-16 scores into five discrete bands, with each FROM-16 band corresponding to a GQ band.

- Numerical cut-off points were considered based on FROM-16 scores that corresponded to a one-step increase in mean, median, and/or mode on the anchor. In case of the overlap between some of the possible discrete categories where a number of FROM-16 scores could have fitted into one of two categories, cut-offs of the FROM-16 score for both possibilities were considered.

- ROC-AUC analysis was used as a separate method for finding cut-off scores between FROM-16 and GQ bands.

- Final cut-off values for FROM score banding was chosen based on weighted Kappa.

- The cut-off value showing a greater agreement between FROM-16 and GQ score indicated by a higher value of weighted Kappa was chosen as the final score banding.

- Final FROM-16 banding are bands: 0-1=No effect, 2-8=Small effect, 9-16=Moderate effect, 17-25=Very large effect, 26-32=Extremely large effect.

CHAPTER 3

Development of an Algorithm for Mapping FROM-16 Scores to EQ-5D-3L Utility Values

3.1 INTRODUCTION

Public healthcare decision-making is increasingly informed by economic analyses of medical interventions. This is important to ensure best use of limited resources in publicly funded health systems such as the NHS. Health economists compare the costs and outcomes of an intervention with the best alternatives to offer information on the cost-effectiveness of healthcare. Currently, such analysis is focused only on outcomes for the patient (Pennington 2020). However, new treatments that improve patients' QoL can also improve the QoL of their family members/partners (Finlay et al. 2022). There may be direct impacts on the QoL of family members (family carers) from medical interventions and also indirect impacts from changes in the patient's health and care requirements. While caring for one's relative can be a rewarding and fulfilling experience, it is nonetheless challenging, sometimes leaving family members/partners of the patient physically and emotionally drained. The impact of caring on the health of family members, mostly termed as 'caring effect', 'family effect' or 'family impact', is well documented (Gallagher and Mechanic 1996; Pinquart and Sörensen 2003; Brouwer 2006; Schulz and Beach 1999) and in many cases exerts a comparable and significant impact on an individual's health (Bobinac et al. 2011), but its economic impact (both direct and indirect) and value to the society has been rarely measured and factored into policy making. Therefore, ignoring this potentially large impact on health-related QoL (HRQoL) of patients' family members/partners may result in inequitable and inefficient evaluation of a medical intervention (Brouwer 2019).

Although the inclusion of family members/informal carers in economic evaluations, where relevant, is encouraged by many health technology assessment agencies, including the National Institute for Health and Care Excellence (NICE), it is seldom reported (Basarir et al. 2019). Some researchers attribute this under-reporting to uncertainty about decision-makers' attitudes toward their inclusion, issues related to how they may be incorporated into economic models, and the availability of suitable utility measures for carers/family members (Basarir et al. 2019). Other researchers have attributed the lack of carer data as the reason for not including this impact in CEAs (Pennington 2020; ICER 2019; Leech et al. 2023). Although all these may be contributing factors for not including carer utility in health economic evaluation, the latter seems to provide a more plausible explanation as a family member/informal carer

inclusion in HTA is a fairly new recommendation with currently no family members/carer data being collected in clinical trials or alongside patient registries. This is a significant research gap that needs to be filled to ensure the inclusion of family members/informal carers in health economic evaluation of medical interventions.

3.2 AIMS & OBJECTIVES

To map FROM-16 scores to EQ-5D-3L utility values to allow the use of FROM-16 in health economic evaluation through:

- Examining the relationship between the FROM-16 and EQ-5D and suggesting a suitable approach for building the mapping model using ordinal logistic regression or multinomial regression
- Constructing a model using the data from a cross-sectional study
- Using the model to predict EQ-5D utility values, testing for accuracy and validity by comparing predicted and actual values.

3.3 METHODS

3.3.1 Data

The data for this study were collected at the same time as the FROM-16 banding study in an online cross-sectional study addressing the FROM-16 score interpretation conducted between April and November 2021. Family members/partners of patients with different health conditions were recruited through 58 UK-based patient support groups, research support platforms [Healthwise Wales-(Hurt et al. 2019), Autism Research Centre-Cambridge University database, Join Dementia Research (JDR)] and Welsh Social Services Departments. Ethical approval for the study was granted by the Cardiff University School of Medicine Research Ethics Committee (SREC reference: 21/19), which conforms to the principles embodied in the Declaration of Helsinki. The study was open to family members/partners (aged ≥18 years) of patients with any health condition living in the UK. Study design, ethical considerations, inclusion/exclusion criteria, sampling, survey design, participant recruitment and PPIE are the same as referred to in Chapter 2.

For this study, family members/partners of patients completed the FROM-16 (Appendix I) and EQ-5D-3L (Appendix XI) questionnaires (Figure 2.1).

3.3.2 EQ-5D-3L

The EQ-5D-3L (Euroqol 5 Dimension 3 level) is a generic HRQoL questionnaire which measures preferences associated with a particular health state. The EQ-5D consists of 5 dimensions (mobility, self-care, usual activities, pain, and anxiety), each with three levels (no problem, some problems, and extreme problems) coded from 1 to 3 (Appendix XI). The EQ-5D-3L descriptive system presents 243 health states that are combined to calculate a single index, where the best health status is "11111", and the worst is "33333". In this PhD project, the index was calculated using the set of specific values (Tariffs) of the UK version of the EQ-5D-3L (Dolan et al.1996). In this tariff, the utility values attached to different EQ-5D health states range from 0.594 to 1, where 1 is defined as perfect health, 0 represents death, and negative values denote health states worse than death. Although other preference-based measures such as HIU, SF-6D, and EQ-5D-5L can be used for utility analysis, EQ-5D-3L was chosen as it is NICE's preferred utility measure for use in health economic evaluation of medical interventions in the UK (Räsänen et al. 2006; NICE 2013). The aim of this study was to map FROM-16 scores to the EQ-5D-3L utility to allow the use of FROM-16 data in heath-economic evaluation when the EQ-5D-3L data is not available.

3.3.3 Mapping

Mapping is defined as 'the development and use of a model or algorithm to predict utility values using data on other indicators or measures of health' (Longworth and Rowen 2011). Mapping is a useful technique that may be particularly of value in situations where descriptive HRQoL scores have been collected and from which researchers need to derive utility values.

There are two types of mapping techniques: direct mapping and indirect or response mapping. Direct mapping uses either the total or subdomain scores to predict preference-based measure (PBM) utility values, while response mapping predicts EQ-5D responses for utilities from the responses on other measures. The most common approach used for direct mapping is the Ordinary Least Squares (OLS).

However, this method has several limitations. First, it assumes that utilities are continuously distributed, and therefore, the probability of the utility value of 1.0 cannot be achieved (Gray et al. 2006). Secondly, in the case of ceiling effects, OLS can produce inconsistent estimates of the coefficients of explanatory variables. Although in recent years, other methods of direct mapping have been explored to overcome these issues (Kiadaliri et al. 2020, Gray et al. 2021), these alternative methods can only provide mapping for a single set of utility values relevant to the country of tariff used. In contrast, response mapping predicts EQ-5D dimension responses from non-PBM, which can be used to derive utility values using any country-specific tariff (Gray et al. 2006). In this study, response mapping was used to predict EQ-5D health utility estimates from FROM-16 responses using regression analysis to allow the use of FROM-16 in health economic evaluation.

Van Hout et al. (2012) argue that analysis for mapping or cross-walking exercises should be restricted to logically consistent responses. The illogical responses may be assumed as random errors. For example, these authors considered responses "inconsistent" when a 3L response corresponded to a 5L response that was two, three, or four levels away (e.g., 1 on 3L with 3 on 5L; or 2 on 3L with 1 on 5L). In this study, responses were considered "inconsistent" if the FROM-16 total score was ≥17 (indicating a very large impact on QoL according to FROM-16 banding criteria) and the EQ-5D utility value was "1" (indicating perfect health) within the same subject. However, an important consideration involved whether to use all data or to restrict the analysis to logically consistent responses. To address this point, the analysis was conducted on the full data set as well as on one with such responses excluded to check whether the model could be improved by removing inconsistent responses.

3.3.4 Data Processing and Statistical Analysis

The frequencies and percentages of each response category of the items of both questionnaires were calculated, along with the mean and standard deviation (SD) for the continuous variables. The distributions of the EQ-5D-3L utility values and FROM-16 dimensions were graphically displayed using histograms, and normality was checked using Shapiro–Wilk's test. Spearman correlations between the EQ-5D-3L utility values and the FROM-16 total score were also calculated. The utility values in this study were

calculated using a SPSS syntax, which was available upon request from EuroQol (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-3l-value-sets.html) (Appendix XII). This syntax calculates individual utility values depending on a subject's EQ-5D domain scores. Most of the analysis was carried out using SPSS version 27, however, the study also used other types of software. SAS version 9.4 was employed for conducting non-proportional odds regression. The SAS was also used to generate cumulative graphs comparing family members' predicted utility values to observed utilities. The 'R' software (a free software environment for statistical computing and graphics) was used to repeat the Monte Carlo simulation 1000 times. R was chosen because it is capable of handling very complicated calculations with little effort, allowing one to summarize results in tables with a user specified ordering of rows and columns. Microsoft Excel was used to generate a random number using uniform distribution for Monte Carlo simulation and to calculate predicted utility values for family members (using EQ-5D probabilities predicted from regression analysis and the expected utility formula). Microsoft Excel was also used to calculate the mean error, mean square error, root mean square error and mean absolute error between observed and predicted utilities. The final algorithm for utility conversion of FROM-16 scores to EQ-5D utility values was also created using Excel.

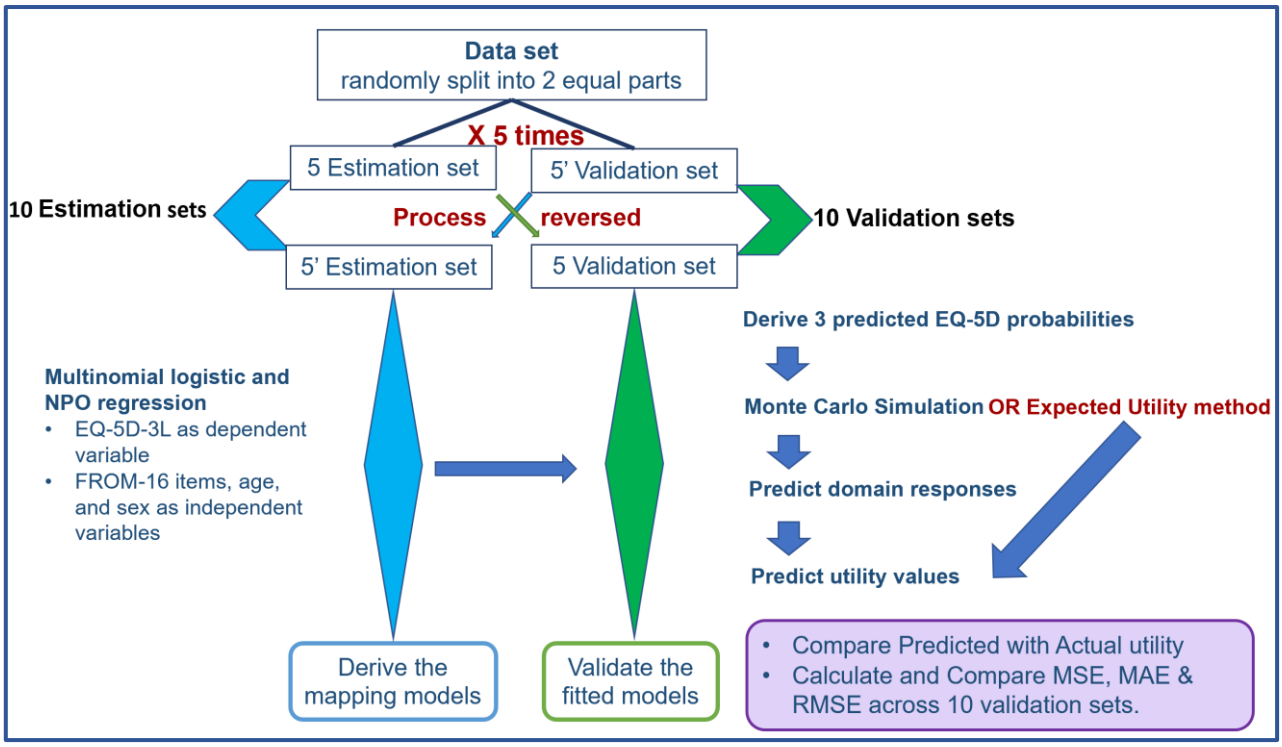
3.3.4.1 Response mapping of FROM-16 to EQ-5D-3L

3.3.4.1.1 SPLIT-HALF CROSS-VALIDATION METHOD

This study employed the split-half validation method used by Ali et al. (2017) for mapping the Dermatology Life Quality Index (DLQI) to EQ-5D, whereby the dataset was randomly split five times into separate estimation and validation sets, using the random number generator in SPSS version 27. The estimation set was used to derive the mapping models, whereas the out-of-sample validation set was utilised for validating the fitted models (Figure 3.1). The five estimation and validation sets were then switched, and the process was repeated (split-half cross-validation), resulting in a total of ten validation sets. The split-half cross-validation method not only improves the overall accuracy of the model but is also able to demonstrate that the accuracy of the predicted utility values is not due to chance (Ali et al. 2017). However, it could be argued that use of this method reduces the sample size of the estimation sample,

leading to reduced precision. In this study, this issue was addressed by re-estimating the model using the full data set after the model had been assessed using the split-half approach (Longworth and Rowen 2013).

Figure 3.1 Flow diagram: Response mapping of FROM-16 to EQ-5D-3L using Split-Half Cross-validation method



Furthermore, the split-half method was seen as the best modelling approach when no external dataset is available to perform external validation, demonstrating how the model will behave outside the sample (Longworth and Rowen 2013).

3.3.4.1.1.1 Model derivation

The multinomial logistic regression (mlogit) and non-proportional odds regression (NPOR) were conducted for each estimation dataset using FROM-16 items, age and sex as independent variables. As the dependent variables (EQ-5D-3L) are ordinal in nature, ordinal logistic regression would be the preferred method. However, the ordered logit model relies on an assumption of proportional odds or parallel regression, which means it generates a set of binary response models for the different ordered categories, in which the intercept varies, but the coefficients for the explanatory variables are the same. The study first attempted ordinal logistic regression but found

that the assumption of proportional odds was violated for all dimensions of EQ-5D-3L (the test for parallelism within SPSS gave significant results for all five EQ-5D dimensions, indicating violation of the proportional odds assumption). Therefore, the alternative methods mlogit and NPOR were used to derive the model.

3.3.4.1.1.1.1 Multinomial logistic regression

Multinomial logistic regression is a type of logistic regression which is used when the outcome variable being predicted is nominal and has more than two categories that do not have a given rank or order. This model can be used even with an ordinal outcome if the proportional odds assumption is not met (Norusis 2005). Furthermore, the multinomial logit model avoids the parallel regression assumption and provides unbiased parameter estimates (Gray et al. 2006). Sainani (2021) demonstrated that the multinomial and ordinal logistic models give similar results, including similar predicted probabilities for the same data, indicating that both models can be used for ordinal data. The advantage of choosing ordinal logistic regression over multinomial is that it increases statistical power as it uses all the data to estimate a single slope/odds ratio compared to multinomial, which estimates multiple slopes with smaller subsets of the data. However, it also means that ordinal logistic regression estimates an average effect of the predictor across all outcome levels, so if the effects are in fact different, the model will miss this (Sainani 2021).

Multinomial regression is a multi-equation model, where an outcome variable with K categories will generate K-1 equations, each of which is a binary logistic regression that compares that group with a reference group, and each of which yields a probability that the observation falls into that category given a particular vector of independent variables (FROM-16 responses, age, and gender). In the case of EQ-5D, there are three categories resulting in two equations.

The probability equation for multinomial regression is given below:

$$P(Y=1) = \frac{1}{1+exp(\alpha_2+\beta_2 X)+exp\,(\alpha_3+\beta_3 X)}$$

$$P(Y=2) = \frac{exp\,(\alpha_2+\beta_2 X)}{1+exp(\alpha_2+\beta_2 X)+exp\,(\alpha_3+\beta_3 X)}$$

$$P(Y=3) = \frac{\exp\,(\alpha_3+\beta_3 X)}{1+exp(\alpha_2+\beta_2 X)+exp\,(\alpha_3+\beta_3 X)}$$

Y' represents the outcome of any given EQ-5D domain (''mobility,'' ''self-care,'' ''usual activities,'' ''pain/discomfort,'' or ''anxiety/depression''). The outcome categories *Y*=1,2, and 3 represent the three possible responses for a given EQ-5D domain, i.e., ''no problems,'' ''some problems,'' or ''extreme problems,'' respectively. The *X* are indicator variables derived from FROM-16 item scores, age, and sex (sex was coded as 0=male and 1=female), while the β's are the regression coefficients associated with the FROM-16 items for a particular level.

3.3.4.1.1.1.2 Non-proportional ordinal logistic regression

Another alternative to ordinal logistic regression is non-proportional ordinal regression (NPOR), which treats outcome variables as ordinal but allows coefficients for explanatory variables to vary. In this study, it was used as another method to explore the relationship between EQ-5D-3L and FROM-16. The SPSS software does not include the technique of NPOR, so a different software program, Statistical Analysis System (SAS), was used to carry out the analysis using the syntax below:

```
Proc logistic data=rub;*Fit unequal slopes;

class fmgender(ref='0') / param=ref; model eq_mobility = fmage fmgender f_worried f_angry f_sad
F_Frustrated F_Talkingaboutthoughts F_Difficultycaring F_Timeforself F_Travel F_Eatinghabits
F_Familyactivities F_Holiday F_Sexlife F_Workorstudy F_Familyrelationships F_Familyexpenses
F_Sleep / unequalslopes;
 run;
```

The above SAS syntax is for the “mobility model” of EQ-5D. The syntax was repeated, replacing “model eq mobility” with “model eq selfcare”, “model eq activity”, “model eq pain” and “model eq anxiety” to derive models for all EQ-5D dimensions.

Once the regression analysis was carried out, the probability was estimated using the formula below (Lund, 2019):

Assuming there are 3 levels for ordered target Y: A, B, C and there are 3 numeric predictors R, S and Z. Let pk,j=probability that k^{th} observation has the target value j=A, B or C.

In this example, the NPOR Model will be represented by two equations:

$\text{Log}\ (p_{k,A} / (p_{k,B} + p_{k,C})) = \alpha_A + \beta R_{,A} * Rk + \beta S_{,A} * Sk + \beta Z_{,A} * Zk$

$\text{Log}\ (p_{k,A} + p_{k,B}) / p_{k,C}) = \alpha_B + \beta R_{,B} * Rk + \beta S_{,B} * Sk + \beta Z_{,B} * Zk$

Here, R, S and Z have different coefficients for the two response equations. Predictors R, S and Z are said to have “unequal slopes”.

Formulas for the probabilities pk,A, pk,B, pk,C can be derived from the two response equations.

To simplify the formulas, let T_k and U_k, for the k^{th} observation, be defined by the equations below:

T_k	$=EXP(\alpha_A + \beta R_{,A} * Rk + \beta S_{,A} * Sk + \beta Z_{,A} * Zk)$
U_k	$=EXP(\alpha_B + \beta R_{,B} * Rk + \beta S_{,B} * Sk + \beta Z_{,B} * Zk)$
Response	Probability Formula
A	$P_{k,A} = 1 - 1/(1+Tk)$
B	$P_{k,B} = 1/(1+Tk) - 1/(1+Uk)$

Adapted from Lund (2019).

3.3.4.1.1.2 Model validation

3.3.4.1.1.2.1 Predicting probabilities

The model was tested on each validation dataset to produce three predicted probabilities per subject per EQ- 5D domain (*Y*=1, 2, or 3).

3.3.4.1.1.2.2 Predicting EQ-5D-3L utilities

The average predicted health utilities were estimated using Monte Carlo simulation and Expected utility methods (Le and Doctor 2011) for each validation set and then compared with the observed health utility estimate of the same set.

3.3.4.1.1.2.2.1 Monte Carlo Simulation

The Monte Carlo methods are a class of techniques for randomly sampling a probability distribution. This method was first used by Gray et al. (2006) in mapping EQ-5D to SF12. It involves generating random numbers between '0' and '1' with a uniform distribution and then assigning to each individual one of the three response levels for each EQ-5D domain by comparing the random number with the predicted probabilities. This approach has been shown to produce a more accurate distribution of responses in each EQ-5D dimension (Gray et al. 2006). For each dimension, three probabilities were available and can be expressed as Pr ($\widehat{y_i}$=1), Pr ($\widehat{y_i}$=2) and Pr ($\widehat{y_i}$=3), with the hat on y indicating a predicted value. Random numbers with a uniform distribution $ui \sim$ uniform (0,1) were compared with these probabilities to predict the response in each EQ-5D dimension for each individual using the following formula (Rivero-Arias et al. 2010; Ramos-Goñi et al. 2013):

$$\widehat{y_i} = \begin{cases} 1 & if\ ui\ \leq \Pr(\widehat{y_i} = 1) \\ 2\ if\ ui\ > Pr(\widehat{y_i} = 1) and\ ui\ \leq Pr(\widehat{y_i} = 1) + Pr(\widehat{y_i} = 2) \\ 3 & if\ ui\ > 1 - \Pr(\widehat{y_i} = 3) \end{cases}$$

Monte Carlo simulation was run for each subject resulting in predicted responses for each of the EQ-5D dimensions (mobility, self-care, usual activities, pain, and anxiety) and, consequently, health utility estimates. The Monte Carlo method ensures that unbiased expected values are obtained and fit individuals into the EQ-5D descriptive system, allowing the predicted utility score or tariff to be calculated using the UK time trade-off (TTO) (Dolan et al. 1996).

3.3.4.1.1.2.2.2 Expected Utility Method

This method was used as an alternative method in this study to predict EQ-5D utilities. This uses the population-based EQ-5D-3L scoring system (Le and Doctor 2011) to

estimate the EQ-5D utility scores for individuals from predicted probabilities to the response levels. The Expected utilities were derived using the formula given in the text box:

Predicted EQ-5D Utility Score=1- [Expected_Disutility(mobility) + Expected _ Disutility(selfcare) + Expected_Disutility(usual activities) + Expected_Disutility(pain/ discomfort) + Expected_Disutility(anxiety/depression) + Expected_ Disutility(any response with some/severe problems) + Expected_Disutility(any response with severe problems)]

where, the Expected Disutility were calculated using formula described by (Le and Doctor 2011), based on the UK population-based EQ-5D scoring system:

Expected_Disutility(mobility)=(0.069) x P_2(mobility) + (0.314) x P_3 (mobility)
Expected_Disutility (selfcare)=(0.104) x P_2(selfcare) + (0.214) x P_3(selfcare)
Expected_Disutility(usual activities)=0.036) x P_2(usual activities)+(0.094) x P_3(usual activities)
Expected_Disutility(pain/discomfort)=(0.123) x P_2(pain/discomfort)+(0.386) x P_3(pain/discomfort)
Expected_Disutility(anxiety/depression)=(0.071) x P_2(anxiety/depression) + (0.286) x P_3(anxiety/depression)

Expected_Disutility (any response with some/severe problems)=(0.081) x P (any response with some/severe problems)
=(0.081) * [1-P_1(mobility) x P_1 (selfcare) x P_1(usual activities) x P_1 (pain/discomfort) x P_1 (anxiety/depression)]

Expected_Disutility (any response with severe problems)=(0.269) x P (any response with severe problems)=(0.269) x {1 - [1- P_3(mobility)] x [1 -P_3(selfcare)] x [1 - P_3(usual activities)] x [1 - P_3(pain/discomfort)] x [1 - P_3(anxiety/depression)]

Here P_1, P_2, and P3 represent predicted probabilities (derived from regression analysis) for an individual family member for being in EQ-5D level 1, 2, or 3.

3.3.4.1.1.3 Testing model accuracy and validity

Mean square error (MSE), root mean square (RMSE) and mean absolute error (MAE) were compared and averaged across ten validation models and plots and histograms of observed and predicted utilities were also examined. While smaller errors are preferred, these may not necessarily be representative of the errors in the estimates when the results are applied to an external dataset. However, they can provide some indication about the magnitude of expected errors (Longworth and Rowen 2011). The final model algorithm was derived using the entire sample. The final algorithm was based on the entire sample of family members/ partners (Longworth and Rowen 2013).

3.4 RESULTS

3.4.1 Sociodemographic Characteristics of the Study Participants

A total of 4413 family members/partners of patients across 27 medical specialities (Table 3.1), with the majority from England and Wales, completed the EQ-5D and FROM-16 questionnaires.

Table 3.1 Medical specialities included in the study

	Medical specialities	**Dataset 4,390 N (%)**	**Dataset 4,228 N (%)**
1	Neurology	1612 (36.7)	1522 (36.0)
2	Psychiatry	321 (7.3)	311 (7.4)
3	Rheumatology	310 (7.1)	302 (7.1)
4	Endocrinology	270 (6.2)	266 (6.3)
5	Respiratory medicine	266 (6.1)	261 (6.2)
6	Oncology	251 (5.7)	241 (5.7)
7	Cardiology	241 (5.5)	239 (5.7)
8	Haematology	183 (4.2)	179 (4.2)
9	Gastroenterology	153 (3.5)	151 (3.6)
10	Paediatrics	142 (3.2)	134 (3.2)
11	Dermatology	135 (3.1)	127 (3.0)
12	Ophthalmology	89 (2.0)	89 (2.1)
13	Nephrology	58 (1.3)	55 (1.3)
14	Genetic/ Rare diseases	44 (1.0)	44 (1.0)
15	Gynaecology	38 (0.9)	37 (0.9)
16	Rehabilitation medicine	30 (0.7)	30 (0.7)
17	Orthopaedics	24 (0.5)	24 (0.6)
18	Urology	21 (0.5)	21 (0.5)
19	Audiology	19 (0.4)	19 (0.4)
20	Immunology	12 (0.3)	12 (0.3)
21	Hepatology	10 (0.2)	10 (0.2)
22	Infectious diseases	10 (0.2)	10 (0.2)
23	Movement disorder	10 (0.2)	10 (0.2)
24	Chronic pain	7 (0.2)	7 (0.2)
25	Otolaryngology	6 (0.1)	6 (0.1)
26	Wound healing	2 (0.04)	1 (0.02)
27	Critical care	1 (0.02)	1 (0.02)
	Multiple health conditions	95 (2.2)	91 (2.2)
	Not stated	30 (0.7)	28 (0.7)

One response was discarded as the EQ-5D was completed by a patient instead of a family member. A further 22 family members did not specify gender and were excluded, leaving 4390 for analysis. Of the 4390 responses,162 were inconsistent. However, analysis was carried out on all data (4390) and data with excluded responses (4228) (Table 3.2).

Table 3.2 Demographics and descriptive statistics

Variables	Categories	N(%) or Mean (SD) (n=4390)	N(%) or Mean (SD) (n=4228)
Patients			
Gender	Male	1990 (45.3%)	1928 (45.6%)
	Female	2390 (54.4%)	2290 (54.2%)
	Prefer not to say	4 (0.1%)	4 (0.1%)
	Other	6 (0.1%)	6 (0.1%)
Age (years)	Mean (SD)	61.6 (20.18)	61.6 (20.18)
	Median	66	66
	Range (IQR)	2-100 (26)	2-100 (26)
Place of residence in the UK	England	1884 (42.9%)	1779 (42.1%)
	Northern Ireland	48 (1.1%)	45 (1.1%)
	Scotland	184 (4.2%)	175 (4.1%)
	Wales	2274 (51.8%)	2229 (52.7%)
Occupation	In paid work	878 (20%)	846 (20%)
	Part-time job	164 (3.7%)	160 (3.8%)
	Unemployed	323 (7.4%)	312 (7.4%)
	In unpaid work	22 (0.5%)	22 (0.5%)
	Education/training	98 (2.2%)	94 (2.2%)
	Homemaker	151 (3.4%)	145 (3.4%)
	Retired	2548 (58%)	2455 (58.1%)
	Rather not say	64 (1.5%)	60 (1.4%)
	Not applicable	142 (3.2%)	134 (3.2%)
Family members			
Gender	Male	1533 (34.9%)	1479 (35.0%)
	Female	2857 (65.1%)	2749 (65.0%)
Age (years)	Mean (SD)	57.50 (14.2)	57.69 (14.2)
	Median	60	60
	Range (IQR)	18-95 (20)	18-95 (20)
Relationship to patient	Spouse/partner	2620 (59.7)	2532 (59.9%)
	Son/daughter	970 (22.1)	921 (21.7%)
	Parent	517 (11.8%)	503 (11.9%)
	Other[†]	283 (6.4%)	272 (6.4%)
Occupation	In paid work	1722 (39.2%)	1629 (38.5%)
	Part-time job	365 (8.3%)	356 (8.4%)
	Unemployed	116 (2.6%)	114 (2.7%)
	In unpaid work	52 (1.2%)	48 (1.1%)
	Education/training	71 (1.6%)	66 (1.6%)
	Homemaker	209 (4.8%)	204 (4.8%)
	Retired	1805 (41.1%)	1761 (41.7%)
	Rather not say	50 (1.2%)	50 (1.2%)
FROM-16 and EQ-5D scores			
FROM-16 total score	Mean (SD)	15.01(8.0)	14.79 (8.1)
	Range	0-32	0-32
EQ-5D-3L utility score	Mean (SD)	0.685 (0.3)	0.673 (0.3)
	Range	-0.594 to 1	-0.594 to 1
EQ-VAS (n=4371)[a] (n=4209)[b]	Mean (SD)	68.86 (21.7)	68.44 (21.9)
	Range	0-100	0-100
FROM-16 & EQ-5D Correlation	r_s	-0.393**	-0.450**

*r_s: Spearman correlation coefficient; *Significant at 1%.*
Other[†]: Brother/Sister, Father/Mother-in-law, Grandparent, Uncle/Aunt, Grandson/Granddaughter, Brother/Sister-in-law, Nephew/Niece, Cousin, Friend; [a] EQ-5D-VAS responses are for 4371 instead of 4390 as 19 family members did not report VAS scores; [b] EQ-5D-VAS responses are for 4209 instead of 4228 as 19 family members did not report VAS scores.

Descriptive analysis of the two sets of data indicated that there was not much difference between them, indicating that exclusion of the “inconsistent” responses was

proportionate across the data set and did not induce bias. The mean (SD) age of family members was 57.5 (14.2) years for the 4390 data set and 57.7 (14.2) years for the 4228 data set, with 65% being female. The mean (SD) age of patients was 61.6 (20.2) years in both data sets, with 54% females. The family members were mostly the patient's spouse/partner (60%), followed by son/daughter (22%) and parent (12%) (Table 3.1). Almost half (47%) of the family members were in paid jobs compared to 24% of patients, while 41% of family members were retired compared to 58% of patients.

3.4.2 FROM-16 and EQ-5D Scores

The means (SD) of the FROM-16 total summary score and the EQ-5D-3L utility score were 14.8 (8.1) and 0.673 (0.331), respectively. Among the FROM-16 items, 'feeling worried' was the most frequently rated impact and 'effect on travel' was the least rated impact, whereas on the EQ-5D-3L domains, ‘anxiety/depression’ was the most frequently rated problem and 'selfcare' was the least frequently rated problem (Tables 3.3 and 3.4).

Table 3.3 FROM-16 individual item scores (n=4428)

FROM-16 item	Not at All N (%)	A little N (%)	A lot N (%)
Worried	239 (5.7)	1805 (42.7)	2184 (51.7)
Angry	1878 (44.4)	1638 (38.7)	712 (16.8)
Sad	645 (15.3)	1769 (41.8)	1814 (42.9)
Frustrated	791 (18.7)	1710 (40.4)	1727 (40.8)
Talking about thoughts	1599 (37.8)	1421 (33.6)	1208 (28.6)
Difficulty caring	1179 (27.9)	1748 (41.3)	1301 (30.8)
Time for self	1660 (39.3)	1543 (36.5)	1025 (24.2)
Travel	2553 (60.4)	991 (23.4)	684 (16.2)
Eating habits	2425 (57.4)	1242 (29.4)	561 (13.3)
Family activities	902 (21.3)	1821 (43.1)	1505 (35.6)
Holiday	1341 (31.7)	1294 (30.6)	1593 (37.7)
Sex life	1901 (45.0)	944 (22.3)	1383 (32.7)
Work/study	2496 (59.0)	1127 (26.7)	605 (14.3)
Family relationships	1929 (45.6)	1530 (36.2)	769 (18.2)
Family expenses	1769 (41.8)	1460 (34.5)	999 (23.6)
Sleep	1233 (29.20	1644 (38.9)	1351 (31.9)

Table 3.4 EQ-5D-3L dimension scores (n=4228)

EQ-5D dimensions	No problems N (%)	Some problems N (%)	Extreme problems N (%)
Mobility	2939 (69.5)	1231 (29.1)	58 (1.4)
Selfcare	3588 (84.9)	540 (12.8)	100 (2.4)
Usual activity	2468 (58.4)	1447 (34.2)	313 (7.4)
Pain and discomfort	2063 (48.8)	1780 (42.1)	385 (9.1)
Anxiety and depression	1618 (38.3)	2157 (51.0)	453 (10.7)

3.4.3 Characterising the Distribution and Conceptual Overlap

Figure 3.2 The distribution plots of the FROM-16 total scores; (a) Distribution of FROM-16 for 4390 dataset; (b) Distribution of FROM-16 for 4228 dataset

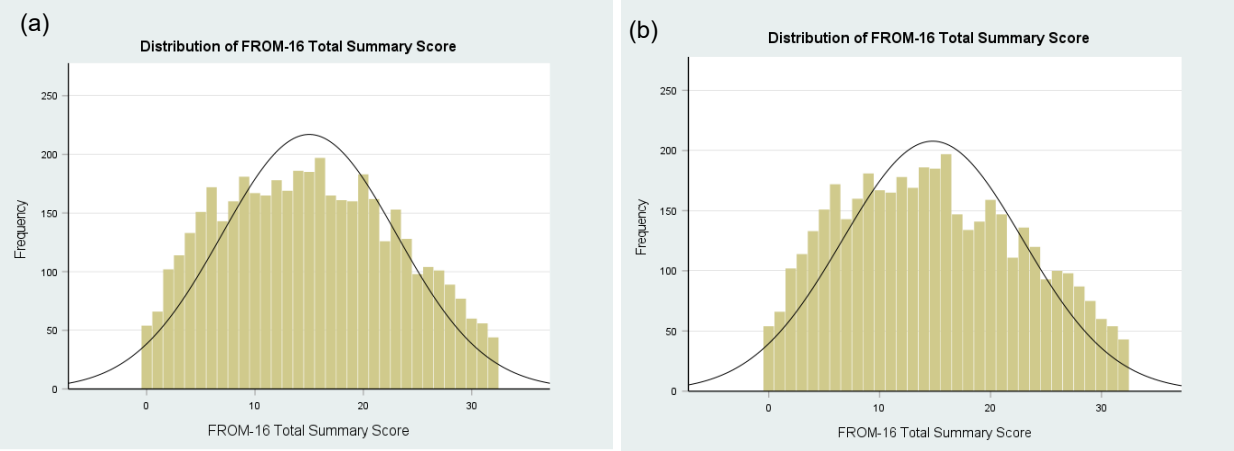
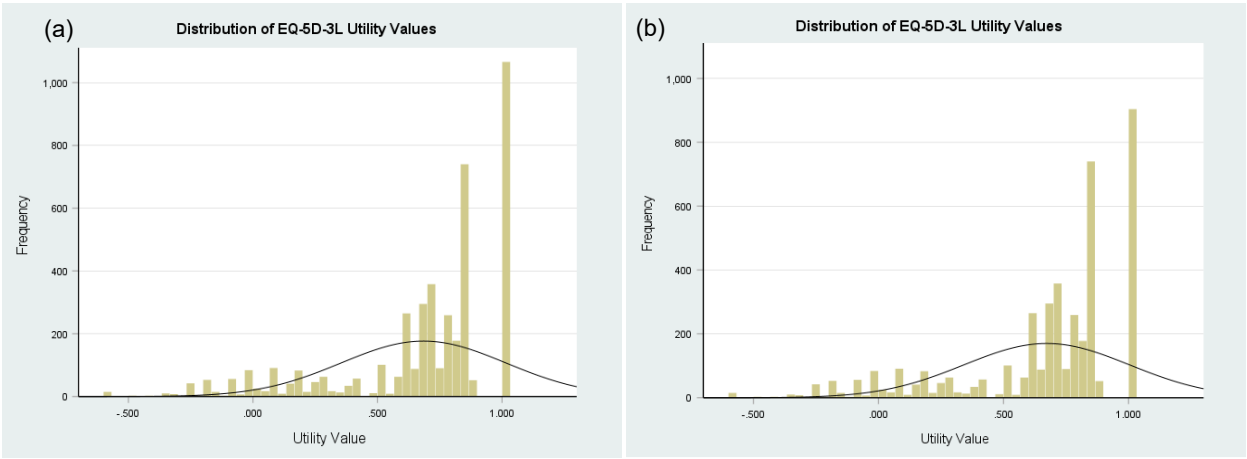


Figure 3.3 The distribution plots of the EQ-5D-3L utility scores; (a) Distribution of EQ-5D-3L for 4390 dataset, (b) Distribution of EQ-5D-3L for 4228 dataset



FROM-16 appears to be normally distributed in both the data sets (Figure 3.2), while EQ-5D-3L appears to be negatively skewed (Figure 3.3). Although the Shapiro–Wilk test was significant for FROM-16 and EQ-5D data sets indicating non-normality, for large sample sizes, histograms are more appropriate (Mishra et al. 2019). The correlation between the FROM-16 total summary score and the EQ-5D-3L utility scores was moderate, with a Spearman's rank correlation coefficient (r_s) of 0.39 ($p<0.001$) for dataset 4390 and (r_s) of 0.45 ($p<0.001$) for dataset 4228. However, the association between FROM-16 and EQ-5D-3L was stronger for data set 4228, indicating better conceptual overlap between the two measures.

The correlation between the FROM-16 domains and the EQ-5D domains was significant ($p<0.001$), with EQ-5D anxiety/depression strongly associated with FROM-16 emotional and personal/social domains and EQ-5D mobility least associated with both FROM-16 domains (Table 3.5).

Table 3.5 Correlation† between FROM-16 and EQ-5D-3L (n=4,228)

FROM-16	EQ-5D-3L Utility	Mobility	Selfcare	Usual activity	Pain/ Discomfort	Anxiety/ Depression
Emotional domain (items 1-6)		0.132**	0.176**	0.279**	0.165**	0.523**
Personal and social domain (items 7-16)		0.190**	0.220**	0.367**	0.239**	0.495**
FROM-16 total score	*0.450***					

† Spearman's rank correlation coefficient; ** p-value <0.001

Regression was run with age and sex alone, FROM-16 items alone, as well as age and sex combined with FROM-16 items (Table 3.6) to evaluate the contribution of age and sex, and collectively the FROM-16 items, and to see if the model could be improved by including age and sex as additional variables. Model comparisons were undertaken by comparing twice the absolute difference in the maximised log-likelihoods with the Chi-square distribution with degrees of freedom equal to the difference in the number of model terms being evaluated (Table 3.6). Due to the improved fit, it was hypothesised that these extra variables may improve the predictive ability of the models.

Table 3.6 Model comparison*using log-likelihood value to measure the goodness of fit

EQ-5D Domain	Covariates: age/sex			Covariates: FROM-16 items			Covariates: age/sex/FROM-16 items		
	-2 log-likelihood	Chi-square comparing to full model	Degrees of freedom (df)	-2 log-likelihood	Chi-square comparing to full model	Degrees of freedom (df)	-2 log-likelihood	Chi-square comparing to full model	Degrees of freedom (df)
Mobility	781.6	151.9	4	4946.9	341.9	32	5173.7	466.1	36
Selfcare	744.8	12.6	4	3582.8	342.2	32	3772.6	352.6	36
Usual activities	1049.8	50.7	4	6258.6	712.0	32	6589.8	764.1	36
Pain and discomfort	1068.3	114.8	4	6885.2	448.4	32	7279.9	551.8	36
Anxiety and depression	1078.1	177.3	4	5975.6	1642.9	32	6298.1	1703.2	36

**The model containing FROM-16 items only and age and sex only compared to the model containing age, sex, and the FROM-16 items for each EQ-5D domain*

3.4.4 Split-Half Cross-Validation and Model Performance

Five times random split of the entire sample (n=4390) into two parts resulted in five derivation and five validation sets of 2195 family members each. For each of the five EQ-5D domains, an mlogit model was derived and used to predict the probability of each EQ-5D response for each subject in each validation set using Monte Carlo simulation (Figure 3.1), and subsequently, the health utility was estimated. The health utility estimates were also calculated using the Expected utility method. The predicted utilities for each validation set were compared to the observed utility (Tables 3.7 and 3.8).

For the Monte Carlo method, the mean square error (MSE) across all ten validation sets ranged from 0.114 to 0.146 with an average of 0.137, Root Mean Square Error (RMSE) ranged from 0.357 to 0.385 (average of 0.373) and the mean absolute error (MAE) across all ten validation sets ranged from 0.257 to 0.283 with an average of 0.272 (Table 3.7).

For Expected methods, MSE across all ten validation sets ranged from 0.082 to 0.095 with an average of 0.090, RMSE ranged from 0.287 to 0.308 with an average of 0.301, and MAE ranged from 0.220 to 0.244 with an average of 0.231 (Table 3.8).

Table 3.7 Split-half Cross-validation using Monte Carlo simulation: Comparison of actual utility values to predicted utility values across ten models (n=2195)

Monte Carlo Simulation Method*										
	Actual Utility**			Predicted Utility**			Actual versus Predicted**			
Cross-validation Set	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Diff in means	MSE	RMSE	MAE
Set 1	0.678 (0.336)	-0.594	1	0.61 (0.260)	-0.34	1	0.059	0.114	0.379	0.283
Set 2	0.684 (0.332)	-0.594	1	0.656 (0.279)	-0.349	1	0.029	0.144	0.379	0.279
Set 3	0.683 (0.332)	-0.594	1	0.669 (0.270)	-0.291	1	0.014	0.142	0.376	0.274
Set 4	0.683 (0.335)	-0.594	1	0.618 (0.247)	-0.536	1	0.065	0.140	0.374	0.278
Set 5	0.679 (0.338)	-0.594	1	0.664 (0.268)	-0.291	1	0.014	0.141	0.375	0.272
Set 6	0.692 (0.325)	-0.594	1	0.650 (0.280)	-0.5	1	0.042	0.146	0.385	0.280
Set 7	0.685 (0.328)	-0.594	1	0.668 (0.264)	-0.291	1	0.017	0.138	0.372	0.268
Set 8	0.687 (0.329)	-0.594	1	0.672 (0.235)	-0.261	1	0.015	0.128	0.357	0.257
Set 9	0.687 (0.326)	-0.594	1	0.692 (0.271)	-0.335	1	-0.005	0.139	0.373	0.269
Set 10	0.691 (0.323)	-0.594	1	0.672 (0.262)	-0.39	1	0.019	0.133	0.364	0.263
Average of 10 Sets	**0.685 (0.330)**	**-0.594**	**1**	**0.658 (0.217)**	**-0.3584**	**1**	**0.027**	**0.137**	**0.373**	**0.272**

**Level 3 (extreme effect) was a reference category; **SD, Standard deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error*

Table 3.8 Split-half Cross-validation using Expected Utility method: Comparison of actual utility values to predicted utility values across ten models (n=2195)

Expected Utility Method*										
Cross-validation Set	Actual Utility**			Predicted Utility			Actual versus Predicted**			
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Diff in means	MSE	RMSE	MAE
Set 1	0.678 (0.336)	-0.594	1	0.624(0.123)	0.224	0.795	0.054	0.092	0.304	0.244
Set 2	0.684 (0.332)	-0.594	1	0.656(0.157)	0.197	0.925	0.028	0.092	0.304	0.234
Set 3	0.683 (0.332)	-0.594	1	0.664(0.151)	0.113	0.917	0.019	0.091	0.301	0.228
Set 4	0.683 (0.335)	-0.594	1	0.648(0.139)	0.208	0.865	0.035	0.092	0.304	0.236
Set 5	0.679 (0.338)	-0.594	1	0.663(0.151)	0.190	0.891	0.016	0.095	0.308	0.232
Set 6	0.692 (0.325)	-0.594	1	0.651(0.167)	0.140	0.918	0.041	0.093	0.304	0.234
Set 7	0.685 (0.328)	-0.594	1	0.667(0.149)	0.140	0.904	0.018	0.089	0.298	0.226
Set 8	0.687 (0.329)	-0.594	1	0.669(0.117)	0.271	0.919	0.019	0.089	0.298	0.229
Set 9	0.687 (0.326)	-0.594	1	0.689(0.150)	0.213	0.925	-0.002	0.090	0.300	0.222
Set 10	0.691 (0.323)	-0.594	1	0.668(0.153)	0.173	0.892	0.023	0.082	0.287	0.220
Average of 10 Sets	**0.685 (0.330)**	**-0.594**	**1**	0.660(0.146)	0.164	0.895	0.025	0.090	0.301	0.231

**Level 3 (extreme effect) was a reference category; ** Here SD, Standard Deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error.*

Across the ten validation sets, the mean difference between actual and predicted values across ten models ranged from -0.005 to 0.065, with an overall mean of 0.027 (3.9% overestimate) for the Monte Carlo method (Table 3.7) and -0.002 to 0.054 with an overall mean of 0.025 (3.6% overestimate) for the Expected utility method (Table 3.8).

Split-half validation was repeated with a data set (n=4228) by removing 162 illogical responses to explore if the model could be improved further. Five times random split of the sample (n=4228) into two parts resulted in five derivation and five validation sets of 2114 family members each. Furthermore, the 'no effect' category was chosen as the reference category instead of the 'Extreme effect' category (least number of responses) as it is considered that using the reference category with the least responses may result in inflated ratios (NCRMUK, 2021). For each of the five EQ-5D domains, a mlogit model was derived, and the probability was predicted for each EQ-5D response for each subject in each validation set using Monte Carlo simulation; subsequently, the health utility was estimated. The predicted utilities for each validation set were compared to the observed utilities using the Monte Carlo and Expected utility methods. In each case, the predicted mean utility value was lower than the actual mean utility value indicating a slight overestimate of poor health (Tables 3.9 and 3.10).

Across the ten validation sets, the mean difference for the Monte Carlo method (Table 3.9) between actual and predicted values ranged from 0.005 to 0.029, with an overall mean of 0.015 (2.2% overestimate) and values for the Expected utility method (Table 3.10) ranged from 0.01 to 0.037, with an overall mean of 0.022 (3.2% overestimate). This 2.2 % overestimate using the Monte Carlo method represents a clinically unimportant effect as it is less than the minimal clinically important difference of the EQ-5D (Coretti et al. 2014).

The results of the Monte Carlo simulation in Table 3.9 are based on a single simulation. However, using R software, when Monte Carlo simulations were repeated 1000 times for each model, the results of 1000 simulations were not much different from a single simulation (R- syntax for 1000 simulations is given in appendix XIII).

Table 3.9 Split-half Cross-validation using Monte Carlo simulation: Comparison of actual utility values to predicted utility values across ten models (n=2114)

Monte Carlo Simulation Method*										
Cross-validation Set	**Actual Utility**			**Predicted Utility**			**Actual versus Predicted**			
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**	**Diff in means**	**MSE**	**RMSE**	**MAE**
Set 1	0.667(0.342)	-0.594	1	0.662(0.262)	-0.239	1	0.006	0.135	0.368	0.267
Set 2	0.669(0.331)	-0.594	1	0.655(0.277)	-0.286	1	0.008	0.136	0.369	0.269
Set 3	0.673(0.331)	-0.594	1	0.646(0.276)	-0.237	1	0.027	0.140	0.374	0.275
Set 4	0.672(0.326)	-0.594	1	0.667(0.277)	-0.349	1	0.005	0.138	0.372	0.267
Set 5	0.680(0.326)	-0.594	1	0.654(0.279)	-0.429	1	0.027	0.132	0.363	0.266
Set 6	0.679(0.320)	-0.594	1	0.659(0.274)	-0.286	1	0.020	0.135	0.367	0.268
Set 7	0.677(0.331)	-0.594	1	0.648(0.273)	-0.222	1	0.029	0.140	0.374	0.274
Set 8	0.672(0.330)	-0.594	1	0.667(0.278)	-0.426	1	0.005	0.141	0.376	0.270
Set 9	0.674(0.336)	-0.594	1	0.657(0.273)	-0.322	1	0.017	0.138	0.371	0.269
Set 10	0.666(0.336)	-0.594	1	0.658(0.273)	-0.322	1	0.007	0.136	0.369	0.268
Average of 10 Sets	0.673(0.331)	-0.594	1	0.658(0.274)	-0.312	1	0.015	0.137	0.370	0.269

**Level 1 (No effect) was a reference category; SD, Standard Deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error.*

Table 3.10 Split-half Cross-validation using Expected utility method: comparison of actual utility values to predicted utility values across ten models (n=2114)

Expected Utility Method*										
Cross-validation Set	**Actual Utility**			**Predicted Utility**			**Actual versus Predicted**			
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**	**Diff in means**	**MSE**	**RMSE**	**MAE**
Set 1	0.667(0.342)	-0.594	1	0.653(0.159)	0.187	0.905	0.014	0.090	0.300	0.229
Set 2	0.669(0.331)	-0.594	1	0.655(0.166)	0.040	0.912	0.014	0.088	0.297	0.226
Set 3	0.673(0.331)	-0.594	1	0.637(0.161)	0.197	0.906	0.037	0.087	0.295	0.229
Set 4	0.672(0.326)	-0.594	1	0.657(0.164)	0.161	0.921	0.015	0.085	0.292	0.222
Set 5	0.680(0.326)	-0.594	1	0.645(0.162)	0.142	0.896	0.035	0.085	0.292	0.226
Set 6	0.679(0.320)	-0.594	1	0.648(0.163)	0.158	0.914	0.030	0.083	0.288	0.223
Set 7	0.677(0.331)	-0.594	1	0.643(0.160)	0.208	0.910	0.033	0.089	0.298	0.230
Set 8	0.672(0.330)	-0.594	1	0.660(0.166)	0.140	0.909	0.012	0.087	0.295	0.224
Set 9	0.674(0.336)	-0.594	1	0.654(0.152)	0.185	0.897	0.020	0.087	0.295	0.227
Set 10	0.666(0.336)	-0.594	1	0.656 (0.162)	0.204	0.921	0.010	0.090	0.299	0.227
Average of 10 Sets	0.673(0.331)	-0.594	1	0.651(0.162)	0.162	0.909	0.022	0.087	0.295	0.226

**Level 1 (No effect) was a reference category; SD, Standard Deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error.*

Furthermore,1000 simulations did not predict the value of “1” for perfect health, which represents 21.4% of the observed utility value and value > 0 (worse than death), which represents 7.2% of the observed utility value of the sample. The average minimum utility and maximum utility values across ten models were 0.150 and 0.915 for 1000 simulations (Table 3.11) and -0.312 and 1 for a single simulation (Table 3.9), indicating that single simulation results were closer to the actual values (Min= -0.594, Max=1) (Table 3.11).

Table 3.11 Monte Carlo Simulation method:1000 repeated simulations in R software

Cross-validation Set	Actual Utility			Predicted Utility			Actual versus Predicted			
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Diff in means	MSE	RMSE	MAE
Set 1	0.667(0.342)	-0.594	1	0.662(0.159)	0.195	0.910	0.005	0.135	0.368	0.279
Set 2	0.669(0.331)	-0.594	1	0.665(0.166)	0.046	0.916	0.005	0.131	0.362	0.274
Set 3	0.673(0.331)	-0.594	1	0.665(0.166)	0.046	0.916	0.009	0.136	0.369	0.278
Set 4	0.672(0.326)	-0.594	1	0.670(0.162)	0.150	0.926	0.002	0.131	0.361	0.274
Set 5	0.680(0.326)	-0.594	1	0.656(0.162)	0.143	0.904	0.025	0.131	0.362	0.276
Set 6	0.679(0.320)	-0.594	1	0.659(0.164)	0.157	0.918	0.020	0.128	0.358	0.273
Set 7	0.677(0.331)	-0.594	1	0.656(0.159)	0.204	0.919	0.022	0.132	0.363	0.279
Set 8	0.672(0.330)	-0.594	1	0.671(0.165)	0.134	0.910	0.002	0.133	0.364	0.276
Set 9	0.674(0.336)	-0.594	1	0.662(0.153)	0.204	0.903	0.012	0.130	0.361	0.274
Set 10	0.666(0.336)	-0.594	1	0.667(0.161)	0.219	0.924	-0.001	0.134	0.366	0.277
Average of 10 Sets	0.673(0.331)	-0.594	1	0.663(0.162)	0.150	0.915	0.010	0.132	0.363	0.276

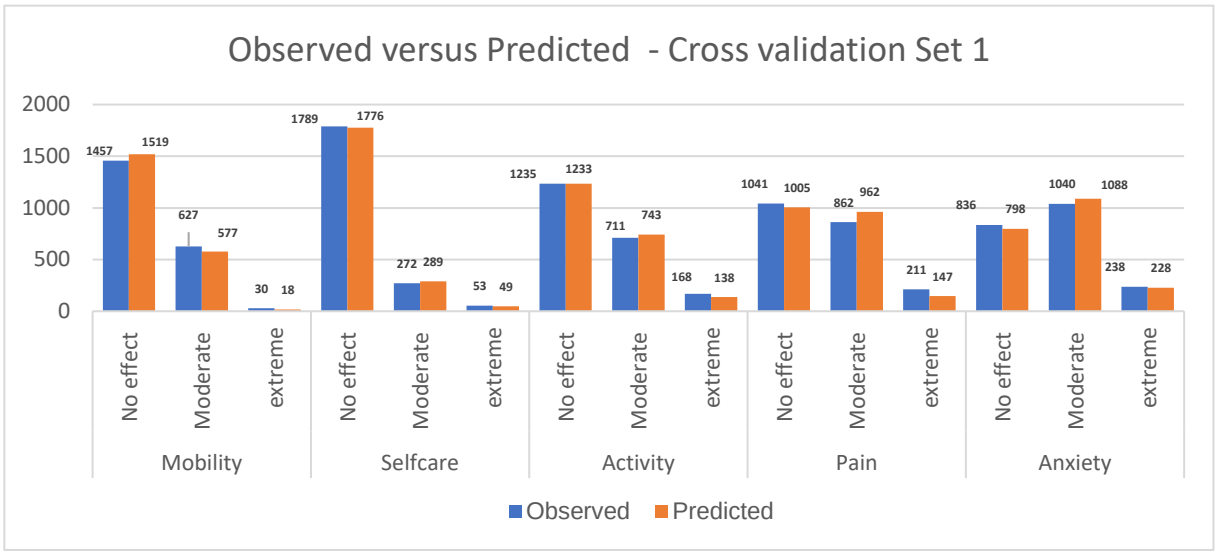
To test the predictive performance of the equations, classification was done using a Monte Carlo approach in which random numbers were compared with the probability values estimated by the mlogit models. Using all FROM-16 questions, age and gender as predictors, the overall proportion of predicted responses allocated to the correct level varied across ten models from 70-100%, with the majority (79%) having accuracy ranging from 90-100%. The accuracy was less than 70% for only a small proportion (4%) of responses (Table 3.12).

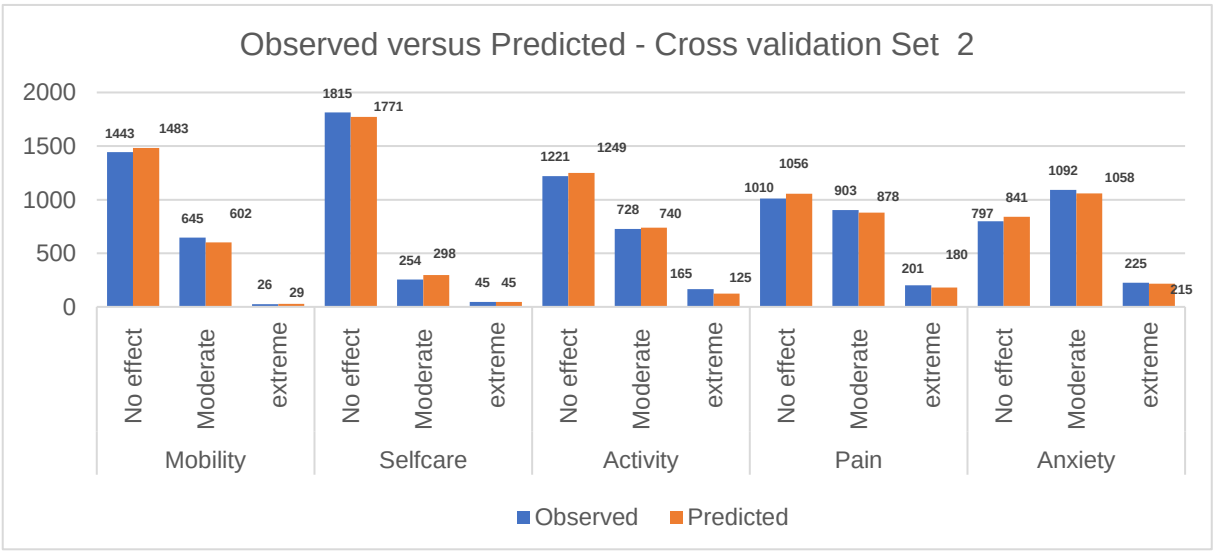
The comparison of responses to EQ-5D-3L dimensions between observed (actual responses given by family members) and predicted (responses derived from a model) across all 10 validation sets (n=2114) showed only a small variation between the two, indicating overall better alignment. In general, predicted levels that were 'off-diagonal' were equally likely to be lower or higher than the actual level (Figure 3.4).

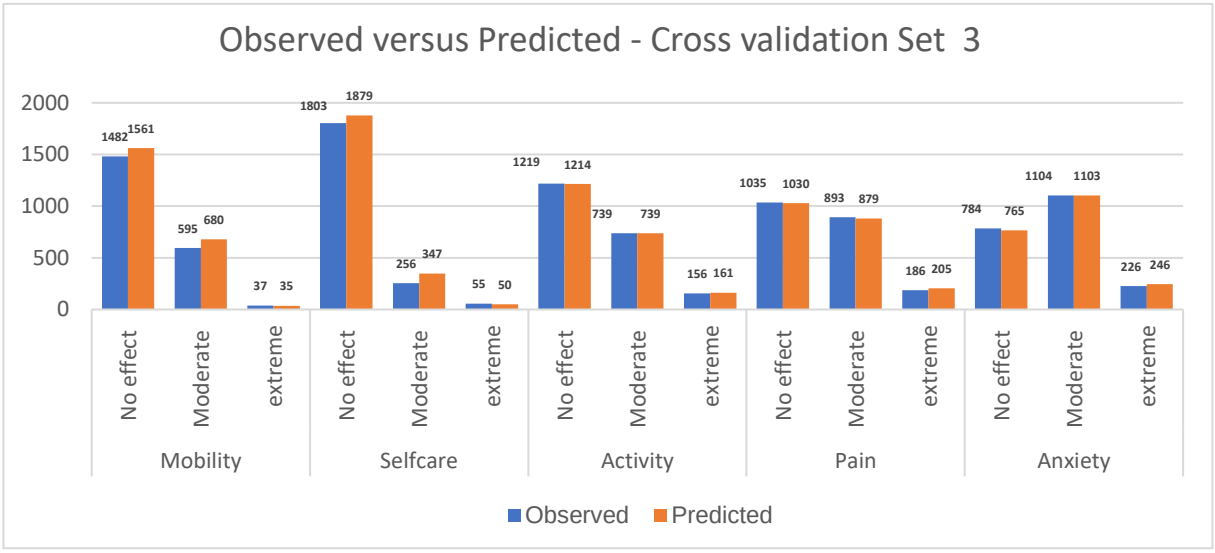
Table 3.12 Accuracy of predicted EQ-5D responses across ten Cross-validation sets

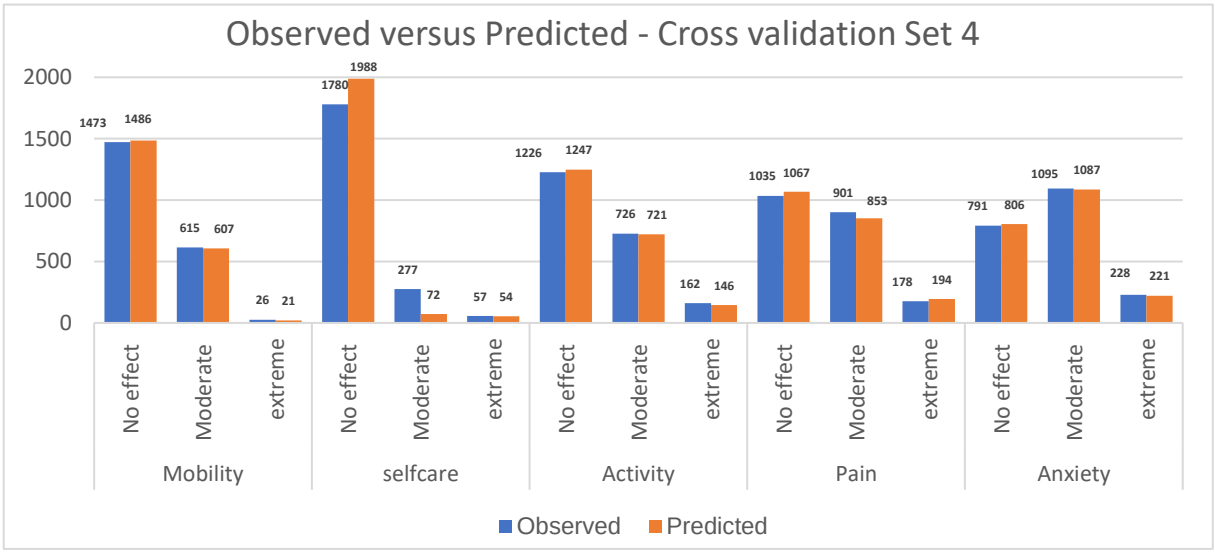
Accuracy (%)	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Average
90-100%	80	86.66	86.66	86.66	86.66	73.33	73.33	73.33	73.33	73.33	79.33
70-100%	93.33	100	100	93.33	100	100	93.33	100	93.33	93.33	96.67
<70%	0.06	0.06	0	0.06	0	0	0.06	0	0.06	0.06	0.04

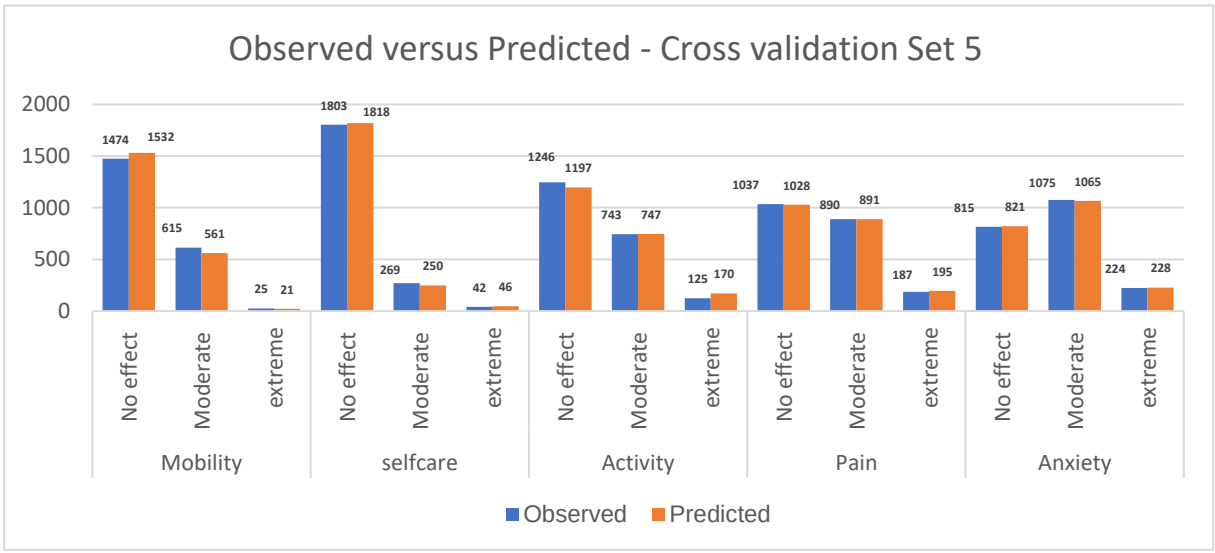
Figure 3.4 Comparison of observed and predicted EQ-5D-3L responses (validation set 1-10)

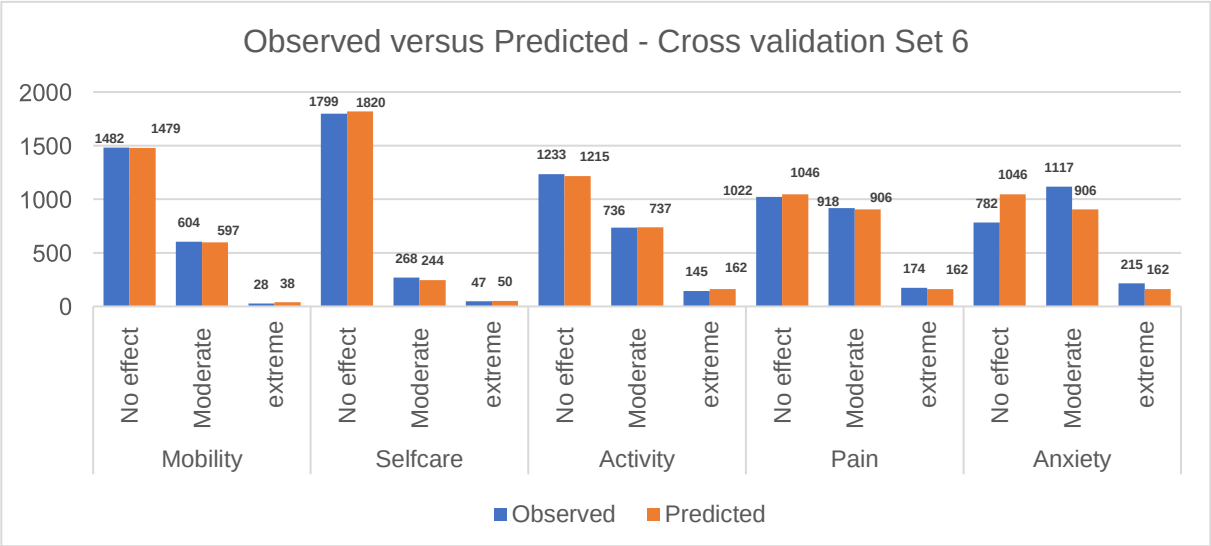


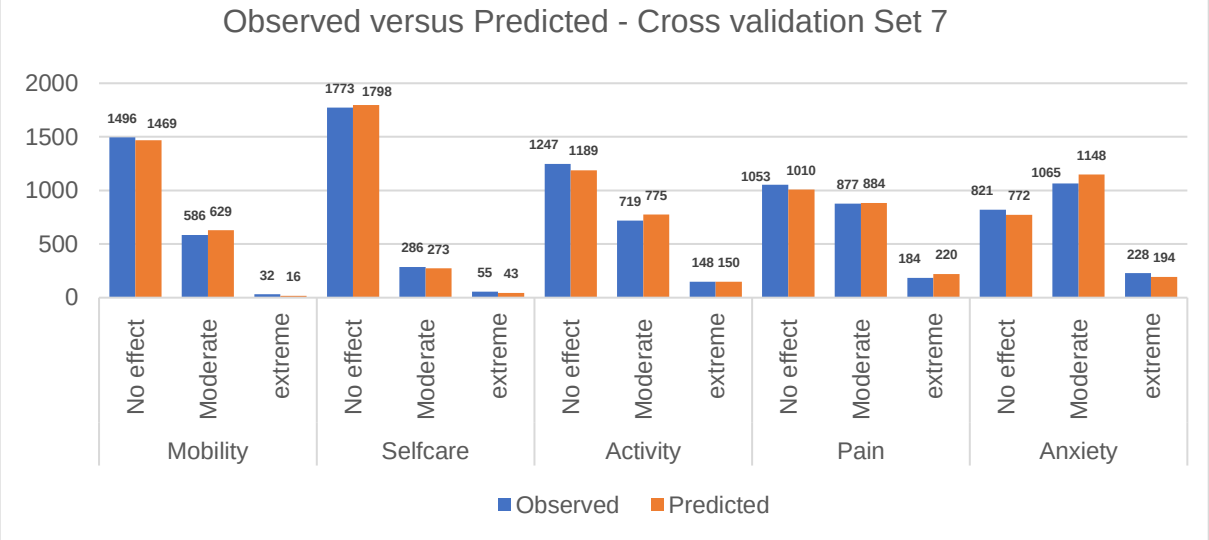


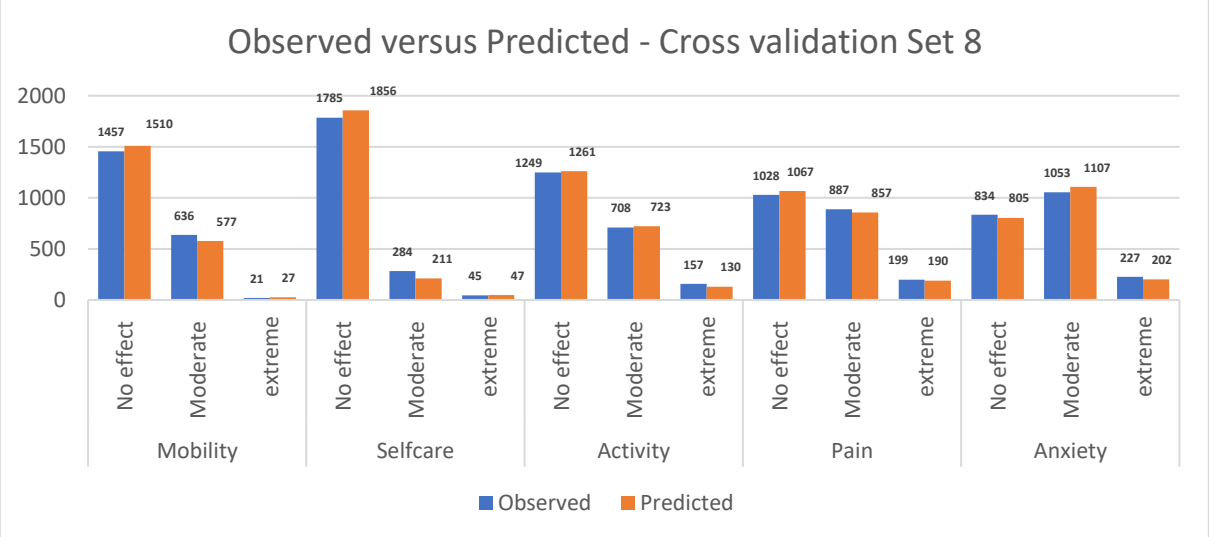

Observed versus Predicted - Cross validation Set 3
2000
1500
1000
500
0
1482 1561
595 680
37 35
1803 1879
256 347
55 50
1219 1214
739 739
156 161
1035 1030
893 879
186 205
784 765
1104 1103
226 246
No effect
Moderate
extreme
Mobility
Selfcare
Activity
Pain
Anxiety
Observed
Predicted

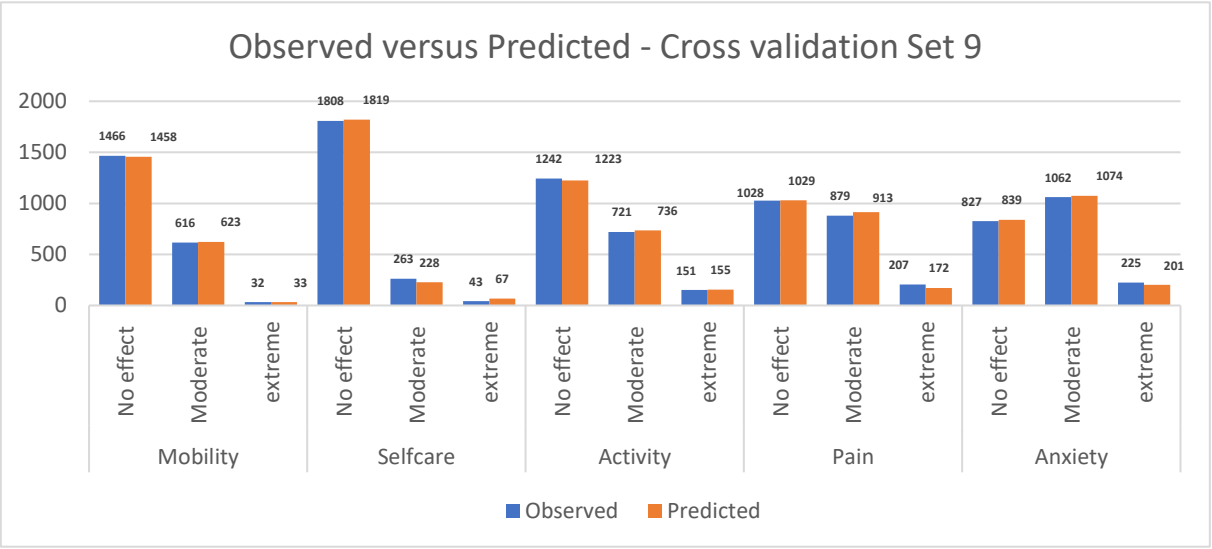

Observed versus Predicted - Cross validation Set 4
2000
1500
1000
500
0
1473 1486
615 607
26 21
1780 1988
277 72
57 54
1226 1247
726 721
162 146
1035 1067
901 853
178 194
791 806
1095 1087
228 221
No effect
Moderate
extreme
Mobility
selfcare
Activity
Pain
Anxiety
Observed
Predicted

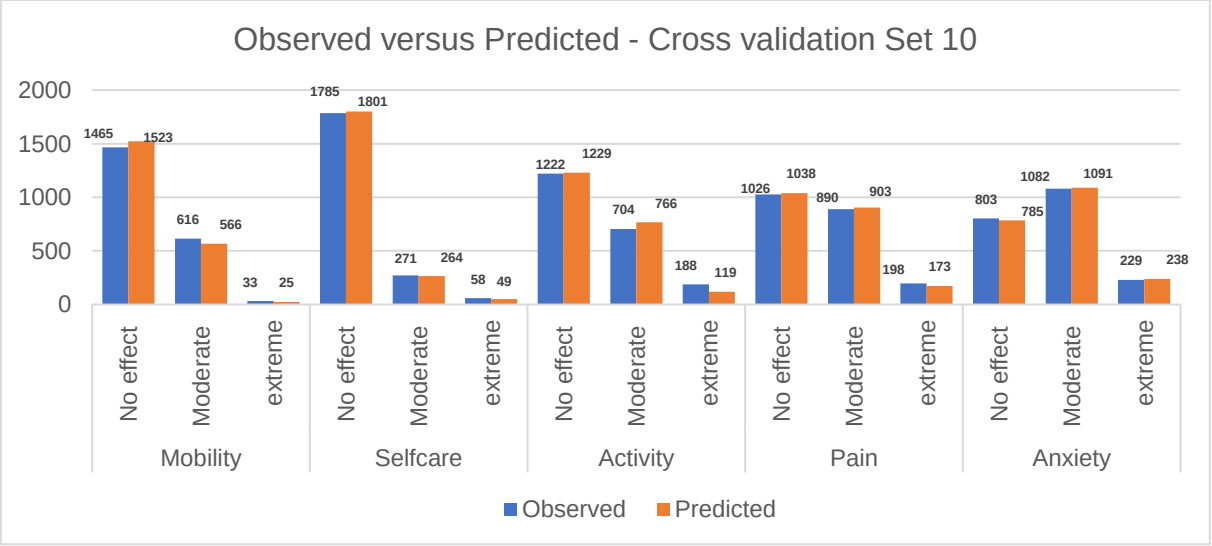

Observed versus Predicted - Cross validation Set 5
2000
1500
1000
500
0
1474 1532
615 561
25 21
1803 1818
269 250
42 46
1246 1197
743 747
125 170
1037 1028
890 891
187 195
815 821
1075 1065
224 228
No effect
Moderate
extreme
Mobility
selfcare
Activity
Pain
Anxiety
Observed
Predicted


Observed versus Predicted - Cross validation Set 6
2000
1500
1000
500
0
1482 1479
604 597
28 38
1799 1820
268 244
47 50
1233 1215
736 737
145 162
1022 1046
918 906
174 162
782 1046
1117 906
215 162
No effect
Moderate
extreme
Mobility
Selfcare
Activity
Pain
Anxiety
Observed
Predicted


Observed versus Predicted - Cross validation Set 7
2000
1500
1000
500
0
1496 1469
586 629
32 16
1773 1798
286 273
55 43
1247 1189
719 775
148 150
1053 1010
877 884
184 220
821 772
1065 1148
228 194
No effect
Moderate
extreme
Mobility
Selfcare
Activity
Pain
Anxiety
Observed
Predicted


Observed versus Predicted - Cross validation Set 8
2000
1500
1000
500
0
1457 1510
636 577
21 27
1785 1856
284 211
45 47
1249 1261
708 723
157 130
1028 1067
887 857
199 190
834 805
1053 1107
227 202
No effect
Moderate
extreme
Mobility
Selfcare
Activity
Pain
Anxiety
Observed
Predicted

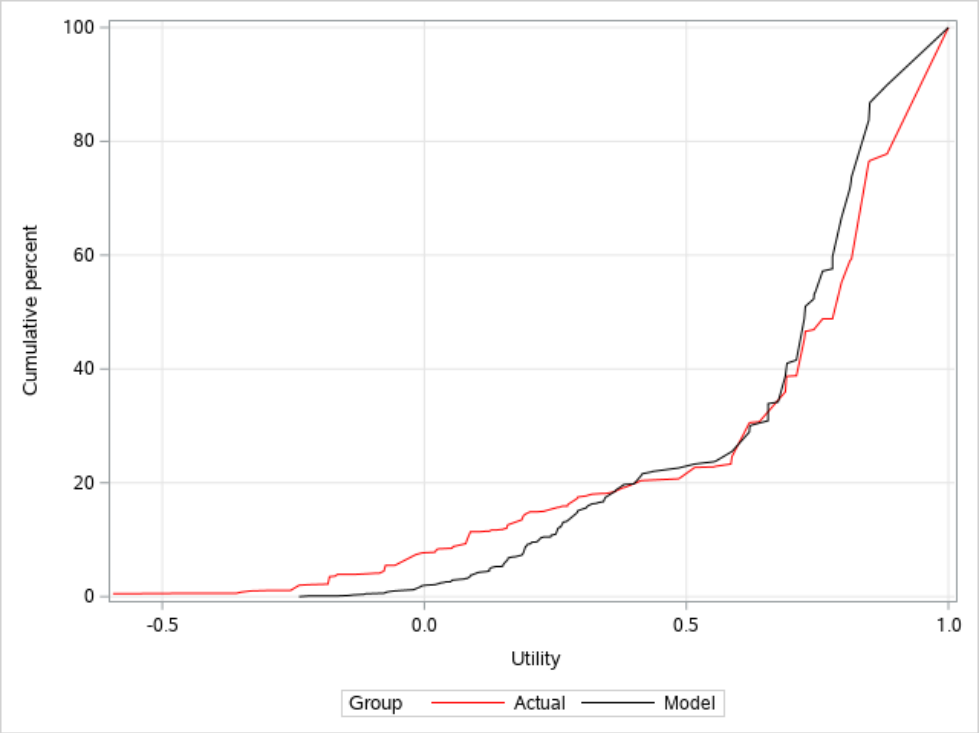




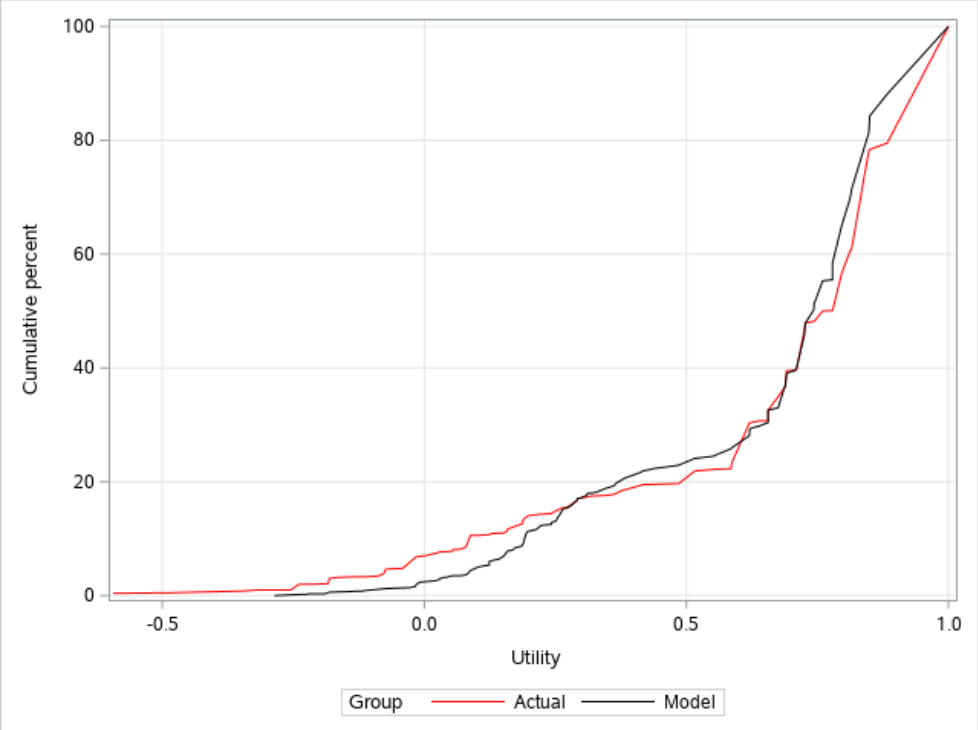
In order to further compare the results, the cumulative distribution of observed and predicted utility data (n=2114) was examined across ten validation models (Figure 3.4).

Figure 3.5 a-j The cumulative percentage of observed EQ-5D-3L data versus simulated data across ten validation sets

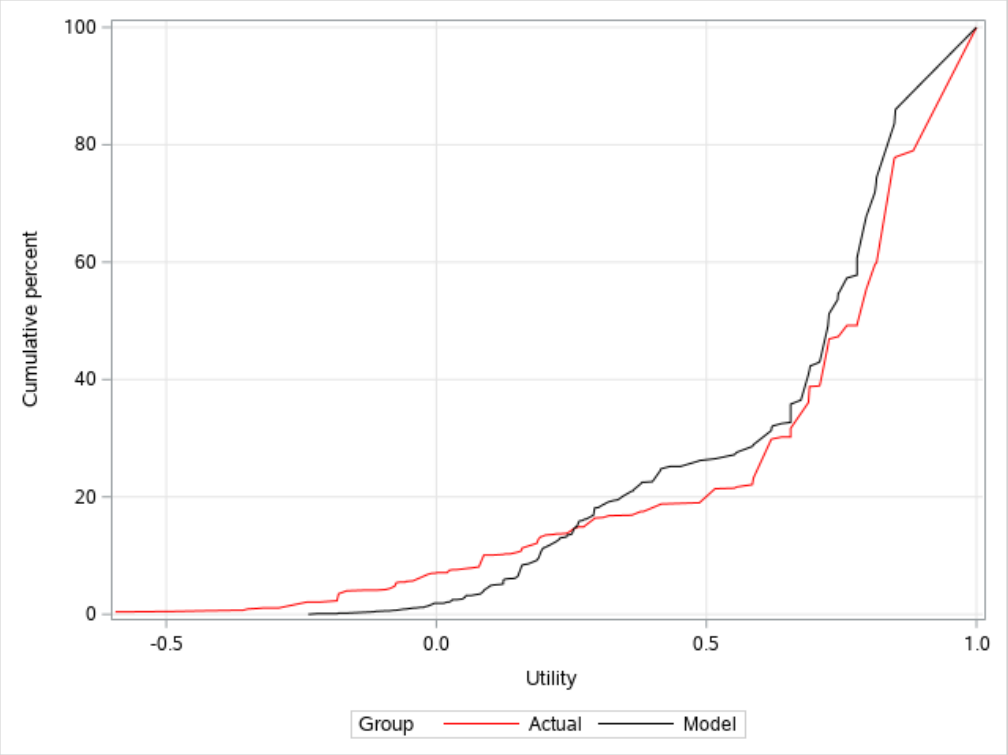
(a) Model one: Cross validation set 1



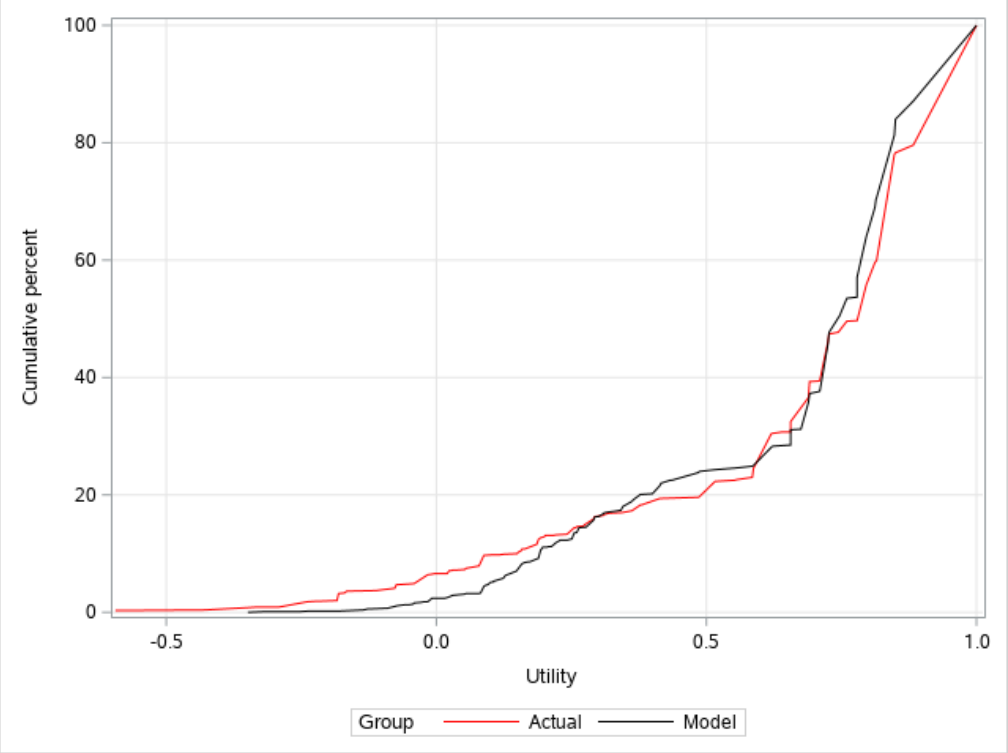
(b) Model two: Cross validation set 2



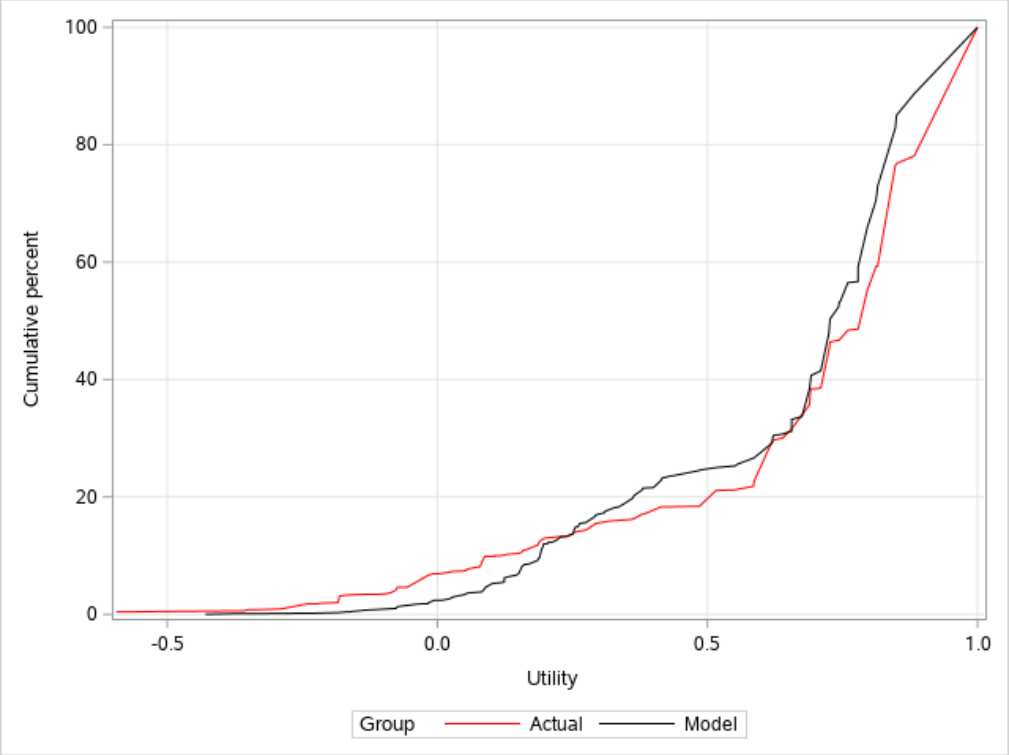
(c) Model three: Cross validation set 3



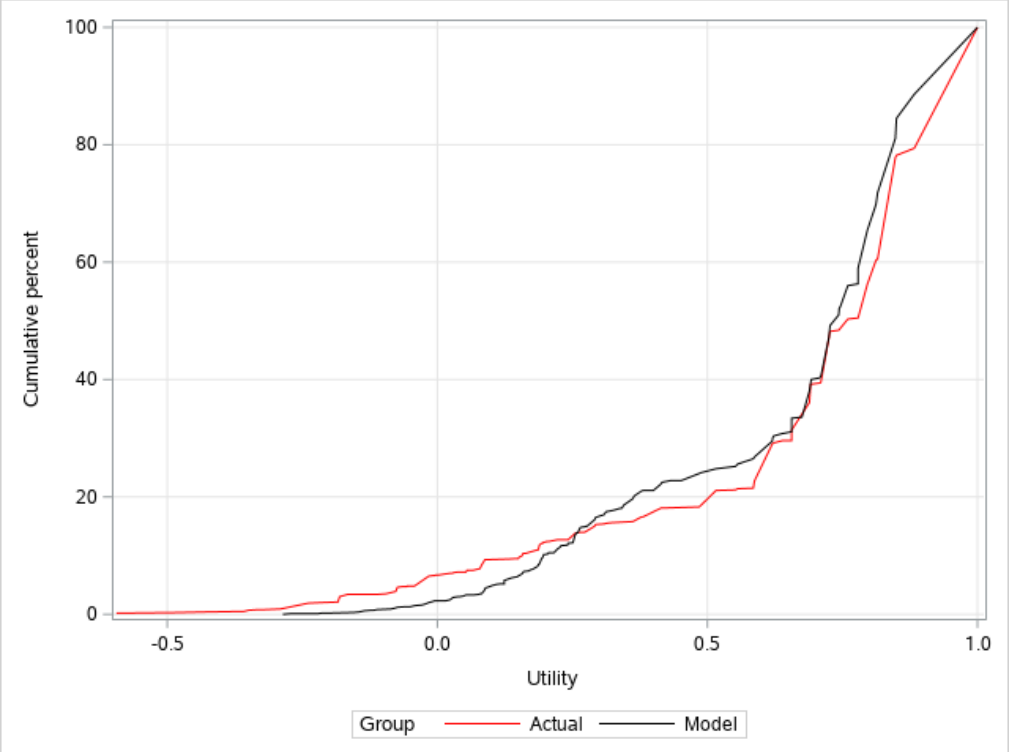
(d) Model four: Cross validation set 4



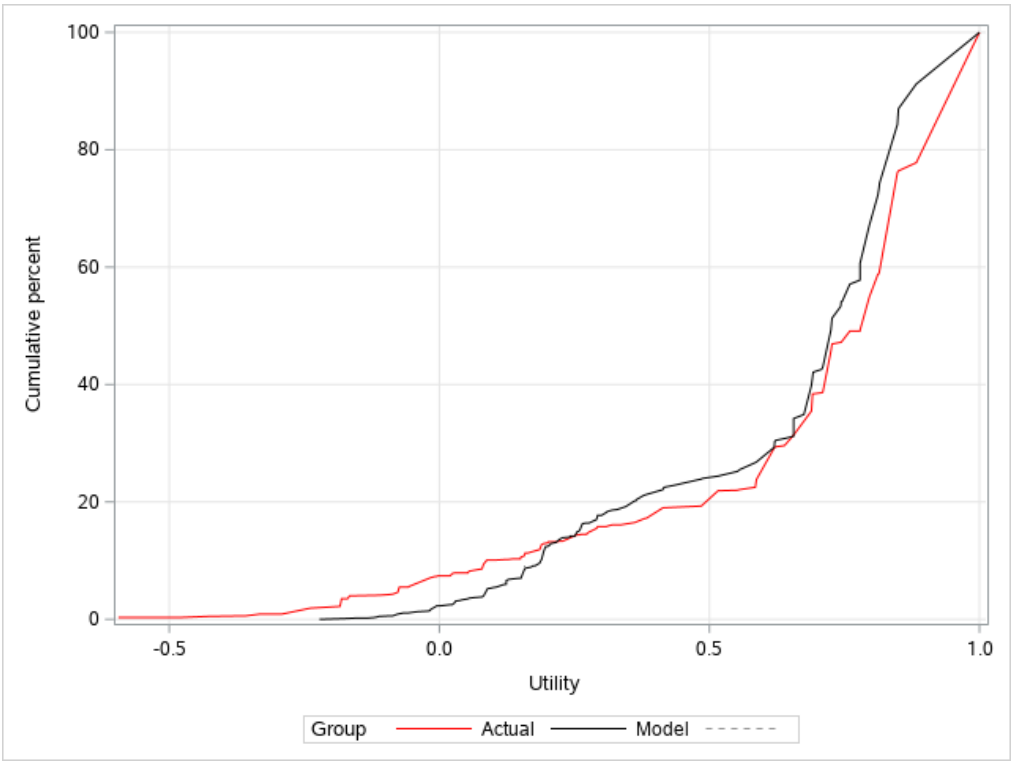
(e) Model five: Cross validation set 5



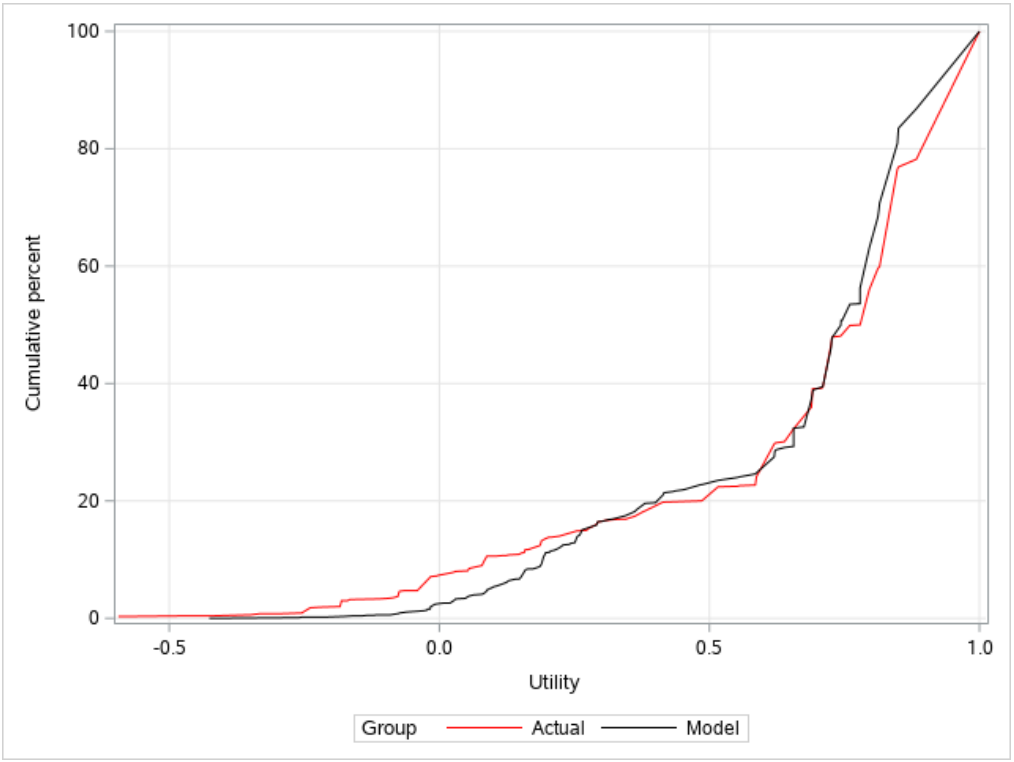
(f) Model six: Cross validation set 6



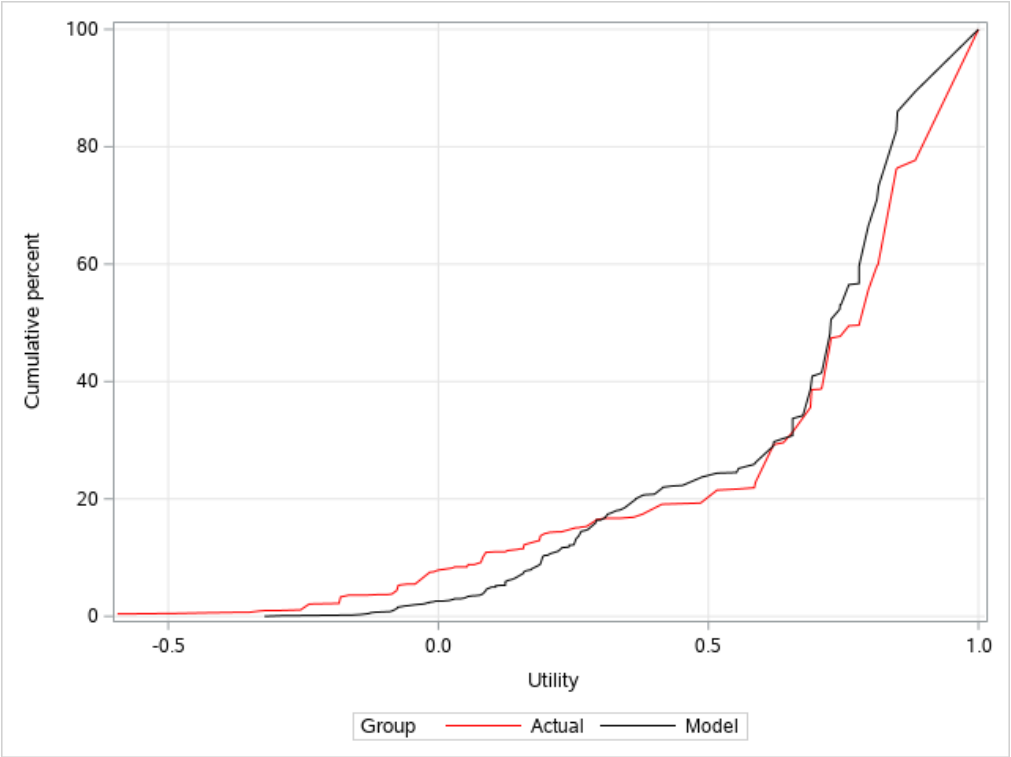
(g) Model seven: Cross validation set 7



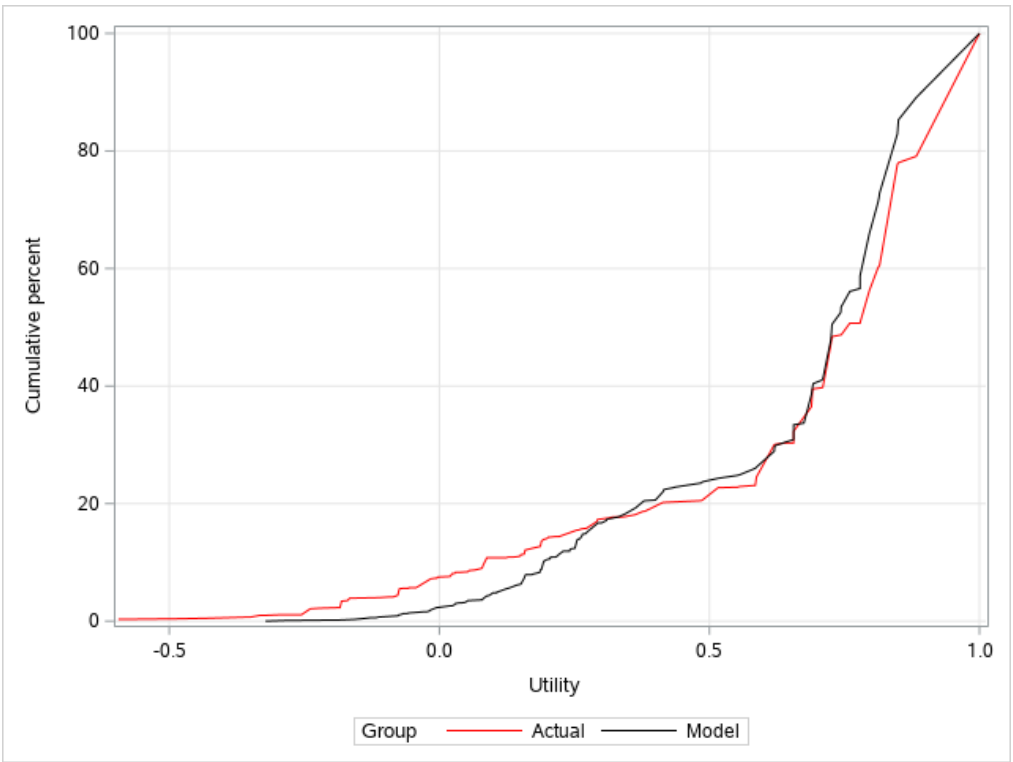
(h) Model eight: Cross validation set 8



(i) Model Nine: Cross validation set 9



(j) Model ten: Cross validation set 10



All plots indicated a small disparity between the predicted and actual utility values which were aligned with the frequency distribution of observed versus predicted EQ-5D-3L responses. For models 2, 4 and 8, the predicted cumulative distribution was closer to the observed data than the other models (Figure 3.5).

The predictive ability of the model at an individual subject level was also examined using histograms (Figure 3.6). All the plots depicted a centrality around '0', which indicates the strong predictive collective capability of the mlogit models. On average across ten validation models, 54% of the individual utility values were predicted to lie within 0.05 of the actual values, 59% within 0.1, 73% within 0.2 and 83% within 0.3 of the actual values (Table 3.13).

Table 3.13 Mean utility value difference across all ten Cross-validation sets

Cross-validation sets (n=4228)	Mean Utility Value Difference	% Utility Values within 0.05 of Actual UV	% Utility Values within 0.1 of Actual UV	% Utility Values within 0.2 of Actual UV	% Utility Values within 0.3 of Actual UV
Set 1	0.006	53.6	58.8	73.4	84.1
Set 2	0.008	54.6	59.5	73.9	83
Set 3	0.027	51.8	56.3	70.2	80.6
Set 4	0.005	58.6	62.9	74.6	83.2
Set 5	0.027	53.3	57.9	73.3	81.8
Set 6	0.02	53.8	58.6	72.8	82.3
Set 7	0.029	51.6	56.5	71.3	81.6
Set 8	0.005	56.6	61.9	75.4	83.8
Set 9	0.017	54.3	59	71.8	81.7
Set 10	0.007	54.5	59.8	73.6	82.9
Average	**0.015**	**54.27**	**59.12**	**73.03**	**82.5**

A separate analysis was carried out using SAS software to explore if this model could be further improved by conducting NPOR. The results of NPOR were very similar to mlogit, with mlogit behaving slightly better (Tables 3.14 and 3.15), indicating that both can be used for response mapping of Non-PBM to EQ-5D utility values. The overall mean RSME, MAE and the difference in means between observed and predicted utility values across ten models was slightly lower for mlogit for both the Monte Carlo and the Expected utility methods.

Figure 3.6 a-j Histograms demonstrating the mean difference between predicted and actual utility scores for each Monte Carlo simulation

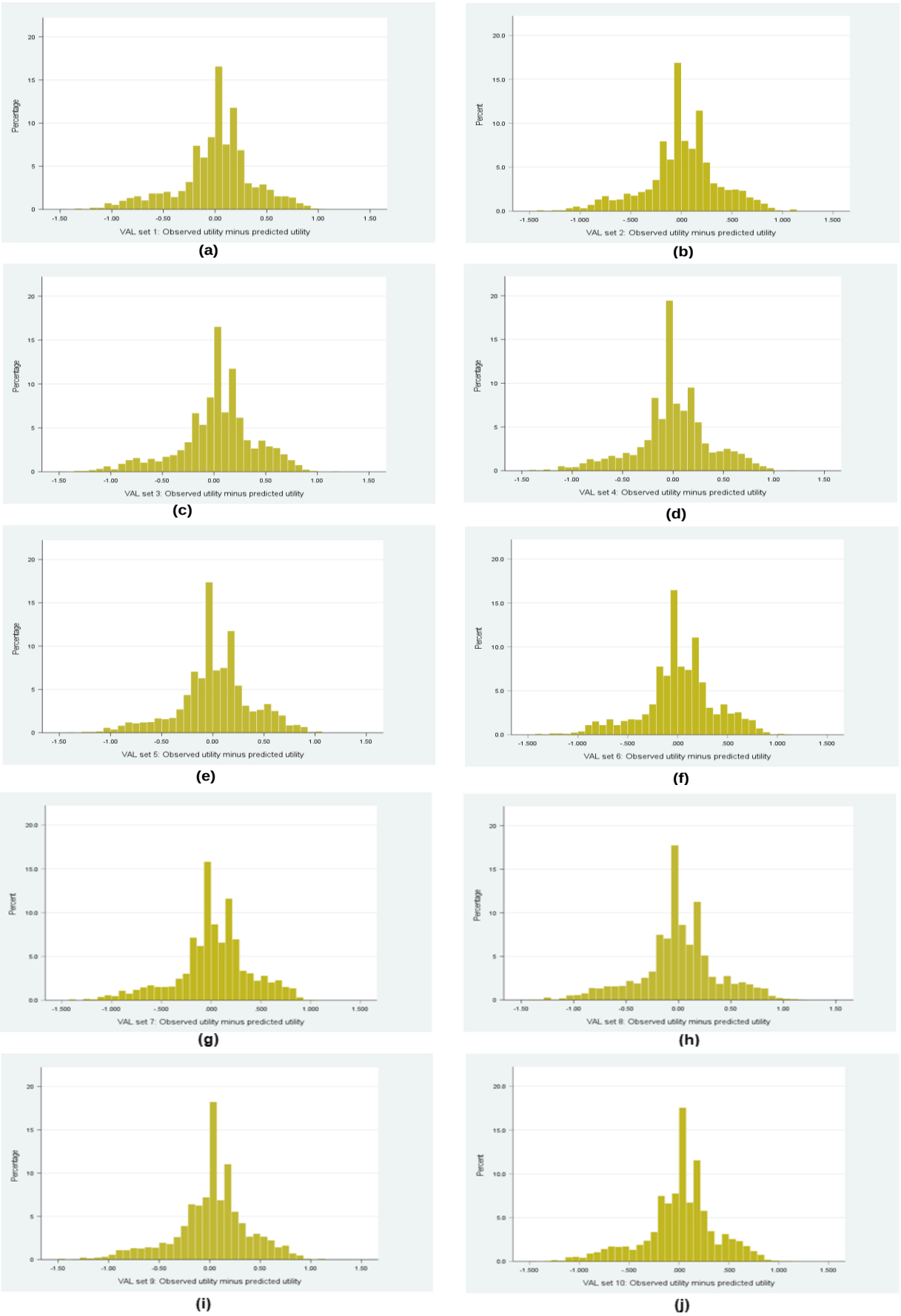


Table 3.14 Split-half Cross-validation using Monte Carlo simulation: Comparison of actual to predicted utility values across ten models derived from NPOR (n=2114)

NPOR - Monte Carlo simulation method*										
Cross-validation Set (n=2,114)	**Actual Utility****			**Predicted Utility****			**Actual versus Predicted****			
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**	**Diff in mean**	**MSE**	**RMSE**	**MAE**
Set 1	0.667(0.342)	-0.594	1.000	0.666 (0.268)	-0.291	1.000	0.001	0.141	0.376	0.274
Set 2	0.669(0.331)	-0.594	1.000	0.706 (0.237)	-0.121	1.000	-0.037	0.131	0.361	0.258
Set 3	0.673(0.331)	-0.594	1.000	0.622 (0.268)	-0.380	1.000	0.051	0.134	0.367	0.269
Set 4	0.672(0.326)	-0.594	1.000	0.610 (0.296)	-0.484	1.000	0.062	0.145	0.381	0.286
Set 5	0.680(0.326)	-0.594	1.000	0.649 (0.272)	-0.380	1.000	0.031	0.135	0.367	0.269
Set 6	0.679(0.320)	-0.594	1.000	0.646 (0.285)	-0.484	1.000	0.032	0.138	0.371	0.271
Set 7	0.677(0.331)	-0.594	1.000	0.664 (0.251)	-0.331	1.000	0.013	0.135	0.367	0.270
Set 8	0.672(0.330)	-0.594	1.000	0.668 (0.273)	-0.426	1.000	0.004	0.137	0.370	0.268
Set 9	0.674(0.336)	-0.594	1.000	0.655(0.265)	-0.371	1.000	0.019	0.140	0.375	0.274
Set 10	0.666(0.336)	-0.594	1.000	0.640 (0.284)	-0.426	1.000	0.026	0.138	0.372	0.270
Average of 10 Sets	0.673(0.331)	-0.594	1.000	0.653(0.270)	-0.369	1.000	0.020	0.137	0.371	0.271

**Level 3 (extreme effect) was a reference category; SD, Standard deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error*

Table 3.15 Split-half Cross-validation using Expected utility method: Comparison of actual utility values to predicted utility values across ten models derived from NPOR (n=2114)

NPOR – Expected utility method*										
Cross-validation Set (n=2,114)	**Actual Utility****			**Predicted Utility****			**Actual versus Predicted****			
	Mean (SD)	**Min**	**Max**	**Mean (SD)**	**Min**	**Max**	**Diff in means**	**MSE**	**RMSE**	**MAE**
Set 1	0.667(0.342)	-0.594	1.000	0.667 (0.147)	0.239	0.900	0.001	0.090	0.300	0.226
Set 2	0.669(0.331)	-0.594	1.000	0.701 (0.129)	0.246	0.915	-0.032	0.090	0.300	0.218
Set 3	0.673(0.331)	-0.594	1.000	0.616 (0.149)	0.178	0.877	0.057	0.088	0.297	0.236
Set 4	0.672(0.326)	-0.594	1.000	0.615 (0.188)	0.112	0.916	0.058	0.090	0.299	0.235
Set 5	0.680(0.326)	-0.594	1.000	0.646 (0.139)	0.181	0.889	0.034	0.085	0.291	0.226
Set 6	0.679(0.320)	-0.594	1.000	0.650 (0.164)	0.160	0.910	0.029	0.083	0.288	0.222
Set 7	0.677(0.331)	-0.594	1.000	0.663 (0.139)	0.297	0.906	0.014	0.088	0.296	0.225
Set 8	0.672(0.330)	-0.594	1.000	0.667 (0.160)	0.172	0.903	0.005	0.087	0.294	0.222
Set 9	0.674(0.336)	-0.594	1.000	0.660 (0.145)	0.230	0.893	0.013	0.087	0.295	0.225
Set 10	0.666(0.336)	-0.594	1.000	0.638 (0.168)	0.175	0.916	0.027	0.090	0.300	0.232
Average of 10 sets	0.673(0.331)	-0.594	1.000	0.652 (0.154)	0.199	0.903	0.021	0.088	0.296	0.227

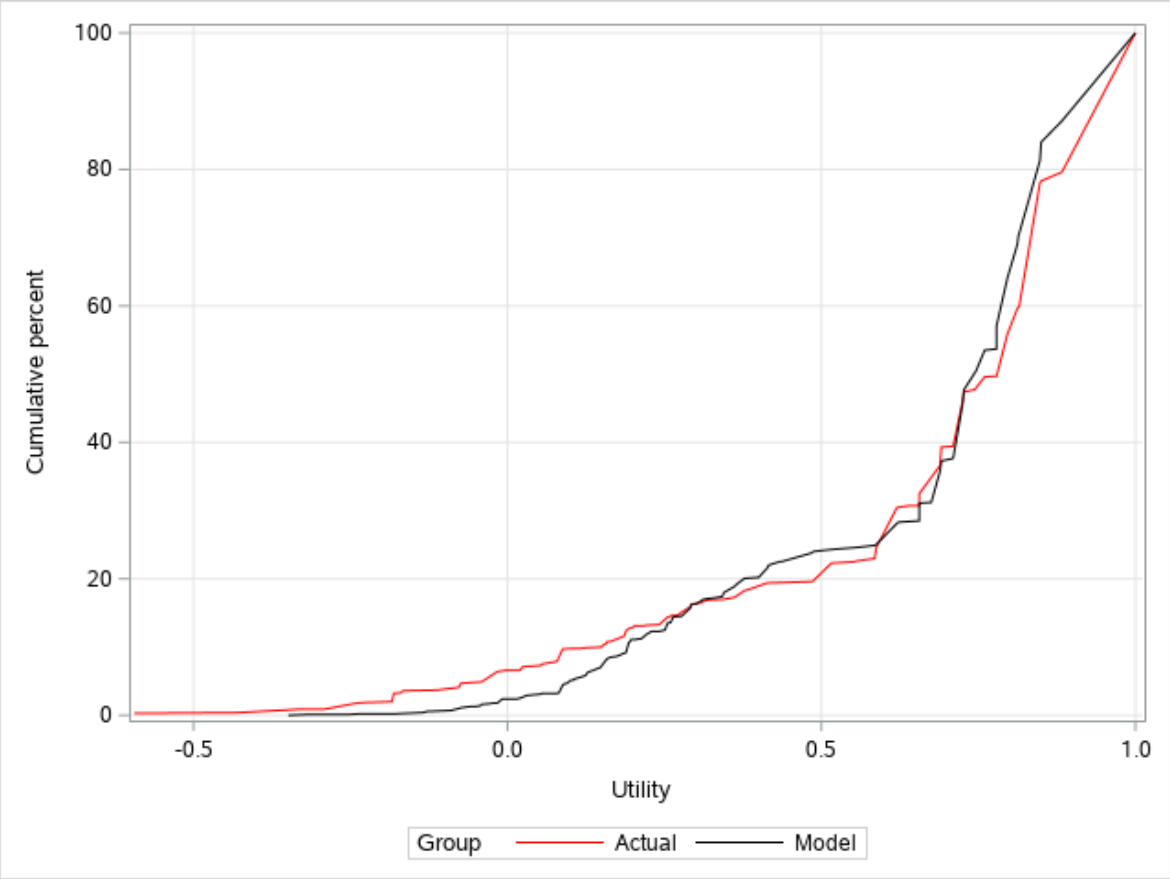
**Level 3 (extreme effect) was a reference category; SD, Standard deviation; Min, Minimum; Max, Maximum; Diff in means, Difference in means; MSE, Mean Square Error; RSME, Root Mean Square Error; MAE, Mean absolute error*

3.4.5 Comparison Between Monte Carlo Simulation and the Expected Utility Method

The Expected utility method resulted in lower values for MSE, RMSE and MAE, indicating that it resulted in lesser errors than the Monte Carlo simulation method. However, the maximum utility value of 1 (indicating perfect health) could not be predicted using the Expected utility method. Furthermore, an informal visual inspection of the cumulative utility graphs (Figure 3.7 a and b) describing actual versus predicted scores suggests that the Monte Carlo method is superior to the Expected utility method.

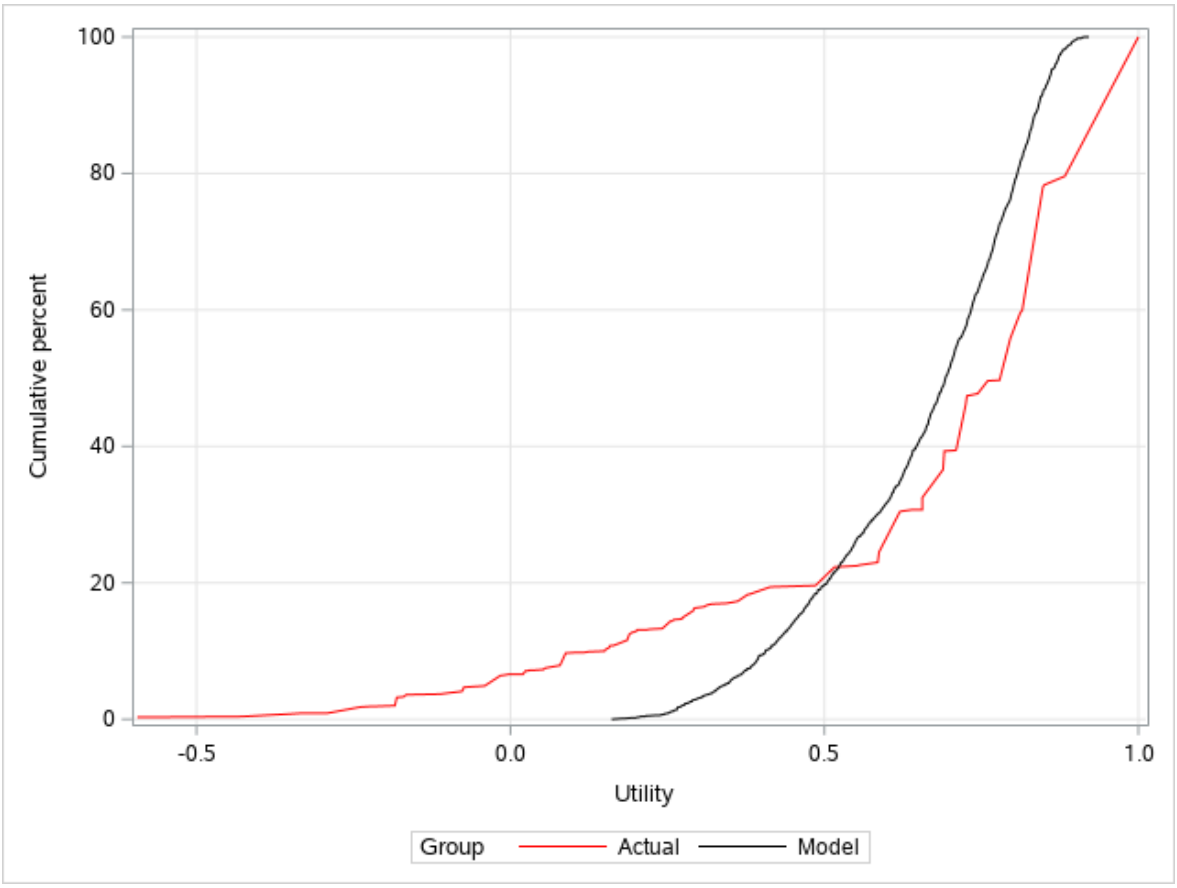
Figure 3.7 The cumulative percentage* of observed EQ-5D-3L utility data versus predicted utility data (a) Monte Carlo method versus (b) Expected utility method

(a)



Graph here represents model 4.

(b)



**Graph here represents model 4.*

Therefore, the final algorithm was derived from mlogit using Monte Carlo simulation to analyse the 4228 subject data set. Details of the final fitted models using data from these 4228 subjects are provided in Table 3.16.

These are the final estimates that will be made available to other researchers should they wish to convert FROM-16 scores to EQ-5D-3L utility values: the estimates will be included in the published manuscript describing this utility values study. To make this process more accessible and easier to use for other researchers, a Microsoft Excel spreadsheet was designed with the relevant estimates and formulae already inputted (available on request from the FROM-16 research team once the study results are published). Following simple instructions (Appendix XIV), researchers will therefore be able to calculate EQ-5D-3L utility values for family members from the FROM-16 scores that they provide.

Table 3.16 Final Model Coefficients (standard errors) for each EQ-5D domain against the 16 items of FROM-16, age and gender using multinomial logistic regression

FROM-16 Items, Age and Gender	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	Some Problems	Extreme Problems	Some Problems	Extreme Problems	Some Problems	Extreme Problems	Some Problems	Extreme Problems	Some Problems	Extreme Problems
Intercept	-3.468 (0.22)*	-7.488 (0.962)*	-3.25 (0.28)*	-6.497 (0.732)*	-2.746 (0.206)*	-5.344 (0.422)*	-2.18 (0.191)*	-4.437 (0.357)*	-1.434 (0.205)*	-4.012 (0.377)*
Age	0.031 (0.003)*	0.008 (0.011)	0.004 (0.004)	0.000 (0.008)	0.019 (0.003)*	0.009 (0.005)	0.026 (0.003)*	0.017 (0.005)*	-0.013 (0.003)*	-0.032 (0.005)*
Gender[a]	-0.05 (0.079)	-0.059 (0.332)	-0.297 (0.105)*	0.153 (0.262)	-0.089 (0.079)	-0.205 (0.148)	-0.008 (0.075)	-0.247 (0.131)	0.269 (0.083)*	-0.037 (0.143)
FROM_Worried	0.276 (0.078)*	-0.14 (0.347)	0.387 (0.11)*	-0.227 (0.26)	0.17 (0.076)*	0.255 (0.158)	0.17 (0.072)*	0.383 (0.138)*	0.522 (0.077)*	0.715 (0.151)*
FROM_Angry	0.094 (0.063)	0.288 (0.236)	0.009 (0.082)	0.221 (0.182)	0.042 (0.062)	0.137 (0.11)	0.081 (0.061)	0.129 (0.101)	0.269 (0.069)*	0.395 (0.107)*
FROM_Sad	-0.303 (0.067)*	0.346 (0.334)	-0.136 (0.092)	0.624 (0.254)*	-0.211 (0.066)*	0.264 (0.138)*	-0.328 (0.063)	-0.352 (0.116)*	0.117 (0.068)	0.353 (0.129)*
FROM_Frustrated	-0.071 (0.067)	-0.078 (0.307)	-0.024 (0.092)	-0.525 (0.22)*	-0.042 (0.065)*	-0.266 (0.13)*	0.025 (0.062)	0.01 (0.115)	-0.021 (0.067)	-0.085 (0.124)
FROM_Talking thoughts	0.199 (0.055)*	0.458 (0.23)*	0.132 (0.073)	0.172 (0.168)	0.203 (0.053)	0.192 (0.099)*	0.134 (0.052)*	0.323 (0.09)*	0.403 (0.058)*	0.777 (0.097)*
FROM_Difficulty caring	0.002 (0.069)	0.341 (0.304)	0.064 (0.091)	0.68 (0.244)*	0.09 (0.066)	0.301 (0.13)*	-0.121 (0.064)*	0.085 (0.114)	0.029 (0.071)	0.223 (0.12)
FROM_Time for self	-0.066 (0.07)	0.204 (0.277)	-0.159 (0.093)	0.124 (0.219)	-0.038 (0.068)	0.228 (0.127)	0.022 (0.067)	-0.267 (0.113)*	0.244 (0.075)*	0.356 (0.12)*
FROM_Travel	0.152 (0.061)*	0.018 (0.207)	0.187 (0.078)*	0.183 (0.164)	0.161 (0.06)*	0.313 (0.1)*	0.093 (0.06)	0.305 (0.096)*	0.102 (0.072)	0.154 (0.105)
FROM_Eating habits	0.221 (0.061)*	0.15 (0.218)	0.292 (0.078)*	0.141 (0.168)	0.107 (0.06)	0.202 (0.103)*	0.094 (0.06)	0.364 (0.095)*	0.198 (0.071)*	0.613 (0.104)*
FROM_Family activities	0.083 (0.071)	0.211 (0.328)	0.031 (0.096)	0.149 (0.256)	0.19 (0.068)*	0.194 (0.141)	0.092 (0.066)	0.035 (0.12)	0.1 (0.072)	0.059 (0.128)
FROM_Holiday	-0.004 (0.063)	0.249 (0.287)	-0.08 (0.086)	0.275 (0.228)	0.027 (0.061)	0.083 (0.124)	0.002 (0.059)	-0.027 (0.107)	0.047 (0.065)	-0.214 (0.112)*
FROM_Sex life	0.095 (0.047)*	-0.06 (0.177)	0.119 (0.063)*	0.000 (0.14)	0.109 (0.046)*	0.202 (0.085)*	0.116 (0.045)*	0.131 (0.076)	0.069 (0.051)	0.073 (0.082)
FROM_Work or study	-0.241 (0.065)*	-0.152 (0.209)	-0.262 (0.082)*	0.227 (0.168)	0.037 (0.064)	0.032 (0.103)	-0.133 (0.064)*	-0.329 (0.099)*	0.031 (0.077)	-0.028 (0.107)
FROM_Family relationships	-0.072 (0.065)	0.455 (0.25)	0.068 (0.085)	0.081 (0.185)	-0.005 (0.064)	0.044 (0.111)	0.076 (0.062)	-0.063 (0.103)	0.21 (0.071)*	0.277 (0.109)*
FROM_Family expenses	0.333 (0.058)*	0.479 (0.231)*	0.346 (0.077)*	0.563 (0.182)*	0.3 (0.056)*	0.395 (0.103)*	0.239 (0.055)*	0.527 (0.095)*	-0.083 (0.063)	0.082 (0.1)
FROM_Sleep	0.127 (0.065)	-0.16 (0.28)	0.223 (0.089)*	-0.258 (0.213)	0.195 (0.063)*	0.133 (0.126)	0.151 (0.061)*	0.598 (0.113)*	0.404 (0.067)*	0.704 (0.12)*

*FROM-16 items represented as FROM_item name; No problem is the comparison group; [a] Gender was coded male=0, female=1; *Significant at 5%*

3.5 DISCUSSION

At the moment, there is no family-specific measure which can be used across all areas of medicine to calculate family member or informal carer utility values for health economic evaluation. Mapping the generic measure FROM-16 to the EQ-5D-3L could fill this research gap by making it possible, in the health economic evaluation of a medical intervention, to measure the costs and impact on family members, whether or not they assume a carer's role.

This mapping of a generic family QoL measure to EQ-5D now facilitates the conversion of a family member and/or informal carer's QoL scores into utility values for health economic evaluation. Although EQ-5D has been mapped to patient-specific generic measures such as SF-12 (Gray et al. 2006) and disease-specific measures (Rivero-Arias et al. 2010; Wójcik et al. 2020; Shafie et al. 2021; Gray et al. 2021; Hoyle et al. 2016; Luan et al. 2021; Ali et al. 2017), there has been no attempt so far to map EQ-5D to family-specific measures.

With an estimated 6.5 million family members in the UK caring for a relative with a health condition and with growing evidence demonstrating the QoL impact of such care provision (Snyder et al. 2022; Shah et al. 2021b; Noghani et al. 2016; Golics et al. 2013b), measurement of this impact and its inclusion in health economic evaluation is of paramount importance. While a broad range of disease-specific and generic outcome measures have been designed to measure this impact (Shah et al. 2021a), none of these can be used for health economic evaluation involving family members/informal carers. For example, the tools CareQol-7D and CES, which measure carer burden, and have been developed for health economic evaluation, are not currently useful in calculations of QALYs which are based on HRQoL. While the inclusion of family member/informal carer utility values is encouraged by NICE and other health technology assessment agencies (Basarir et al. 2019), it is the lack of an appropriate family-specific QoL tool comparable to measures of patient HRQoL that has delayed including family member/carer utilities. Currently, EQ-5D is being used to measure carer utility, however, it was not designed for this purpose, and hence its use may be inappropriate (Al-Janabi et al. 2011). For example, the EQ-5D question on

'mobility as a moderate effect' may mean to family members/informal carers an inability to go out to meet people or travel for work/ study, while 'mobility as an 'extreme effect'' may confuse family caregivers as to why they should be 'confined to bed'. Furthermore, EQ-5D asks questions which are general in nature and does not specifically ask questions related to the QoL impact of caring for relatives, such as the effect on sleep, sex life, family relationships and family expenses that can have a huge impact on HRQoL. The FROM-16 includes items which reflect the true impact experienced by family members living with or caring for their relative. However, the emerging evidence from a recent study comparing five QoL instruments for carers across four conditions has shown that the EQ-5D had some validity and may be appropriate for use in health technology evaluations (McLoughlin et al. 2020). The main advantage of using the EQ-5D to measure family member/informal carer QoL is that it can easily be combined with patient QoL, allowing greater comparability across appraisals. Therefore, mapping FROM-16 to EQ-5D can potentially provide equivalence to EQ-5D utility values, allowing calculation of QALYS for family carers when EQ-5D data is not available.

However, for successful mapping, it is important that there is a conceptual overlap between the source and target instruments (Longworth and Rowen 2011). This study found significant correlations between the FROM-16 summary values and EQ-5D utility values. A significant association was also found between the FROM-16 domains and EQ-5D domains, with the emotional domain strongly correlated to anxiety/depression followed by activity, self-care, pain, and mobility. The personal and social domain of FROM-16 was also strongly correlated to anxiety/depression, followed by activity, pain/discomfort, self-care, and mobility. The correlation between individual FROM-16 items and EQ-5D domains was also observed, as demonstrated in Table 3.16. When compared to the correlation of EQ-5D-3L with other carer measures (Zarit burden, r_s=-0.021; time spent on instrumental activities of daily living (T-IADL), r_s=-0.014; Adult Social Care Outcomes Toolkit (ASCOT)-carer, r_s=0.36 and CES Index, r_s=0.36) (Reed et al. 2017, Rand et al. 2019), FROM-16 showed a stronger relationship to EQ-5D-3L (r_s=0.45) indicating the better ability of FROM-16 to predict EQ-5D utility values than such other carer measures.

This study has created an algorithm to calculate EQ-5D utility values from FROM-16 scores following an iterative process and has identified the model which predicts utility

values most closely to observed values. Regression analysis was first carried out on the full sample of 4,390 family members (2195 training set and 2195 testing set), with the mean difference between actual and predicted utility across the 10 models being 0.027 (3.94% overestimate), MSE=0.137, RMS=0.373 and MAE=0.272. This difference could have been explained by the presence of some erroneous and illogical responses in the data set; however, the model was improved by removing these clearly irrelevant and illogical responses, reducing the sample size to 4228 family members (2114 training set and 2114 testing set). The difference in means between observed and predicted utility across ten validation sets then changed from 0.027 to 0.015, indicating a slight overestimate of poor health, however, not reaching a clinically important level. Although the mean errors MSE and MAE were slightly higher than reported by Ali et al.'s (2017) DLQI mapping study (MSE 0.0728 to 0.0818, average=0.0766; MAE 0.1873 to 0.2009, average=0.1934), it should be noted that the study has been modelling a family-specific measure to EQ-5D, rather than a patient-specific measure and hence such variation may be expected. This difference between predicted and observed utility values highlights that family members were able to express their QoL impact more appropriately in their responses to FROM-16, a family-specific tool, than in their responses to the patient focussed EQ-5D. Furthermore, compared to direct methods, any response mapping method is penalised for any incorrect prediction, leading to increased MSE (Gray et al. 2006; Rivero-Arias et al. 2010).

Despite this difference, the model reliably predicts EQ-5D scores, in particular at a group level, demonstrated through a split-half cross-validation process resulting in very close health utility estimate predictions. On average, 54% of the individual utility differences were predicted to lie within 0.05 of the actual values: this is comparable to Gray et al.'s (2006) results of 50% within 0.05. Sixty per cent were predicted to lie within 0.1, 73% within 0.2 and 83% were within 0.3 of the actual values. These are still important differences on a scale of 0-1, but the model's group-level performance demonstrates a better predictive ability. While overall predictions were strongly correlated to the observed scores at a group level, the individual predicting power of the model may require further testing. The challenges of mapping accurately between two PROs at an individual subject level are clearly much greater than when mapping combined data from a large group of subjects.

Cross-validation is widely used in statistical analysis to assess how a predicted model performs with an unknown dataset. Holdout cross-validation is the simplest of cross-validation methods where the sample is divided randomly into two parts, i.e., the training set and the testing set. However, this method can give misleading results if only a single run is carried out: this process does not result in true randomisation, and the results could be subject to possible statistical bias (Ali et al. 2017). Ali and colleagues (2017) overcame this disadvantage by adopting the split-half cross-validation method, in which they divided the sample five times randomly into two parts (training and testing sets) and then reversed the process resulting in ten cross-validation sets, with each having a chance to be a training set as well as a testing set. Thus, for each set, the predictive accuracy was assessed using the respective training and validation data and finally averaging the results over all the sets. The split-half cross-validation method not only improves the overall accuracy of the model but also shows that the accuracy of the predicted utility values was not due to chance (Ali et al. 2017). However, it could be argued that it reduces the sample size of the estimation sample, which can lead to reduced precision in the coefficients of the mapping function. Longworth and Rowen (2013) recommend that a mapping model should be re-estimated using the full data set once the model specification is assessed using the split-half approach. Though study sample was large enough not to be affected by the splitting of data, the final model algorithm was based on the entire sample of data from 4228 family members/partners. Although the split-half method can provide information on how accurately model performs on multiple and different subsets of data, the model may predict poorly if the sample is not representative of the population. Since study sample came from a UK population of family members/partners of patients across 27 medical specialities experiencing a wide range of condition severities (from no effect to extremely large effect), it is believed mapping model developed in this study is generalisable to the UK population of family members and caregivers.

Van Hout et al. (2012) contend that mapping analysis should be restricted to logically consistent responses. In this study, for comparison, the mapping exercise was carried out on the full data set of 4390 and on an ‘excluded’ dataset of 4228. Removing "inconsistent" responses led to model improvement (Van Hout et al. 2012). It was decided with the research team to remove "inconsistent" responses to minimise the

influence of illogical responses as the weights contributed by those responses could lead to an inaccurate mapping algorithm. The decision to base the FROM-16 mapping on the consistent data set employed a decision rule that considered response to be "inconsistent" if FROM-16 scores were ≥17, indicating a very large impact on family members (Shah et al. 2023) and the EQ-5D health state was 11111 indicating perfect health (Dolan et al.1996) within the same individual). Removing these "inconsistent" responses was proportionate across the data and did not induce bias (Table 3.2).

In this study, the response mapping approach was used, which more closely follows the logic of the EQ-5D instrument by predicting health states and then attaching the utility tariff values to these. This method has the advantage that it allows the predicted response values to be used in different countries using a country-specific tariff. This is particularly important as the evaluation in this study was based on the UK population and values derived from a UK value set tend to be lower than for populations in other countries (Rivero-Arias et al. 2010). Although cultural norms and attitudes might influence HRQoL and utility responses, this may not always be the case. For example, Ali et al. (2019) showed that a model created on an Italian population worked equally well when tested on a Norwegian population, indicating uniformity with respect to such variations within the European context.

The algorithms developed in this study could be used by researchers and health economists for calculations of EQ-5D health utility estimates from FROM-16 responses. An easily accessible version in a Microsoft Excel spreadsheet© with pre-programmed formulae will be available from the FROM-16 research team once study results are published.

3.6 CONCLUSIONS

The inclusion of QoL data of family members/informal carers in health economic evaluation is important and is encouraged by health economists and health care resource allocation decision makers. However, it is seldom reported, primarily due to the lack of a suitable family-specific tool to measure utilities. This study fills this important research and practice gap by mapping EQ-5D utility values to the generic family-specific QoL measure FROM-16. The algorithm developed in this study can be

used by economists and researchers to calculate EQ-5D-3L utility values from FROM-16 scores, thus allowing the inclusion of the economic worth of the impact on the QoL of family members/informal carers in health economic evaluation.

3.7 SUMMARY

- The effect of patients' health conditions on the lives of their family members and partners is a huge secondary burden. Although economists encourage including family member/informal carer utility in health economic evaluation, this is often omitted due to a lack of suitable utility measures of disease impact on family members/informal carers.

- The FROM-16, a generic FQoL instrument, could potentially be used to estimate utility values in family members. Therefore, this study aimed to predict EQ-5D-3L utility values from FROM-16 data to allow the use of FROM-16 in health economic evaluation.

- Data from 4,390 family members/partners of patients recruited to an online cross-sectional study through 58 UK-based patient support groups, three support platforms and SSDs in Wales were included in the analysis. The family members/partners completed basic demographic details, and the FROM-16 and EQ-5D-3L questionnaires.

- Although the analysis was first conducted on all data (n=4390), it was thought the model could be improved by removing the inconsistent responses. Therefore, the analysis was repeated with a data set (n=4228) improved by removing 162 illogical responses.

- The study used the split-half cross-validation method to map FROM-16 scores to EQ-5D-3L utility values. The dataset was randomly split five times into separate estimation and validation sets using the SPSS version 27 random number

generator. The estimation set was used to derive the mapping models, whilst the out-of-sample validation set was utilised for validating the fitted models.

- The five estimation and validation sets were then switched, and the process was repeated (split-half cross-validation), resulting in a total of ten models.

- The multinomial logistic and non-proportional Odds regression was conducted for each pair of datasets using FROM-16 items, age, and sex as independent variables.

- The model was tested on each validation dataset to produce three predicted probabilities per subject per EQ-5D domain.

- These three predicted probabilities were used to estimate the health utility for each individual by employing the Monte Carlo simulation and Expected Utility methods. While Monte Carlo simulation used regression probabilities first to predict domain responses and then health utility estimates, the Expected utility method used regression probabilities directly to derive utility estimates.

- The average predicted health utility estimate for each validation set was then compared with the observed health utility estimate of the same set.

- The model's performance was assessed by calculating, comparing and averaging errors (ME, MSE MAE and RMSE) across ten validation models. The visual plots of predicted versus observed utility, the frequency distribution of observed versus predicted EQ-5D -3L responses and histograms of the difference in means across all ten validation sets were also examined.

- The model was highly predictive, and its repeated fitting using multinomial logistic regression demonstrated a stable model.

- The predicted utility based on data set 4428 were closer to observed utility values than the predicted utility based on data set 4390, indicating that excluding irrelevant and illogical responses improved the model.

- The mean differences between predicted and observed health utility estimates for data set 4228 using Monte Carlo simulation ranged from 0.005 to 0.029 across the ten modelling exercises, with an average overall difference of 0.015 (a 2.2 % overestimate of poor health, not of clinical importance) while for data set 4390, it ranged from -0.005 to 0.065 with an average of 0.027.

- The final model algorithm is based on the entire sample of data from 4,228 family members/partners.

- An Excel spreadsheet designed with the relevant estimates and formulae already inputted will be available from the FROM-16 research team once the study results are published.

- The algorithm developed will enable researchers and economists to calculate EQ-5D health utility estimates from FROM-16 scores, thus allowing the inclusion of the family impact of disease in health economic evaluation of medical interventions.

CHAPTER 4

Assessing Responsiveness of FROM-16 to Change Over Time

4.1 INTRODUCTION

In the previous chapter, an algorithm was developed to allow the use of FROM-16 in health economic evaluation. However, to use FROM-16 for such analysis, it is important to establish its responsiveness, an aspect of validity in a longitudinal setting. Patient health impairment and/or treatment can be associated with a major impact on the quality of life (QoL) of their family members/partners. Although the importance of including family members/informal carers' utility values in health economic evaluation is emphasised and encouraged by the National Institute for Health and Care Excellence (NICE) in the UK (NICE 2013) and the second US panel on cost-effectiveness (Sanders et al. 2016) as discussed in the previous chapter, it is seldom reported, possibly because of uncertainty concerning the suitability of available carer measures or possibly because of the additional resources needed to gather such information. One of the fundamental psychometric qualities that needs to be met for such a measure to be used in economic analysis is to demonstrate sensitivity to change over time. This sensitivity is referred to as "responsiveness". The terms "sensitivity to change "and "responsiveness" are often used interchangeably; however, they connote different meanings. "Sensitivity to change" is the ability of an instrument to measure change in a state regardless of whether it is relevant or meaningful, while "responsiveness" is the ability of an instrument to measure a meaningful or clinically important change in a clinical state. Liang et al. (2000) argue sensitivity to change is a necessary but insufficient condition for responsiveness, while others have objected to the use of "sensitivity" as it might be confused for terms used in the evaluation and interpretation of diagnostic tests (i.e., sensitivity, specificity)(Liang et al. 2000). In this study the researcher preferred to use the term "responsiveness".

Terwee et al. (2003) have classified definitions of responsiveness into three categories:

1. Responsiveness as the ability to detect change in general, any kind of change, regardless of whether it is relevant or meaningful. It is often defined as a statistically significant change after treatment. This definition is synonymous with the concept of 'sensitivity to change' given by Liang (2000).

2. Responsiveness as the ability to detect clinically important change and requires an explicit, although often subjective, judgment on what is to be important (Anchor).
3. Responsiveness as the ability to detect real changes in the concept being measured. This definition is seen as a further extension of the previous two as it not only requires a judgment on what changes are important but also requires comparison with a "gold standard" measurement for the concept being measured.

The COSMIN defines "responsiveness" as the ability to detect change over time in the construct to be measured (Mokkink et al. 2010), and this definition is synonymous with third definition by Terwee et al. (2003) of responsiveness. Responsiveness is considered as longitudinal validity and therefore, it should be assessed in a longitudinal study design with at least two assessments with time points chosen in such a way that it can be expected that at least portion of the study population will change regarding the impact of the construct (Mokkink et al. 2021). Intuitively, the time point of the second assessment should be fixed according to when the maximal effect or change is expected, if possible. In the case of pharmacological interventions, this could be predicted based on the pharmacokinetic and pharmacodynamic activity of the respective product.

The literature review reported in Chapter 1 revealed that most Family QoL measures were not validated for responsiveness, indicating that these measures cannot be used for assessing the effect of a patient's treatment on family members/informal carers. Evidence of responsiveness is essential for family-reported outcome (FRO) instruments to be validated as useful for clinical monitoring or as an outcome measure in the assessment of the value of interventions. This chapter, therefore, evaluates FROM-16 for its responsiveness to change over time in the assessment of QoL of family members of patients with different health conditions.

4.2 AIM

- To assess the responsiveness of FROM-16 to change over time.
- To assess if FROM-16 is responsive to change in patient QoL over time.

4.3 METHODS

The data for this study (FROM-16 responsiveness) and study 4 (FROM-16 MCID, discussed in Chapter 5), assessing FROM-16 score change over time, were collected at the same time.

4.3.1 Study Design

This was a longitudinal study involving patients who visited the outpatient clinics of dermatology, rheumatology, endocrinology, gastroenterology and haematology at the University Hospital of Wales and University Hospital Llandough, Cardiff. The data collection took place from August 2022 to April 2023.

4.3.2 Ethical Considerations

The ethical issues considered and addressed include ethical approval, respecting COVID-19 restrictions, minimising F2F contacts, using a GDPR compliant survey platform, gaining informed consent, ensuring voluntary participation, anonymity and maintaining confidentiality. There is an added layer of ethical complexity when considering the involvement in a study of both patients and their family members, such as seeking patients' permission to involve their family members in the study in addition to seeking family members' consent to participate in the study. Although the study was approved by the HRA and HCRW (approval 20/EE/0242) (Appendix II), as Covid restrictions were still in place in March 2022, it was difficult to conduct these studies face-to-face. Therefore, an amendment was sought from the HRA and HCRW Ethics committee (IRAS Project ID: 281134; Ref: SPON1817-20_NSA02) to conduct these studies online with NHS patients within Cardiff and Vale University Health Board in order to reduce face-to-face interaction with patients and family members and also to reduce any impact on already pressured NHS services post-pandemic (Appendix XV). The amendment was approved on 20 June 2022 (Appendix XVI). According to the amendment, patients and their family members/partners would not complete the questionnaire in the clinic but at their homes, answering an online questionnaire using GDPR-compliant Jisc platform (Jisc 2021).

The ethics of recruitment were also considered during the study design. The patients were first informed about the study by the clinician when attending an outpatient clinic, and if they were interested, then the investigator would explain the study in detail to these patients. Interested patients would be provided by the investigator with a link to the online questionnaire using the Cardiff University email. For those patients who were not able to use electronic devices, the option of completing a questionnaire by post was available. Patients and family members had a choice not to participate in the study. The online questionnaire asked participants to read the participant information sheet before providing electronic consent. The participant then had a choice either to participate or not to participate, or to withdraw at any point in the studies (FROM-16 Responsiveness and FROM-16 MCID).

All information collected from participants was kept strictly confidential. The data from each study participant was given a unique code number to ensure anonymity in data handling. Only the investigator (RS) had access to the participant details that linked with each code number, and these have been kept securely within the Cardiff University offices at Glamorgan House, Cardiff University School of Medicine, to ensure confidentiality.

4.3.3 Inclusion/Exclusion Criteria

4.3.3.1 Inclusion criteria for patients

- Attending the outpatient departments of dermatology, diabetology, rheumatology, haematology, and gastroenterology at Llandough University Hospital and the University Hospital of Wales, Cardiff
- Starting a new or follow-up treatment due to therapy failure, or on existing treatment with a change in dosage where the clinician expected to see a change in the QoL of a patient within three months
- Able to read and understand English
- Have the mental capacity to give electronic informed "written" consent (electronic or paper-based) and to complete the questionnaires using an electronic device or by answering a postal questionnaire.

4.3.3.2 Inclusion criteria for family members

- An immediate family member or partner living with or caring for a patient diagnosed with one or more medical conditions under the care of one of the following specialities: dermatology, diabetology, rheumatology, haematology, and gastroenterology
- Able to give informed consent
- Able to read and understand English
- Have the mental capacity to give electronic informed "written" consent (electronic or paper-based) and complete the questionnaires using an electronic device or by answering a postal questionnaire**.**

4.3.3.3 Exclusion criteria for patients

- Stable on current treatment without any need for change in therapy
- Not having the mental capacity to give written informed consent (electronic or paper-based) or answer a postal or an online questionnaire.

4.3.3.4 Exclusion criteria for family members

- Aged under 18 years
- Their unwell relative being stable on existing treatment or not starting on a new medication
- Unable to read and understand English
- Unable to give written informed consent (electronic or paper-based) or answer a postal or an online questionnaire
- Paid carers or people not considered family members by patients.

4.3.4 Selection of Medical Specialities

The medical specialities chosen were those where clinicians could expect a change in a patient’s QoL within three months following either the prescription of a new medication, or treatment change following the failure of a previous treatment, or a change in the existing treatment, for example change in dosage or type of insulin in patients with diabetes. Based on this, five specialities were chosen: dermatology, diabetology, rheumatology, haematology, and gastroenterology.

4.3.5 Sampling

This study used non-probability convenience sampling. Although this process does not guarantee that the recruited participants will be representative of the target population, it is the most applicable and widely used recruitment method in clinical research (Elfil and Negida 2017). However, to reduce inherent selection bias, various appropriate strategies were used. For example, a choice to answer a postal questionnaire was provided if participants could not use electronic devices to access the survey. There is a possibility of non-responder bias as certain groups of people may be less likely to participate. This type of bias was minimised by following up patient and family members with a second and third reminder. Furthermore, to minimise selection bias, steps were taken to ensure that people whose attendance times at clinics were limited were not excluded from the possibility of being recruited by arranging clinics for recruitment at different times across the week (morning /afternoon sessions).

The data for FROM-16 responsiveness and MCID was collected the same time.

4.3.6 Sample Size Calculation

The sample size was based on the sample size calculation shown below:

$$n = 2\left(Z_{\alpha} + Z_{1-\beta}\right)^2 \left(\frac{\sigma}{\delta}\right)^2$$

Where *n* is the required sample size, for Z_{α}, *Z* is a constant (set by convention according to the accepted α error (type I) and whether it is a one-sided or two-sided effect. For this study, it was considered that this would be a two-sided effect. Therefore, setting α at 5%, the Z_{α} would be 1.96. For Z1-β, Z is a constant set by convention according to the power of the study. The power was decided to be 80% and for this power, Z1-β would be 0.842. σ is the standard deviation, while δ is the difference between the treatment means. The ratio $\frac{\delta}{\sigma}$ is termed the effect size. The effect size agreed upon by the research team for these studies was 0.5.

The sample size required for an effect size of 0.5 is therefore n=64. Assuming a 10% withdrawal rate, the researcher needed to recruit approximately 70 patients and 70

family members. A sample size of 50-99 is considered adequate for such studies (Mokkink et al. 2019).

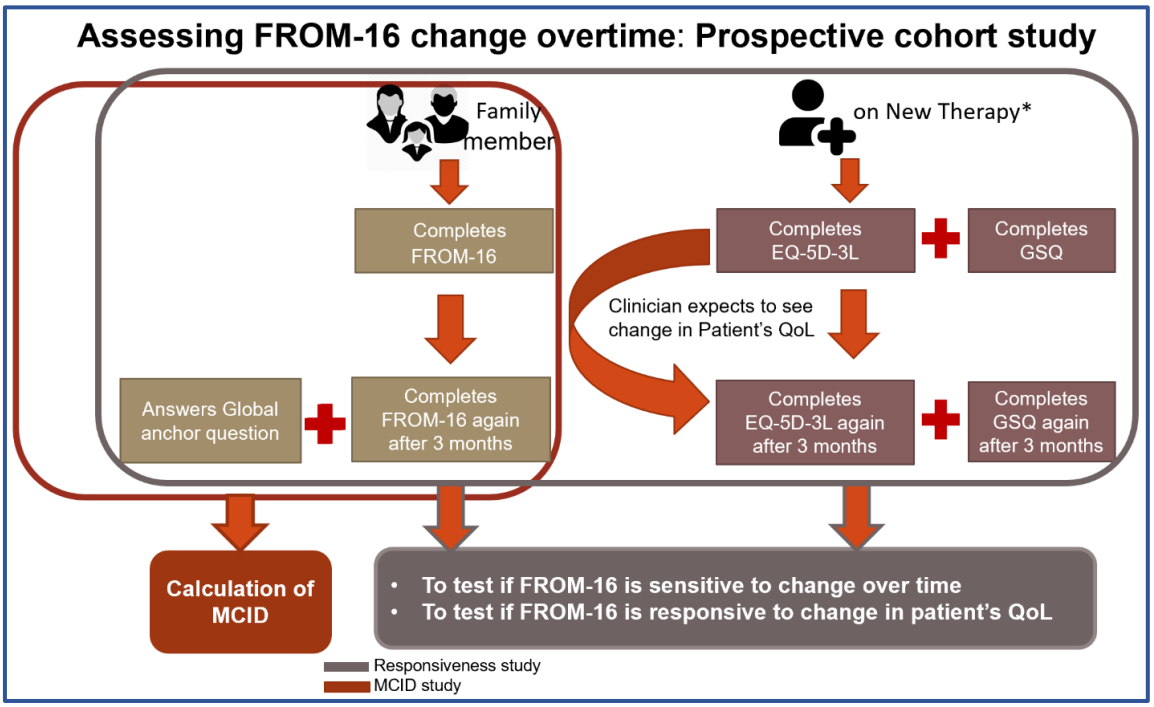
4.3.7 Survey Design

Two sets of surveys were created to collect the baseline and the follow-up data.
Baseline survey: This survey had two sections. Section one was to be completed by the patient. This section asked the patient to provide some basic demographic details (age, gender, ethnicity), details related to their health condition (diagnosis, whether or not any new treatment was prescribed, date of start of the new treatment or change in therapy), complete the EQ-5D questionnaire and answer a Global Severity Question (GSQ) to rate their disease severity. The EQ-5D-3L was chosen for the measurement of patient QoL as it is a short tool minimising respondent burden. Furthermore, given the time limitation of this PhD project, it was thought prudent to use the EQ-5D-3L as approval from Euroqol for the use of an electronic version of the EQ-5D-3L was already in place. It could be argued that the use of the EQ-5D-5L which has 5-point Likert scale options could be more responsive as it provides respondents with more options to choose small variations between assessments. However, the use of a 5-point scale would not have allowed family members to respond with similar options to the FROM-16, which has three options for each question. In contrast, the EQ-5D-3L also has three response options, making it more appropriate for data comparison with FROM-16. As the study aimed to check if FROM-16 was responsive to change over time in parallel to the patient's QoL, it makes sense to have similar Likert options for family members and patients.
The family member/partner of the patient was asked to provide some basic demographic details (age, gender, occupation, relationship to the patient) and complete the FROM-16 questionnaire.
Follow-up survey: This survey was emailed to the participants three months after the completion of the baseline survey. This survey had two sections. Section one was to be completed by the patient, asking the patient to complete the EQ-5D and the GSQ. Section 2 was to be answered by a family member/partner. Family members/partners were asked to complete the FROM-16 and answer a Global Rating of Change Question (GRCQ) to indicate how much (if any) they perceived their QoL had changed. To

maximise the response rate, either a text message/phone call or email was sent as a reminder.

The data for FROM-16 responsiveness and FROM-16 MCID studies was collected at the same time (Figure 4.1). The FROM-16 responsiveness study involved data from patients and their family members/partners, whereas the FROM-16 MCID study involved only family member data (involving the same family members as for the responsiveness study and additionally family members of paediatric patients).

Figure 4.1 Flow diagram: Assessing FROM-16 score change over time



**Patients on a new therapy or having a change in treatment following the treatment failure or change in dosage/device of existing medication*

4.3.8 Participant Recruitment

Patients were initially approached by their regular clinician to seek their consent to involve their relatives in the study and to gain permission for the investigator to contact the patient and introduce them to the study. The patients who gave their consent to their clinician to be contacted by the researcher with further information completed the questionnaire at their home by answering an online questionnaire using a GDPR-compliant platform, Jisc Surveys, operated via https://admin.onlinesurveys.ac.uk. The link was sent through the Cardiff University email. However, if family members were unable to operate electronic devices, they could choose to respond using a postal

questionnaire that was provided. The patients were given enough time (2-7 days) to process the information and decide on their participation. They were also provided with the investigator's contact details in case they had any queries about the study. The participants in the study gave informed electronic/written consent after reading the Participant Information Sheet (embedded in the online questionnaire or enclosed in the postal questionnaire) (Appendix XVII).

The study involved patients and family members/partners completing questionnaires at two assessment time points: baseline and three months later. In this chapter, the two time points, baseline and follow-up, will be represented by the letters "B_" and "F_" in the relevant Tables and Figures.

4.3.9 Patient and Public Involvement and Engagement - PPIE

One patient (HA) and a family member (MN) were involved in the planning and data collection stage, and in addition, one patient (SJN) contributed to the data analysis stage of the study.
One patient and one family member were involved in the study from the start of the research project planning discussions. These partners were involved in reviewing the survey and study protocol, ethics application, design and administration of anchor questions and all patient/family member documents (participant information sheets, draft email addressed to patients and family members for baseline and follow-up study). The research partners also tested the baseline and follow-up online study questionnaire to check if it was respondent-friendly and easy to understand and navigate. SJN contributed to the discussion on data analysis study outcomes. All research partners, HA, MN and SJN, were involved as co-authors and reviewed the study manuscript for publication.

4.3.10 Determining Responsiveness for FROM-16

Responsiveness should be based on triangulation of multiple approaches such as distribution- and anchor-based applying various patient-rated and disease-specific variables.

4.3.10.1 Distribution-based Approach

This method uses statistical properties of the distribution of outcome scores, particularly how the scores differ between subjects (in this study, family members) and include methods based on Effect Size (ES) and on Standardised Response Mean (SRM) (Revicki et al. 2008; Rai et al. 2015; Basra et al. 2015). This method was used as a primary method of analysis for this study to establish responsiveness of FROM-16 (Basra et al. 2007; Basra et al. 2015; McLoughlin et al. 2020).
In this study, the effect size was calculated to detect the magnitude of that change in the FROM-16 scores. Effect size (ES) is calculated as a ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation of the scores at the first assessment. An ES of 0.2 is considered small, 0.5 moderate and 0.8 large (Cohen 1988). The standardised response mean (SRM) is an effect size index used to assess the responsiveness of outcome measures, calculated from the ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation of that difference. An SRM >0.8 is considered to indicate large responsiveness, 0.5–0.8 moderate, and 0.2–<0.5 low responsiveness (Morrow et al. 2016).

4.3.10.2 Anchor-based Approach

Anchor-based methods examine the relationship between an HRQoL instrument and another measure of clinical change, “the anchor” (Rai et al. 2015). Anchors used can be derived from patients’ self-reported evaluation of change, such as the Global Rating of Change scale, the Global Severity scale or clinical outcomes such as laboratory values, psychological measures, and clinical rating performance measures (Rai et al. 2015). The “Global” aspect of these scales allows the participants (patients or family members) to decide what they consider important. This may mean that the specific constructs each patient takes into account are unknown and may vary. However, this assumption allows the individual participant (patient or family member) to focus on those concerns that are most relevant to them (Kamper et al. 2009). Regardless of the instrument chosen as an external criterion, it is important that the anchor is well

understood by the study participants and reasonably associated with the target HRQoL questionnaire (Guyatt et al. 2002).

In this study, an anchor-based approach was used to assess responsiveness of FROM-16 to change over time. Family members/partners answered a 15-point Likert scale anchor question, the Global Rating of Change Question (GRCQ), at three months follow-up (Fulk et al. 2010; Basra et al. 2015; Yuksel et al. 2019). A 15-point scale was chosen as it allows a respondent to record even a very small change (improvement or deterioration).

The question asked was:

"Thinking about the effect of your family member/partner's condition on you, how much has your quality of life changed since you first took part in this study?"

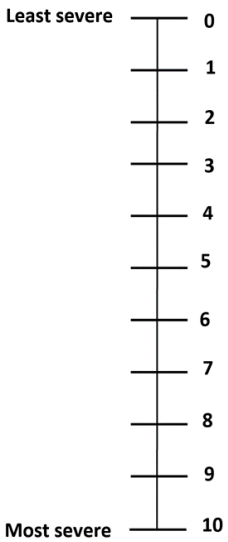
Global Rating of Change Question (GRCQ)

Improved	Same	Deteriorated
1. A tiny bit better	0. About the same	-1. A tiny bit worse
2. A little bit better		-2. A little bit worse
3. Somewhat better		-3. Somewhat worse
4. Moderately better		-4. Moderately worse
5. Quite a bit better		-5. Quite a bit worse
6. A great deal better		-6. A great deal worse
7. A very great deal better		-7. A very great deal worse

In the online questionnaire, respondents initially had to choose from three options, "Improved", "The same" or "Deteriorated". If they chose "Improved" they were then given the options: 1 to 7. If they chose "Deteriorated" they were given the options -1 to -7.

Despite the argument that the GRCQ is subject to recall bias, it has been widely used because of its simplicity, sensitivity to change (both positive and negative), and because of it being a person's own evaluation of his or her change in health state (Hagg et al. 2002; Norman et al. 1997; Kamper et al. 2009). In order to reduce the impact of recall bias, it is recommended that a short follow-up interval is used. In this study, 12 weeks was chosen as the follow-up time as it is within the time frame during which the clinicians expected to see a change in the patient's QoL following a new treatment or change in existing treatment. This is a relatively shorter time frame than used in other studies (Chuang et al. 2013; Den Oudsten et al. 2013).

Additionally, a Global severity question (GSQ) was used as another anchor to provide the patients' evaluation of the severity of their health condition over time at baseline and follow-up. This was then used to demonstrate if the change in family members' QoL over time between baseline and follow-up was associated with the change in the patients' QoL over time demonstrated by GSQ. The question asked to the patients was: "*Thinking about your health, on a scale of 0 to 10 how severe do you consider your disease is today?".*



The patients were asked to enter the number in the online questionnaire to indicate their disease severity.

4.3.11 Data Processing and Statistical Analysis

The normality was assessed by observing histograms and statistical methods of Skewness and Kurtosis (Hair Jr 2010; Kline 2011). The responsiveness of FROM-16 was assessed through several methods, including testing various hypotheses. The study used the construct approach (Prinsen et al. 2018), by testing predefined hypotheses about expected correlations among measures, area under the ROC Curve, and effect sizes. Although distribution-based methods are simple and widely used for assessing responsiveness of QoL instruments, they are influenced by intervention type and adherence, sample size, and heterogeneity (de Vet et al. 2011). The COSMIN guidelines recommend not drawing conclusions about the responsiveness of an instrument based on *P* values or effect size estimates alone (de Vet et al. 2011). Therefore, responsiveness was also examined using a construct approach, making

informed a priori hypotheses about the direction and magnitude of effect sizes and correlations between the change in FROM-16 scores and the single-item family GRCQ and patient GSQ scores (Mokkink et al. 2010; de Vet et al. 2011; Prinsen et al. 2018). All hypotheses for testing responsiveness are listed in Table 4.1 and were formulated according to the COSMIN methodology and previous studies assessing responsiveness (Mokkink et al. 2010; de Vet et al. 2011; Prinsen et al. 2018).

Table 4.1 Hypothesis for testing responsiveness of FROM-16

1. Family members/partners indicating improvement on the associated GRC scale should have a positive mean change score.
2. Family members/partners indicating worsening on the associated GRC scale should have a negative mean change score.
3. The mean change score of family members/partners indicating improvement should be higher than the mean change score of unchanged family members/partners, which in turn should be higher than the mean change score of worsened family members/partners.
4. ROC curve demonstrating responsiveness of FROM-16 should have AUC ≥ 0.7.
5. An improvement /deterioration in the QoL of family members was hypothesised in relation to a significant improvement/deterioration in patient HRQoL.
6. Moderate to strong positive correlation between the FROM-16 change scores and the GRC scale measuring a similar construct and low to moderate positive correlation between the FROM-16 change score and the patient's disease severity change score measuring a dissimilar construct.
7. Low to moderate negative correlation between the FROM-16 change score and EQ-5D change score measuring related but dissimilar construct.
8. An improvement/deterioration in QoL of family members was hypothesised in relation to a significant improvement/deterioration in patient disease severity between baseline and follow-up as recorded on the GSQ.
9. A change in proportion of family members across FROM-16 severity score bands between two assessments.

Additionally, changes in score meaning descriptor bands between two assessment points were used to assess the responsiveness of FROM-16. This simple and visual display of change in FROM-16 bands provides evidence of responsiveness of the instrument and can be used as supportive evidence for responsiveness. The responsiveness was considered sufficient if ≥ 75% of the hypotheses (Table 4.1) were confirmed (Prinsen et al. 2018).

The internal responsiveness, which characterises "the ability of a measure to *change* over a particular prespecified time frame" (Husted et al. 2000), was assessed through a paired-sample t-test. Distribution-based approaches, effect size (ES) and standard response mean (SRM) were also used to assess internal responsiveness by measuring the magnitude of change in the FROM-16 score from baseline to follow-up. The ES was calculated as a ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation at the first assessment. An ES of 0.2 is considered small, 0.5 moderate and 0.8 large (Cohen 1992). The SRM was calculated as the ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation of that difference. Based on the responsiveness studies conducted for patient and family quality of life measures (Basra et al. 2007; Basra et al. 2015), ES and SRM of small to moderate value was hypothesised for FROM-16.

The external responsiveness (the extent to which changes in a measure over a specified time frame relate to corresponding changes in a reference measure) (Husted et al. 2000) was assessed through an anchor-based approach and correlational approach. Anchor-based approaches were used to examine the relationship between the change in scores of FROM-16 and the GRCQ score. Pearson's correlation was conducted between the mean change in FROM-16 scores and GRCQ score, and a correlation coefficient >0.3 was considered a good relationship between the two measures for using the anchor-based method (Revicki et al. 2008). It was hypothesised that family members indicating improvement on the associated GRCQ scale should have a positive mean change score; family members indicating worsening on the associated GRCQ scale should have a negative mean change score; the mean change score of family members indicating 'improvement' should be higher than the mean change score of 'unchanged family members', which in turn should be higher than the mean change score of 'worsened family members' (Prinsen et al. 2018).

The ROC analysis was used as another method to assess the responsiveness of FROM-16 against an external measure, the GRCQ. It involved dichotomizing the outcomes on the GRCQ into "improved" and "not improved [worsened and the same group]" and "worsened" and “not worsened [Improved and the same group]". The ROC analysis was run separately to test the responsiveness of FROM-16 to improvement and deterioration in the QoL of family members. It was hypothesised that the AUC ≥0.7

would be indicative of adequate responsiveness (de Vet et al. 2011; Prinsen et al. 2018).

An improvement in QoL of family members was hypothesised in relation to a significant improvement in patient HRQoL (and vice versa for a worsening in patient HRQoL). This hypothesis was tested by assessing the strength of the correlation between family member measures (FROM-16 and GRCQ score) and patient measures (EQ-5D, EQ-VAS, GSQ) using Pearson's correlation analyses. A moderate to high correlation was expected between related and similar constructs (FROM-16 and GRCQ). A low to moderate correlation was expected between related but dissimilar constructs (FROM-16 and patient measures). The probability of type I error was set at $p<0.05$ level. Cohen's criteria were used as a guide for the magnitude of correlations: values of a correlation between 0.1 and 0.3 are viewed as being "small", 0.3 and 0.5 considered "moderate" and values above 0.5 as being "large" (Cohen 1992). Additionally, the magnitude of change in the family members' FROM-16 scores and the patients' scores of EQ-5D, GSQ and EQ-VAS were assessed to see if FROM-16 was responsive to changes indicated by these patient measures.

An improvement in QoL of family members was hypothesised in relation to a significant improvement in the patient's disease severity (and vice versa for a worsening in the patient’s disease severity). This hypothesis was tested by comparing change scores between patients and family members in response to changes in patients' disease severity.

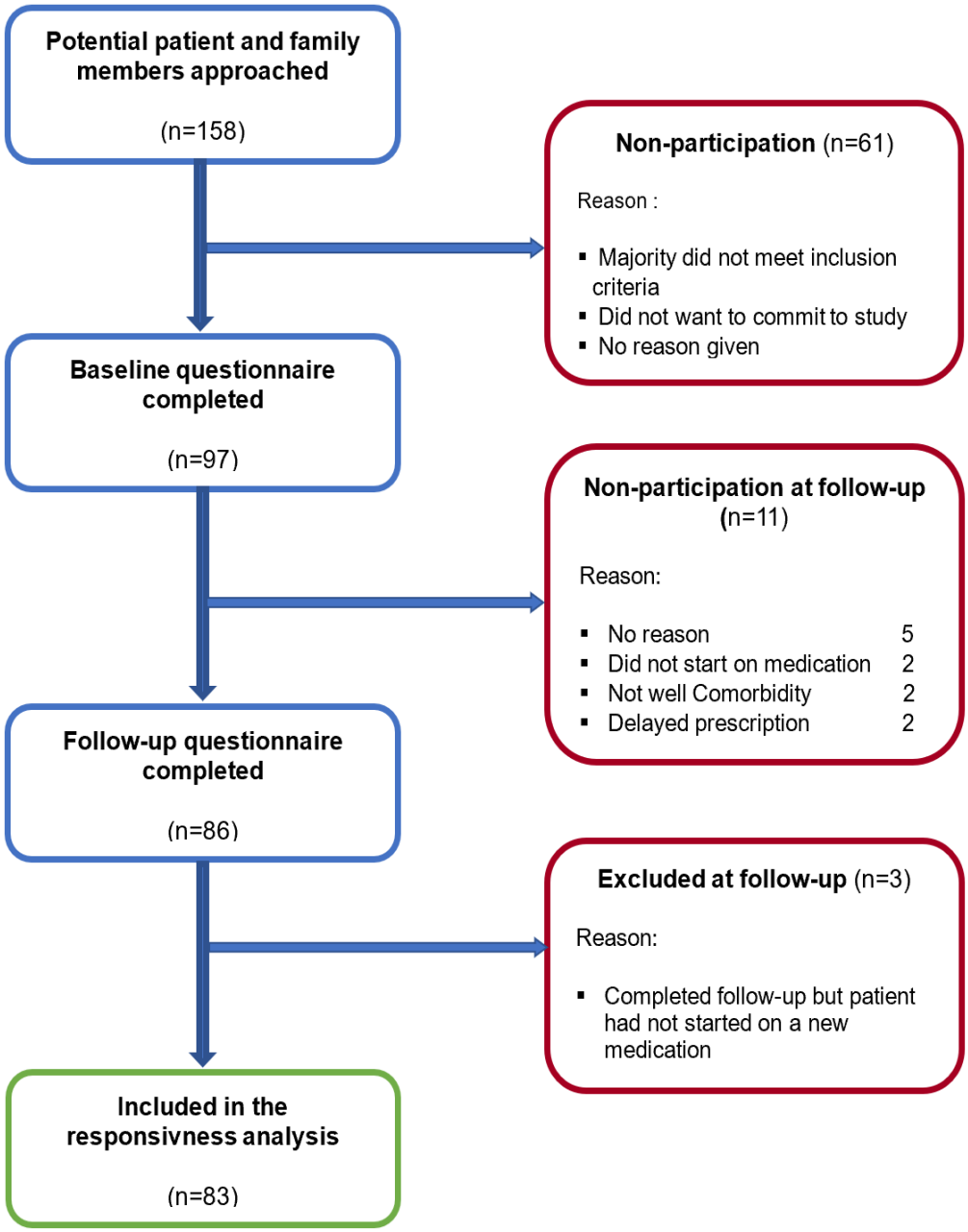
This study applied FROM-16 score banding to assess change over time between two assessments. This is a unique contribution of this thesis to the literature as to our knowledge no other study has so far tested responsiveness of a QoL tool using banding application. This involved application of score banding to family members’ FROM-16 scores at first and second assessment and recording the number of family members falling under each of the five categories (no effect on QoL of family members, FROM-16 scores=0-1; little effect, 2-8; moderate effect, 9-16; very large effect,17-25; and extremely large effect on QoL of family members, 26-32). The change in the proportion of family members across the five bands between two assessments would be indicative of responsiveness of FROM-16. All analyses were undertaken using IBM SPSS Statistics 27.

4.4 RESULTS

4.4.1 Response Rate

Although 97 patients and their family members completed the baseline questionnaire, only 86 (83.5%) completed follow-up (Figure 4.2). Five patients and their family members did not respond to follow-up, two patients did not start on a new medication,

Figure 4.2 Flow chart of recruitment: Baseline to follow-up



another two were suffering from severe comorbidity and therefore were not eligible to participate in the follow-up, and two patients had delayed prescriptions. Of the 86 patients and family members who completed follow-up questionnaires, three patients had no change in treatment hence their responses were not included, leaving 83 responses from patients and family members for analysis.

4.4.2 Sociodemographic Characteristics of the Study Participants

Eighty-three patients with 15 different health conditions (mean age=51 years, SD=18.7; range=18-89; female 51.8%; White=89.2%) across dermatology, rheumatology, diabetology, haematology and gastroenterology and their family members (mean age=50.75 years, SD=15.48; range=18–83; female=55.4%) were included in the responsiveness analysis. The family members were mostly spouses/partners (80.5%) from White (91.6%) ethnic backgrounds. The commonest conditions were diabetes type 2 (23%), followed by rheumatoid arthritis (12%), hidradenitis suppurativa (12%), diabetes type 1 (12%) and psoriasis (12%) (Table 4.2).

4.4.3 FROM-16 and EQ-5D Scores

The normality was assessed through the Shapiro-Wilk test and histograms for all continuous variables. The skewness and kurtosis values were within the bounds of normality, indicating normal distribution (Hair Jr 2010; Kline 2011). Therefore, t-test were used to analyse data. The mean FROM-16 score at baseline was 9.5 (SD=6.8). The mean FROM-16 score at follow-up was 8.1 (SD=6.9) (Table 4.3). There was no significant difference between male and female FROM-16 scores at baseline (females: mean=10.5, SD=6.7; male: mean=8.3, SD=6.9; p=0.071) and at follow-up (male: mean score=7.2, SD=7.6; female: mean score = 8.8, SD=6.4; p=0.127) (Table 4.4). There was no significant difference in age or FROM-16 scores at baseline between responders and non-responders (those who dropped out and, therefore, were not eligible for follow-up). The main differences between responders (n=83; males=44.6%; females=55.4%) and non-responders (n=14; males=35.7%; females=64.3%) were as follows: mean age of responders=50.75 years and mean age of non-responders=57.07 years (p=0.161); mean baseline FROM-16 score of responders=9.54 and mean baseline FROM-16 score of non- responders=11.00 (p=0.489).

Table 4.2 Socio-demographic characteristics of the study participants

Characteristic		Number (%) or Mean (SD)
Patient (n=83)		
Age (years)	Mean age	51.0 (18.7)
	Range	18-89
Gender	Male	40 (48.2)
	Female	43 (51.8)
Ethnicity	White	74 (89.2)
	Asian/Asian British	6 (7.2)
	Black/African/Caribbean/Black British	2 (2.4)
	Prefer not to say	1 (1.2)
Occupation	In paid work	44 (53.0)
	Unemployed	5 (6.0)
	Homemaker	6 (7.2)
	Retired	25 (30.1)
	Rather not say	3 (3.6)
Heath condition	Acne	5 (6.0)
	Eczema	6 (7.2)
	Psoriasis	10 (12.0)
	Urticaria (Hives)	1 (1.2)
	Rosacea	1 (1.2)
	Hidradenitis Suppurativa	10 (12.0)
	Rheumatoid Arthritis	10 (12.0)
	Seronegative Arthritis	1 (1.2)
	Psoriatic Arthritis	2 (2.4)
	Ankylosing Spondylitis	1 (1.2)
	Enteropathic Arthritis	1 (1.2)
	Myeloma	5 (6.0)
	Type 1 Diabetes	10 (12.0)
	Type 2 Diabetes	19 (22.9)
	Ulcerative Colitis	1 (1.2)
Family member/partner (n=83)		
Age (years)	Mean age	50.8 (15.48)
	Range	18-83
Gender	Male	37 (44.6)
	Female	46 (55.4)
Ethnicity	White	76 (91.6)
	Asian/Asian British	4 (4.8)
	Black/African/Caribbean/Black British	2 (2.4)
	Prefer not to say	1 (1.2)
Occupation	In paid work	49 (59.0)
	Unemployed	1 (1.2)
	Homemaker	5 (6.0)
	Education/training	1 (1.2)
	Retired	24 (28.9)
	Rather not say	3 (3.6)
Relationship to patient	Spouse/Partner	67 (80.5)
	Parent	6 (7.2)
	Son/Daughter	8 (9.6)
	Brother/Sister	1 (1.2)
	Other	1 (1.2)

Table 4.3 Mean baseline and follow-up scores for family members and patients (n=83)

	Family members		Patients					
	B_FROM	F_FROM	B_EQ-5D	F_EQ-5D	B_EQVAS	F_EQVAS	B_Disease severity	F_Disease severity
Mean	9.54	8.11	0.74	0.80	60.16	68.64	5.17	4.34
Median	9.00	6.00	0.81	0.81	60.00	70.00	5.00	4.00
SD	6.83	6.92	0.22	0.18	22.75	20.13	2.48	2.45
Minimum	0.00	0.00	0.21	0.21	5.00	3.00	0.00	0.00
Maximum	27.00	29.00	1.00	1.00	95.00	100.00	10.00	10.00
Mean Change	1.43 (SD=5.01; p= 0.011)		-0.059† (SD=0.143; p<0.001)		-8.56 (SD=19.43; p=0.015)		0.964 (SD=3.11; p=0.006)	
ES	0.210		0.263		0.402		0.388	
SRM	0.286		0.412		0.473		0.309	

† EQ-5D and EQ-VAS improvement is in the opposite direction to FROM-16; B_FROM and F_FROM refer to baseline and follow-up FROM-16 scores; B_EQ-5D and F_EQ-5D, baseline and follow-up patient EQ-5D-3L utilty score (health states based on UK TTO; B_EQ-5D-VAS and F_EQ-5D-VAS refer to baseline and follow-up EQ-5D visual analogue scale score; B_Disease severity and F_Disease severity refer to baseline and Follow-up Disease severity; ES, Effect size: 2-5=small change, 5-8=Moderate change,> 8=large change. SRM, Standard response mean

Table 4.4 Independent t-test for differences between male and female genders

	Mean		Mean difference	p-value *
	Male Mean (SD)	Female Mean (SD)		
Family members	(n=37)	(n=46)		
B_FROM	8.32 (6.9)	10.52 (6.7)	-2.20	0.146
F_FROM	7.24 (7.6)	8.80 (6.4)	-1.56	0.311
Patients	(n=40)	(n=43)		
B_EQ-5D	0.75 (0.22)	0.73 (0.23)	0.02	0.607
F_EQ-5D	0.82 (0.17)	0.78 (0.20)	0.04	0.376
B_EQ-5D-VAS	60.25 (23.7)	58.91 (22.2)	1.34	0.791
F_EQ-5D-VAS	69.83 (18.6)	67.74 (21.1)	2.09	0.636
B_GSQ	5.23 (2.8)	5.26 (2.2)	-0.03	0.956
F_GSQ	3.95 (2.3)	4.58 (2.5)	-0.63	0.242

*Significant at < 0.05 level. B_GSQ is the baseline global severity question score; F_GSQ is the follow-up global severity question score.

The mean EQ-5D score for patients at baseline was 0.74 (SD=0.22), and at follow-up was 0.80 (SD=0.18) (Table 4.3). There was no significant difference between patients mean EQ-5D scores between males and females at baseline (male=0.75, SD=0.22; female=0.73, SD=23; p=0.607) and follow-up (male=0.82, SD=17; female=0.78, SD=0.20; p=0.376). There was no difference between patient mean EQ-VAS scores and disease severity scores between male and female at baseline and follow-up (Table 4.4).

The mean EQ-5D scores of patients varied across the five medical specialities, with rheumatology patients having the lowest EQ-5D health states (n=15, B_EQ-5D=0.68; F_EQ-5D=0.76) and IBD (n=1, B_EQ-5D=0.81; F_EQ-5D=1) having the highest EQ-5D values at baseline and follow-up (Table 4.5).

Table 4.5 Change in scores in patients and their family members across medical specialities (n=83)

	Family Member/Partner					Patient				
Medical specialty	**B_FROM**	**F_FROM**	**Mean diff FROM**	**ES**	**SRM**	**B_EQ-5D**	**F_EQ-5D**	**Mean diff EQ-5D**	**ES**	**SRM**
Dermatology (n=33)	9.03	7.12	1.91	0.258	0.310	0.71	0.80	-0.09	0.374	0.552
Diabetes (n=29)	8.38	6.93	1.45	0.242	0.423	0.79	0.80	-0.01	0.055	0.125
Rheumatology (n=15)	11.40	11.27	0.13	0.022	0.024	0.68	0.76	-0.08	0.489	0.517
Haematology (n=5)	13.60	12.60	1.00	0.101	0.365	0.78	0.79	-0.01	0.099	0.447
IBD (n=1)	12.00	5.00	7.00			0.81	1.00	0.19		

IBD, Inflammatory Bowel Disease; ES, Effect Size; SRM, Standard Response Mean

The mean FROM-16 scores of family members also varied across the five medical specialities, with family members of haematology patients having the highest FROM-16 scores (n=5, B_FROM=13.60; F_FROM=12.60). The lowest baseline FROM-16 score was for family members of diabetes patients (n=29, B_FROM=8.38) (Table 4.5).

The most highly scoring FROM-16 items at both stages were items 1, 3 and 4 concerning the emotional health of family members, while the lowest scoring item was item 13, asking about the effect on work and study (Table 4.6).

Correspondingly, the most significant differences according to the magnitude of change between the two assessments were reported for items 1, 3, 4 and 16. The smallest change was observed for item 9 (Table 4.6).

Table 4.6 FROM-16 item and total scores at baseline and follow-up, showing the mean change with ES and SRM (n=83)

FROM-16		Baseline	Follow-up	Mean Change	ES	SRM
Total FROM-16 score		9.54	8.11	1.43*	0.210	0.286
Domains						
1	Emotional	4.13	3.45	0.687*	0.28	0.31
2	Personal and social	5.40	4.66	0.747*	0.15	0.22
Items						
1	Worried	**1.25**	**1.07**	**0.18***	**0.26**	**0.30**
2	Angry	0.41	0.35	0.06	0.10	0.11
3	Sad	**1.05**	**0.77**	**0.28****	**0.42**	**0.39**
4	Frustrated	**0.99**	**0.73**	**0.25***	**0.32**	**0.35**
5	Difficulty talking about thoug	0.43	0.52	-0.08	-0.17	-0.10
6	Difficulty caring	0.59	0.47	0.12	0.17	0.20
7	Time for self	0.45	0.40	0.05	0.07	0.09
8	Every day travel	0.25	0.23	0.02	0.05	0.05
9	Eating habits	0.25	0.24	0.01	0.02	0.02
10	Family activities	0.73	0.63	0.11	0.14	0.17
11	Holiday	0.59	0.63	-0.04	-0.05	-0.06
12	Sex life	0.77	0.66	0.11	0.13	0.16
13	Work or study	0.20	0.13	0.07	0.16	0.15
14	Family relationships	0.25	0.22	0.04	0.07	0.07
15	Family expenses	0.57	0.48	0.08	0.11	0.13
16	Sleep	**0.75**	**0.58**	**0.17***	**0.22**	**0.25**

ES, Effect Size; SRM, Standard Response Mean.

4.4.4 Responsiveness to Change of the FROM-16

The responsiveness analysis, using the paired-samples t-test, showed that the FROM-16 was responsive to change. The mean FROM-16 score of 83 family members/partners at baseline was 9.54 (SD=6.8) and 8.11 (SD=6.9) at follow-up, with a mean change of 1.43 ($p<0.05$) (Table 4.3).

4.4.4.1 Distribution-based methods

The distribution-based methods, the ES and SRM, were used to assess responsiveness of FROM-16 to change. The ES of the FROM-16 change score between baseline and follow-up was 0.2 while the SRM was 0.3, both indicating a small effect according to Cohen's criteria (Table 4.3). The ES and SRM provide useful interpretation of magnitude of change.

4.4.4.2 Anchor-based method

Family members (n=9) who recorded an improvement on the GRCQ had a positive mean change score of 6.89 (ES=0.83) [confirming hypothesis # 1] (Table 4.7), and family members (n=8) who recorded a worsening on the GRCQ had a negative mean score change of -1.38 (ES = -0.171) [confirming hypothesis # 2]. The mean score change in family members (n=66) who recorded no change on GRCQ had a positive change score of 1.03 (ES=0.173) (Table 4.6). The mean change score of family members indicating improvement was higher than the mean change score of unchanged family members, which in turn was higher than the mean change score of family members who became worse [confirming hypothesis # 3].

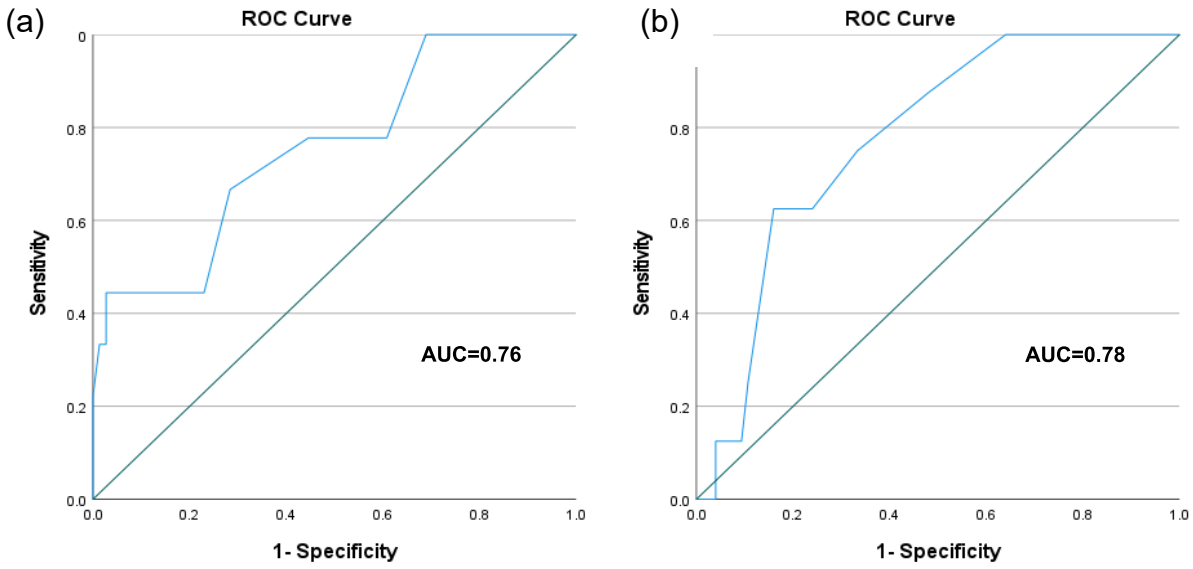
Table 4.7 GRCQ scale and associated FROM-16 scores

GRC scale	Hypotheses	B_FROM score Mean (SD)	F_FROM score Mean (SD)	FROM change score Mean (SD)	ES	SRM	Hypotheses Met Yes/No
Improvement (n=9)	Mean change improved should be positive	11.44 (8.28)	4.56 (4.75)	6.89 (8.22)	0.832	0.838	Yes
Deterioration (n=8)	Mean change worsened should be negative	16.75 (8.03)	18.12 (6.81)	-1.38 (2.26)	-0.171	-0.607	Yes
No change (n=66)	Mean change should be between improvement and deterioration	8.41 (5.94)	7.38 (6.18)	1.03 (4.19)	0.173	0.246	Yes
	Mean change improvement >Mean Change unchanged >worsened	6.9> 1.0> -1.4					Yes

B_FROM, baseline FROM-16 score; F_FROM, follow-up FROM-16 scores; FROM-16 change score, difference between baseline and follow-up FROM score; ES effect size; SRM, standard response mean; SD, standard deviation.

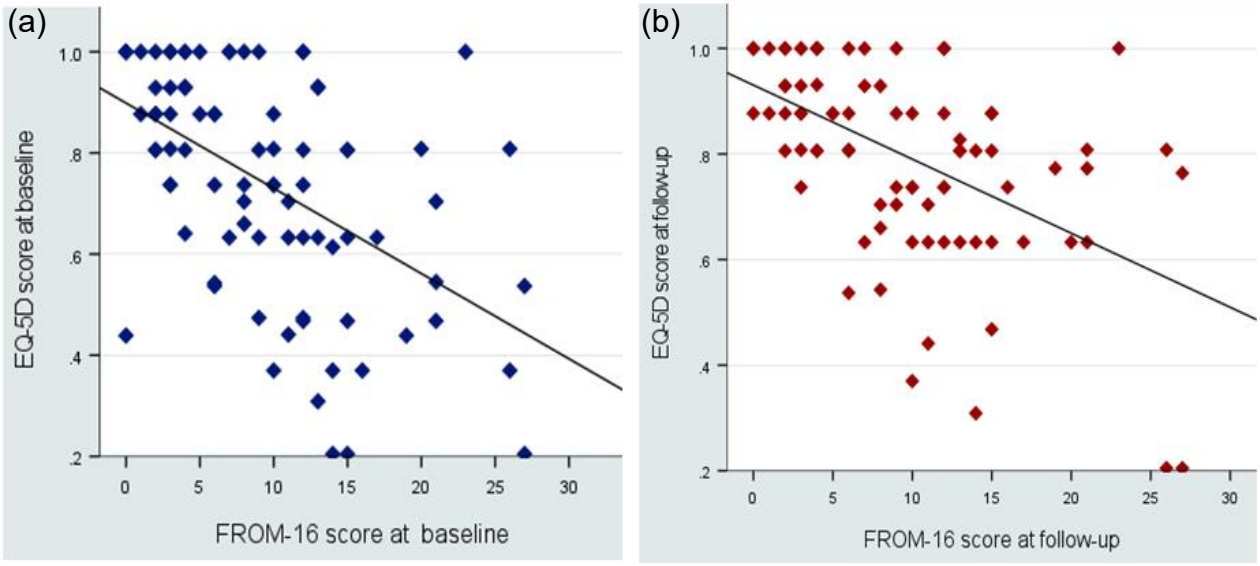
The ROC curve analysis provides a very useful overview of the responsiveness of the instrument by showing whether the instrument can discriminate between improved and not improved and worsened and not worsened. The ROC_{AUC} value ≥ 0.7 indicates good responsiveness. The ROC_{AUC} value was 0.76 for improvement and 0.78 for deterioration (Figure 4.3), indicating that FROM-16 is sensitive to changes in scores when a family member's QoL improves or deteriorates [confirming hypothesis # 4].

Figure 4.3 ROC curve indicating responsiveness of FROM-16 (a) Improvement versus no improvement (b) deterioration versus no deterioration



The QoL of family members changed in parallel to the QoL of patients over three months (Table 4.2). The magnitude of change in patient's QoL observed through change in EQ-5D scores (ES=0.3, SRM=0.4,) EQ-VAS score (ES=0.4, SRM=0.4) and GSQ (ES=4, SRM=3) indicated that the small change in effect size according to Cohen's criteria was closely related to family member FROM-16 score changes (ES=2, SRM=3) [confirming hypothesis # 5] (Table 4.3). The scatter plot (Figure 4.4) shows a negative linear relationship between baseline and follow-up EQ-5D and FROM-16 scores (Figure 4.4).

Figure 4.4 Scatterplots of the relationship between the FROM-16 scores and the EQ-5D scores at (a) baseline and at (b) follow-up



4.4.4.3 Correlation Matrix – Relationships between variables

These results are further confirmed with correlation analysis between the two measures (Table 4.8). Pearson's correlation between family members' FROM-16 scores and patients' EQ-5D, EQ-VAS and GSQ scores demonstrated that the FROM-16 was responsive to changes in the patients' QoL. There was a positive moderate correlation between the FROM-16 change score and GRCQ score ($r=0.388$, $p \leq 0.001$), and FROM-16 change score and patient's disease severity change score ($r=0.374$, $p \leq 0.001$) [confirming hypothesis #6] and a low negative correlation between the FROM-16 change score and EQ-5D change score ($r=-0.243$, $p < 0.05$) [confirming hypothesis #7]. There was a high negative correlation between family members' FROM-16 baseline and patient EQ-5D baseline (r=0.515**) and FROM-16 follow-up and EQ-5D follow-up ($r=0.622$, $p \leq 0.001$). There was a moderate negative correlation between baseline FROM-16 score and patient EQ-VAS score ($r =-0.496$, $p \leq 0.001$) and follow-up scores of these measures ($r=-0.492$, $p \leq 0.001$) (Table 4.8).

Table 4.8 Pearson's correlation between FROM-16, GRCQ and patient measures (n=83)

	FROM change score	B_FROM	F_FROM	GRC-score	B_EQ-5D	F_EQ-5D	EQ-5D score change	B_EQ-VAS	F_EQ-VAS	EQ-VAS score change	B_DS	F_DS	DS score change
FROM change score	1												
B_FROM	0.347**	1											
F_FROM	-0.381**	0.735**	1										
GRCQ score	0.388**	-0.173	-0.451**	1									
B_EQ-5D	-0.028	-0.515**	-0.487**	0.188	1								
F_EQ-5D	0.153	-0.518**	-0.622**	0.391**	0.773**	1							
EQ-5D score change	-0.243*	-0.136	0.042	-0.212	0.567**	-0.085	1						
B_EQ-VAS	0.039	-0.496**	-0.517**	0.235*	0.705**	0.668**	0.240*	1					
F_EQ-VAS	0.224*	-0.334**	-0.492**	0.390**	0.547**	0.675**	-0.016	0.593**	1				
EQ-VAS score change	-0.184	-0.241*	-0.104	-0.122	0.269*	0.095	0.298**	0.569**	-0.325**	1			
B_DS	0.222*	0.174	0.011	-0.003	-0.282**	-0.143	-0.257*	-0.296**	-0.095	-0.250*	1		
F_DS	-0.250*	0.237*	0.414**	-0.420**	-0.306**	-0.410**	0.05	-0.439**	-0.468**	-0.038	0.203	1	
DS score change	0.374**	-0.047	-0.316**	0.327**	0.015	0.207	-0.245*	0.109	0.292**	-0.17	0.639**	-0.623**	1

*** Correlation is significant at the 0.01 level (2-tailed).*Correlation is significant at the 0.05 level (2-tailed).; **Green shaded areas** are patient measures.*
FROM, FROM-16; EQ-5D, Euroqol Five-dimension three level; EQ-VAS, Euroqol Visual analogue scale; DS, Disease severity.
B_FROM, B_EQ-5D, _B_EQ-VA and B_DS refer to baseline scores of these measures; F_FROM, F_EQ-5D, F_EQ-VA and F_DS refer to follow-up scores of these measures; Score change refers to change in score between baseline and follow-up.

4.4.5 Relationships Between FROM-16 Responsiveness and Disease Severity

An improvement/deterioration in QoL of family members was hypothesised in relation to a significant improvement/deterioration in patient disease severity between baseline and follow-up. The patient disease severity ranged from 0 to 10 (least severe 0, most severe 10). The mean disease severity at baseline was 5.17 (SD=2.48) and follow-up was 4.34, (SD=2.45) with mean difference of 0.964 (SD=3.11; ES=0.39, p=0.006) (Table 4.3).

The improvement in disease severity was reflected with significant improvement in patient EQ-5D score (mean=-0.10, ES=0.4, SRM=0.7, p< 0.001) (Table 4.9).

Parallel significant improvement was noticed in family members' FROM-16 scores (mean=2.7, ES=0.4, SRM=0.6, p<0.001) (Table 4.9), related to improvements in patient disease severity, indicating high responsiveness of FROM-16 to changes in patient's disease severity (hypothesis # 8). However, a small improvement was recorded by patients (mean=-0.01, ES=0.06, SRM=0.06) and family members (mean=0.41, ES 0.06, SRM=0.08) in response to worsening in disease severity, but this improvement was not statistically significant.

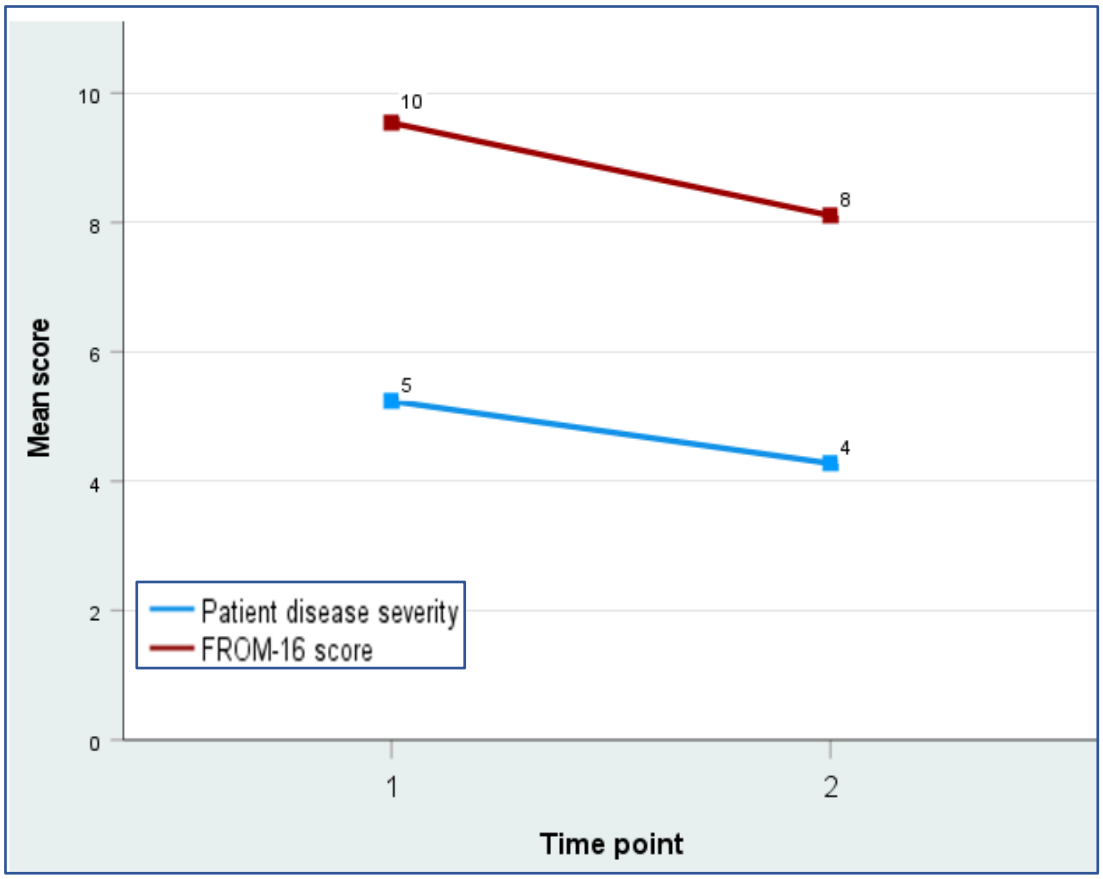
Table 4.9 Change in patient's HRQoL[a] based on changes in disease severity recorded on GSQ, and corresponding change in family member'/partner's QoL[b].

	Health state	Baseline	SD_B	Follow-up	Change scores†	SD_C	ES	SRM
Patient	Improved (n=42)	0.71	0.23	0.81	-0.10**	0.14	0.44	0.73
	Worsened (n=27)	0.72	0.23	0.73	-0.01	0.17	0.06	0.06
Family member	Improved (n=42)	9.21	6.88	6.52	2.69**	4.82	0.39	0.56
	worsened (n=27)	11.22	6.73	10.81	0.41	5.27	0.06	0.08

*[a]Patient's HRQoL measured with EQ-5D-3L; [b] family member'/partner's QoL measured with FROM-16; † EQ-5D scale runs in opposite direction to FROM-16 for improvement and deterioration; **Significance <0.001; Baseline and Follow-up patient EQ-5D-3L health states based on UK TTO; Change scores refers to difference between scores between baseline and follow-up; ES effect size; SRM, standard response mean. SD_b, standard deviation of baseline score; SD_c, standard deviation of change score.*

Figure 4.5 shows the trend in the reduction of both the FROM-16 and the GSQ scores from baseline to follow-up, implying that there was a parallel improvement in patients' self-assessed disease severity to family members' QoL, shown by the reduction in FROM-16 scores (i.e., improved QoL).

Figure 4.5 FROM-16's responsiveness to change in patients' disease severity

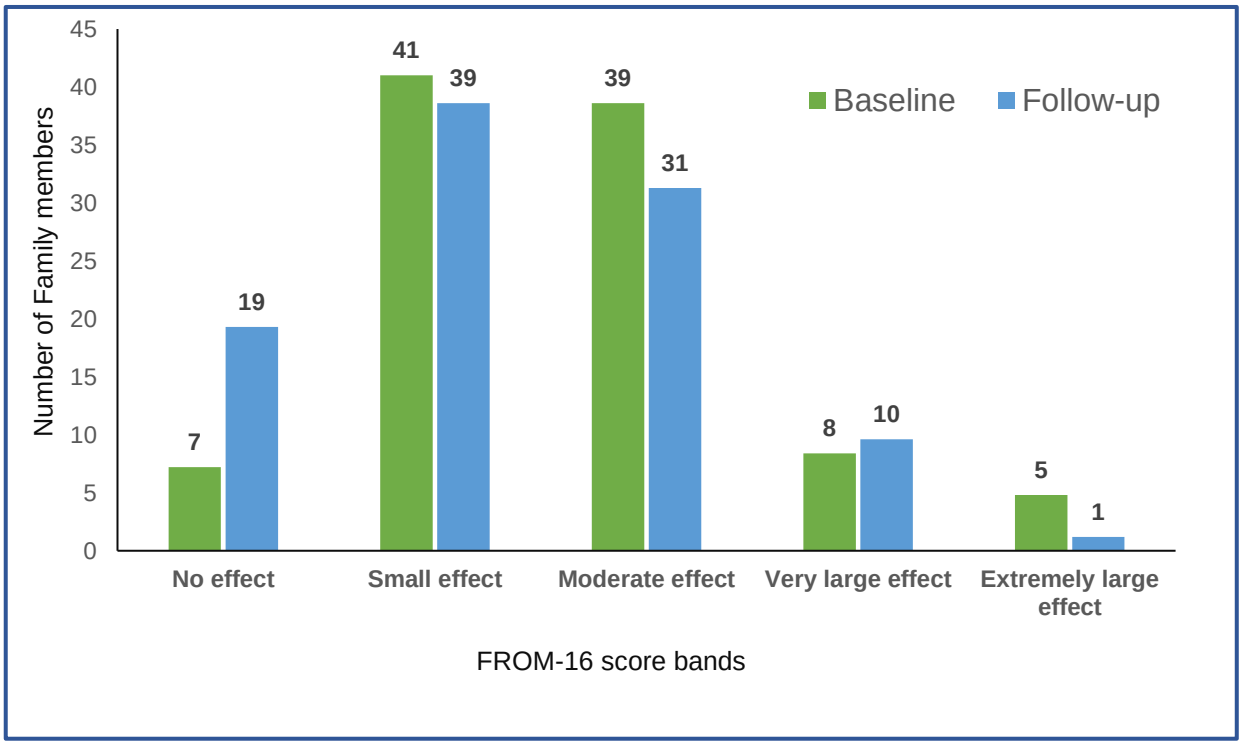


4.4.6 Application of FROM-16 Score Bands System to its Responsiveness

Responsiveness of FROM-16 to change in scores over time was also demonstrated by visual inspection of score bands between baseline and follow-up (Figure 4.6), confirming hypothesis #9. A bigger proportion of family members in the band 'No effect' on QoL of family members at follow-up compared to baseline and a smaller proportion of family members in the band 'Extremely large effect' at follow-up compared to

baseline, indicated that some family members experienced positive change in their QoL following their relative's treatment with new medication

Figure 4.6 Change in distribution of scores between baseline and follow-up indicated by FROM-16 descriptive bands demonstrates FROM-16's responsiveness to change (n=83)



The study results confirmed all nine hypotheses set in Table 4.1, establishing responsiveness of the FROM-16 to change over time.

4.5 DISCUSSION

This study investigated for the first time the responsiveness of FROM-16. The study has demonstrated that the FROM-16, which was developed for measuring the impact of a persons' health condition on their family members'/partners' quality of life, is responsive and could identify changes in outcomes over time. Husted et al.(2000) used the term 'internal responsiveness' for the ability to measure change over time and 'external responsiveness' for the extent to which changes in a measure over time related to corresponding changes in a reference measure of health status. In this study, GRCQ and GSQ were used as the family member and patient reference measures.

The external responsiveness is measured either through the receiver operating characteristic (ROC) method or correlational analysis. The use of ROC for assessment of responsiveness was first proposed by Deyo and Centor in 1986 (Deyo and Centor 1986). In the context of ROC, responsiveness is defined in terms of sensitivity (probability of the measure to correctly classify patients [in this study family members] who show change on an external criterion) and specificity (probability of the measure correctly classifying patients [in this study family members] who do not show change on the external criterion) (Deyo and Centor 1986; Stucki et al. 1995).

The study employed distribution-based and anchor-based methods to explore the responsiveness of the FROM-16. While anchor-based methods involved the family members' perspective of change in their QoL, the distribution-based method, based on the statistical distribution of QoL scores, provided insight into the magnitude of change that has occurred between the two assessments. The study results indicate that there had been a small change in family members/partners' QoL over the three months' period following patient treatment with a new medication. This is not surprising given that patients had also experienced a small change indicated by a small effect size on the EQ-5D. Although the magnitude of change in the patients was small, the overall mean change in scores was clinically important and within the range (0.03-0.5) of the minimal clinical important difference for EQ-5D-3L (Coretti et al. 2014). The study results confirm the hypothesis that FROM-16 was able to record change over time in family members/ partners of the patient. The study results suggest that family members/partners experienced a major impact on their emotional health (feeling worried, sad and frustrated) and sleep due to their relative's health condition; however, significant improvement was noticed in these items at follow-up. Apart from these items, a small effect was also seen on family activities as well as on the sex life of family members/partners of patients.

The study used a 15-point GRCQ as an external measure to test the responsiveness of FROM-16. The GRCQ showed a significant moderate correlation to changes in FROM-16 scores between two assessments ($r= 0.388$ $p<0.01$) as shown by previous studies (the numerical pain rating scale $r=0.49$; the DLQI, $r=0.32$, Euroqol $r=0.42$;) (Stewart et al. 2007; Basra et al. 2007; van der Roer et al. 2006). The study results confirmed the hypothesis that the mean change in FROM-16 scores of family members (denoted by

the anchor categories) were ordered in the expected direction. The mean change in FROM-16 scores for family members who recorded an improvement on the GRCQ was positive: the change in scores of family members who recorded worsening was negative, and the mean change in those who improved was greater than the mean change in those who were unchanged. This change was, in turn, greater than for those whose QoL was recorded as worsened on the GRCQ. The effect size for "improvement" was large on the GRCQ, indicating excellent responsiveness to improvement in QoL following patient treatment. The ROC analysis also demonstrated that FROM-16 was responsive to improvement (AUC=0.76) and deterioration (AUC =0.78) in family members' QoL, as recorded on the GRCQ. Surprisingly, only 17 out of 83 family members recorded change on the GRCQ. The advantage of the GRCQ 15-point scale is that it offers granulated change options, which help the respondent to select the smallest change experienced. However, in this study, most family members recorded 'no change' on the GRCQ. This could be attributed to the design of the online anchor question, which allowed participants to answer this question in two steps: first, choose from one of the three categories 'improved', 'same' or 'deteriorated' and then, if the participant clicked improvement or deterioration, they could see the further detailed options. Although this was designed to try to make the questionnaire simple for family members, this two-step process might have obscured the multiple options for improvement and deterioration from the participant, unless they chose one of these options. They were therefore not aware of the subtle choices available before making this initial selection, possibly making it more likely that they chose "same" as the only option available to them. However, results from the anchor-based method are consistent with the responsiveness demonstrated by the distribution method.

Even though GRCQ scales are considered the best single measure of the importance of change from the patient's (in this case family member’s) perspective (Crosby et al. 2003), it is not possible to establish evidence that these scales provide a correct assessment of change. This is because perception of change is dependent on the subjective experiences of a person, which can be impacted by a number of factors beyond disease impact. Furthermore, participants may not accurately remember their baseline or pre-treatment QoL experience, resulting in recall bias and discrepancies in recorded changes. Nonetheless, GRCQ scales have been proven to be sensitive to

both positive and negative changes, as is confirmed by this study (Hägg et al. 2002; Kamper et al. 2009).

Apart from the responsiveness of FROM-16 to change over time, this study also explored the responsiveness of FROM-16 to patients' disease severity and to associated patient QoL scores. The study found a close association between FROM-16 scores at baseline and follow-up and patient scores of EQ-5D, EQ-VAS and GSQ. The change in patients' disease severity, recorded on GSQ between the two assessments, was parallel to the changes in the patients' EQ-5D scores, though opposite in direction as expected since the two scales run in opposite direction. Sixty-nine out of 83 patients experienced change in disease severity following a new treatment or treatment change. The mean change in patient scores who recorded an improvement (n=42) on the GSQ scale was positive with moderate effect size. The family members showed parallel improvement in FROM-16 scores to patients' improvement on GSQ suggesting family member improvement was directly linked to patient's improvement and indicative of how new treatments can make a difference to family members' QoL. Interestingly, neither patients' nor family members' QoL worsened in response to worsening in disease severity (n=27) recorded on GSQ. Instead, a very small improvement was noticed by both the patient and the family member. This suggests that worsening in disease severity, as recorded by patients on GSQ, might be in the construct not covered by EQ-5D or it could also be argued that improvement with a new treatment did not meet the patients' expectations.

The patients involved in this study were from five different specialities and had 15 different health conditions. Presumably, the treatments and therapies they received were different, and hence one could expect varying efficacy experienced by the patients and variability in score changes. For example, diabetes patients in this study included not only those with poor glycaemic control starting on insulin treatment but also those having dose adjustment for better glucose control. Although dose adjustment changes can have a major effect in controlling patients' glycaemic levels, they may only have a subtle effect on the QoL of patients and family members, because most of these patients and family members have been living with diabetes for a long time. In contrast, myeloma patients starting on biologics or having transfusion may take longer to see a beneficial qualitative change as many often experience

treatment side effects when starting therapy. While this variability in the patient's response to treatment may have resulted in an overall small change, it is important to include a range of conditions from mild to severe when testing generic tools.

Even though a period of three months post-treatment may normally be sufficient for evaluating a treatment effect, a longer follow-up period might be necessary to measure some QoL aspects in certain conditions. In this study, most of the patients in rheumatology and dermatology were on biologics and with such therapy, people can experience benefit within a few weeks, but there may be situations where it takes longer than six months (Robinson 2022). Currently, there is no uniform recommended time for follow-up across all biologics.

It is important to point out that measuring the responsiveness of a FQoL tool is not as straightforward as measuring the responsiveness of a PROM. Family members/partners may be influenced by factors other than a choice of follow-up period that can affect responsiveness to change. For example, the Family Dermatology Life Quality Index (FDLQI) was able to demonstrate responsiveness over a six-month period (Basra et al. 2007). In contrast, the study that compared the responsiveness of carer care-related QoL measures such as the Carer Experience Scale-CES (Al-Janabi et al. 2008), CarerQoL-7D (Brouwer et al. 2006), and Adult Social Care Outcomes Toolkit for Carers- ASCOT-Carer (Rand et al. 2015), found that none of the measures exhibited clear responsiveness to changes within a year (McLoughlin et al. 2020). The study's author claimed that these tools were developed for use in health economic evaluation, yet their responsiveness is contested. Although a small effect size was detected for FROM-16 change over time, the responsiveness of the FROM-16 should be viewed in the context of the magnitude of change in patient QoL, which was small for this study.

One of the strengths of this study is that patients were directly involved in reporting their QoL changes over time following the intervention. Many studies have looked at the comparison of patients' QoL changes with family members/carers, but these have used proxy reporting by family members (Basra et al. 2007; McLoughlin et al. 2020). However, such proxy reporting does not always match self-reports (Claes et al. 2012).

Most patients that participated in the study were from dermatology and diabetology. Eighteen were recruited from rheumatology, five from haematology and only one from

gastroenterology. Although it was aimed to have an equal number of participants across all five specialities, this was not possible due to delays in recruitment as COVID-19 restrictions were still in place, most consultations were still taking place online and some staff who could support recruitment were on leave due to COVID-19 infection.

A sample size of >50 is considered adequate for studies investigating responsiveness (Mokkink et al. 2010; Cohen 1988, pp 8–14); therefore, the sample size of 83 for this study would be considered sufficient. The study results have implications for economic evaluation and health technology assessment. This study establishes the longitudinal validity of FROM-16 and suggests that FROM-16 can be used in health economic evaluation to include family member/informal carer impact. The study not only demonstrated how family/informal carer health-related quality of life (HRQoL) changes over time, but it was also related to the clinical severity of a patient's disease in the expected direction (Ben-Gashir et al. 2002).

4.6 CONCLUSIONS

The results of this study provide evidence of responsiveness of FROM-16 for measuring QoL impact on family members/partners of patients. Although this study has shown that the FROM-16 is capable of measuring change over time, it is important to know the magnitude of change that could be clinically meaningful. The next chapter of this thesis will explore the minimal clinically important change in FROM-16 scores.

4.7 SUMMARY

- In Chapter 3, the algorithm was developed to allow the inclusion of FROM-16 scores as a family burden in health economic appraisals. However, to use FROM-16 in such analysis, it should be able to demonstrate responsiveness to change over time.

- This study aimed to establish the responsiveness of FROM-16 to change and assess whether FROM-16 is responsive to changes in patient QoL over time (including changes in disease severity).

- This was a prospective cohort study conducted between August 2022 and April 2023 and included patients and their family members/partners recruited from outpatient clinics of dermatology, diabetology, rheumatology, haematology and gastroenterology at University Hospital Wales and University Hospital Llandough, who completed the study on an online platform.

- Eighty-three patients and their family members/partners completed baseline and follow-up questionnaires. The patient completed EQ-5D-3L and GSQ at baseline and at three months follow-up, while family members completed FROM-16 at baseline, and GRCQ and FROM-16 at follow-up.

- Responsiveness was assessed using the distribution-based (ES and SRM) and anchor-based (ROC-AUC analysis) approaches. For Cohen's d, effect sizes are small (0.2), medium (0.5), and large (0.8). AUC of ≥ 0.7 is considered good responsiveness.

- The responsiveness was also assessed by testing hypotheses on expected correlation strength between family member measures (FROM-16, GRCQ) and patient measures (EQ-5D-3L and GSQ). Moderate to high correlation was expected between related measures with similar constructs while low to moderate correlation was expected between related but dissimilar constructs. According to COSMIN guidelines, responsiveness is appropriate if 75% of the hypotheses are confirmed.

- All hypotheses for testing responsiveness highlighted in Table 4.1 were confirmed, indicating that FROM-16 was responsive to change over time.

- Internal responsiveness was confirmed by a significant t- test, indicating FROM-16 can measure change in scores between baseline and follow-up. The ES and SRM were 0.21 and 0.29, indicating small change. The parallel small change

observed in patients' scores between baseline and follow-up was indicative of family members' responsiveness to patient HRQoL.

- External responsiveness was confirmed by the AUC value >0.7 and by the expected correlational strength between patient measures (EQ-5D-3L, GSQ) and family members' measures (FROM-16 and GRCQ).

- The AUC was 0.76 for improvement and 0.78 for deterioration, indicating FROM-16 responsiveness.

- There was a moderate correlation (0.388**) between FROM-16 score change and GRCQ. As expected, there was a moderate correlation between the FROM-16 change score and the patient disease severity change score.

- The family member's GRCQ score and change in the associated FROM-16 score were in the expected direction. Family members indicating improvement on the associated GRCQ had a positive mean change score (change in scores between baseline and follow-up). Family members indicating worsening on the associated GRCQ had a negative mean change score. The mean change score of family members indicating improvement was higher than the mean change score of unchanged family members/partners, which in turn was higher than the mean change score of "worsened" family members/ partners.

- Although only a few family members had recorded change in GRCQ, the study used a number of methods (distributional, correlational and anchor approaches-GRCQ and patient GSQ) to demonstrate FROM-16 responsiveness.

Chapter 5

Estimation of Minimal Clinically Important Difference (MCID) for FROM-16

5.1 INTRODUCTION

Chapter 4 of this thesis demonstrated the responsiveness of FROM-16 to change over time, however, change in QoL of individuals over time may be statistically significant but not clinically important or relevant to the patient (in this case family member). It is important to ascertain whether the measured improvement in a patient (in this case family member) is merely caused by random measurement fluctuations or a real change. It is also important to know whether the change is clinically relevant, assessed by considering whether score change reaches the minimal clinically important difference. Although a wide range of terminology has been used to describe clinically important change, including minimal important change (MIC), minimal clinically important difference (MCID), Minimal important difference (MID) and meaningful change threshold, all these descriptors have a common denominator aiming to quantify changes that are considered clinically relevant (Sedaghat 2019; Draak et al. 2019; Terwee et al. 2021). In this chapter, the term MCID, MID and MIC have been used interchangeably to define important change. The MCID can be defined as the smallest change in the QoL scores that a patient (in this case, a family member) perceives to be beneficial. Jaeschke and colleagues (1989, p. 408) described the term MCID as follows:

… “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management”.

The above definition has been paraphrased to more patient-centred definitions, for example, MID (Guyatt et al. 2002) and MIC (de Vet et al. 2006), by being formally defined based on what patients (in this case, family members) consider to be minimally important. The main difference between MID and MCID is that MID omits the “clinical” of MCID, thereby reducing focus on 'clinical' interpretations and placing a greater weight on the preferences of (informed) patients than clinicians in studying the MID (Schunemann and Guyatt 2005, Schünemann et al. 2005).

The MCID is an important concept and a yardstick that helps clinicians to understand if a medical intervention improves perceived outcomes in patients. Once the MCID is known for the FROM-16, clinicians and researchers will be able to understand whether changes in FROM-16 scores are meaningful, and therefore whether medical

interventions improve outcomes in family members of patients. The FROM-16 score banding described in Chapter 2 gives meaning to scores and could be used to interpret score changes, however score banding does not provide information on MCID (Delong & Chen 2012), and the “smallest important change” may be within a single score band descriptor or straddle across two bands.

With the rapid growth in novel medical treatments across all areas of medicine and their associated costs, there is an increasing need to provide objective data about the quality of care and to inform the allocation of healthcare resources. Patient-reported outcomes (PROMs) play a central role in this evaluation. The MCID provides a measure for the critical threshold needed to demonstrate treatment effectiveness, and implies clinical significance, providing justification for incorporating treatment into clinical practice. However, as mentioned in Chapter 4, the impact of a new medication is also experienced by family members of the patient. Family-reported outcome measures (FROMs) could therefore be used alongside PROMs to inform healthcare allocation decisions. Furthermore, the MCIDs of PROMs are used by pharma companies for understanding the effectiveness of new medication and as a primary threshold for assessment of score change in PROMs in clinical trials. Given that there is likely to be an impact of an effective new treatment on family members/partners of the patient, FROMs could be used as secondary outcome measures in clinical trials. Therefore, this chapter reports the development of the estimation of MCID for FROM-16.

5.2 METHODS

5.2.1 Study Design

The data for this study were collected at the same time as for the FROM-16 responsiveness study (Figure 4.1). This was a longitudinal study involving family members/partners of patients from the outpatient clinics of dermatology, rheumatology, endocrinology, gastroenterology and haematology at the University Hospital of Wales and University Hospital Llandough, Cardiff, between August 2022 and April 2023. The study was approved by the HRA and HCRW (20/EE/0242). Inclusion criteria were adult family members/partners of a patient starting on a new treatment for the first time, or of

a follow-up patient starting on a new treatment or changing existing treatment (for example, in diabetes, moving from basal to basal-bolus therapy) where the clinician expected to see a change in QoL of patients within three months. Patients and family members were excluded if suffering from significant comorbidity or if family members were less than 18 years of age. The information about detailed study design, ethical considerations, sampling, inclusion/exclusion criteria, survey design and PPIE is the same as referred to in Chapter 4 (FROM-16 responsiveness study).

5.2.2 Participant Recruitment

This study used family member data from the FROM-16 responsiveness study and additionally data from family members of paediatric patients to estimate MID for FROM-16. Family members of paediatric patients were recruited from dermatology department.

This study involved family members of patients completing the online questionnaire at two time points: baseline and at three months' follow-up (Figure 4.1).

At the baseline, the family member completed demographic details (age, gender, ethnicity, employment status, relationship to the patient) and a FROM-16 questionnaire. At the three months' follow-up, the family member/partner, in addition to completing FROM-16, also scored a Global Rating of Change Question (GRCQ) to indicate how much (if any) they perceived their QoL had changed (Terwee et al. 2021). In order to maximise the response rate at the follow-up, either a phone call or text message was used to remind the study participants.

5.2.3 Approaches Used for Estimating MID

This study used both anchor- and distribution-based methods to estimate the MID of the FROM-16 based on triangulation of such methods to achieve a single value for the MID.

5.2.3.1 Anchor-based approach

In this study, the anchor approach was used as the primary method to estimate MID of FROM-16. The study used the Global Rating of Change Question (GRCQ) as an

anchor to calculate the MID value for FROM-16, the smallest change in scores over time (from baseline to 12 weeks follow-up) that family members consider important. Using GRCQ as an anchor allows family members to give a self-assessment of the change since baseline in, for example, overall QoL: whether it has improved, remained the same or deteriorated (Jaeschke. et al. 1989). The GRCQ has a 15-point scoring system with responses ranging from "a very great deal better" (+7) to "no change" (0) to "a very great deal worse" (-7). Some studies have used a 7-point rating scale for GRCQ (Kvam et al. 2011; Kwakkenbos et al. 2013; Solberg et al. 2013), however, this study used a 15-point scale as this allows a respondent to record even a very small change (improvement or deterioration) (Fulk et al. 2010; Basra et al. 2015; Yuksel et al. 2019) resulting in greater sensitivity to change. Although GRCQ questions are subject to recall bias, they have been used widely in the estimation of MID of HRQoL measures due to their simplicity, sensitivity to change (both positive and negative), and to their being a person's own evaluation of his or her change in health state (Hagg et al. 2002; Norman et al. 1997; Kamper et al. 2009).

In this study, the GRCQ question posed to family members was:

"Thinking about the effect of your family member/partner's condition on you, how much has your quality of life changed since you first took part in this study?"

Global Rating of Change Question (GRCQ)15-point rating

Improved	Same	Deteriorated
1. A tiny bit better	0. About the same	-1. A tiny bit worse
2. A little bit better		-2. A little bit worse
3. Somewhat better		-3. Somewhat worse
4. Moderately better		-4. Moderately worse
5. Quite a bit better		-5. Quite a bit worse
6. A great deal better		-6. A great deal worse
7. A very great deal better		-7. A very great deal worse

Anchor approaches used in this study to estimate MID include average change score (MIC_{mean}), Receiver Operating Characteristic (ROC) curve analysis (MIC_{ROC}), and the more recently suggested predictive modelling method (MIC_{pred}) (Terwee et al. 2021).

5.2.3.1.1 AVERAGE CHANGE METHOD

The average change method takes a mean of the change scores between baseline and follow-up for categories representing small but important changes in the anchor. Respondents whose scores were 2, 3, –2 or –3 were considered to have experienced a small but important change equivalent to a minimally important difference. To calculate MCID using this method, anchor scores of "2. A little better' and '3. Somewhat better' represents a small but important change for improvement and '-2. A little worse' and '-3. 'Somewhat worse' represents a small but important deterioration. Those with scores of 4, 5, –4 or –5 were considered to have experienced a moderate change, and those with scores of 6, 7, –6 or –7 were considered to have experienced a large change. Respondents with scores representing about the same '0', a tiny bit better '1', and a tiny bit worse '-1' were classified as unchanged or having a small but unimportant change (Juniper et al.1994; Jaeschke et al.1989). This method was first used by Juniper et al. (1989) and was subsequently used to determine MID in a number of studies (Yost et al. 2011; Chuang et al. 2013; Basra et al. 2015; Amtmann et al. 2016; Hung et al. 2019; Kazmers et al. 2019; Lapin et al. 2019; Kazmers et al. 2021). This simple and most widely used method for the estimation of MID can, however, lead to an imprecise MID value if the subgroup of patients who report 'little better' or 'somewhat better' is small (Terwee et al. 2021).

5.2.3.1.2 ROC CURVE ANALYSIS

This method involves treating anchor outcomes as dichotomous and dividing the outcome as improvement/no improvement ('no improvement' included 'the same' and 'worsened') or worsening/no worsening ('no worsening' included the 'same' and 'improved'). However, the analysis needs to be calculated separately for improvement and worsening. An area under the curve (AUC) ≥ 0.7 is considered good. The cutoff point at which the sum of sensitivity and specificity is maximised gives the MID. This method has been used in many studies for the estimation of MID/MIC values (Le et al. 2013; Stephan et al. 2019; Kenney et al. 2019; Hung et al. 2019; Alanne et al. 2015; Forlenza et al. 2021; Chuang et al. 2013; Hoehle et al. 2019; Ren et al. 2021). This method has the advantage of using the entire study sample, resulting in more reliable

estimates compared to the MIC_{mean}. A disadvantage is that if the percentage of improved patients is lower than 50%, the MIC_{ROC} could be biased (Terluin et al. 2017).

5.2.3.1.3 PREDICTIVE MODELLING APPROACH

In predictive modelling, the predicted probability of a patient (in this case family member) being in the improved group (based on the anchor) is derived from the observed change scores (Terluin et al. 2015). This method involves logistic regression analysis, with 'improved' versus 'not improved [stayed the same or worsened]' based on the anchor question as a dependent variable and change scores on the measure of interest (which in the case of this study is FROM-16) as an independent variable. The $MIC_{predict}$ is the change score associated with a likelihood ratio of 1, where the post-test probability of belonging to the improved group (after knowing the patient's PROM change score- in this case family member's FROM score) equals the pre-test probability of belonging to the improved group (before knowing the patient's PROM change score - in this case the family member's FROM score). The pre-test probability is the percentage of improved patients (in this study, family members/partners) in the sample (Terluin et al. 2015; Terluin et al. 2017). However, Terwee et al. (2021) recommend using adjusted MIC_{pred} if the number of responses in improved versus not improved is less or more than 50%, to account for underestimation or overestimation of the MIC value. Therefore, adjusted MICpred was calculated using the formula given by Terwee et al. (2021), as the number of responses for Improved versus Not improved group was less than 50%.

The MIC_{pred} was calculated using the formula below using regression values for C and B:

$$MIC_{predict} = (\log(Odds_{pre}) - C/B$$ (Terwee et al. 2021)

Where C is a constant, also known as the intercept, and *B* is the regression coefficient for improvement/deterioration.
The adjusted MIC was calculated using the formula below:

$$MIC_{predict(adjusted)} = MIC_{predict} - (0.090 + 0.103 * Cor) * SD_{change} * \log(odds_{pre})$$

Where $MIC_{Adjusted}$ = adjusted minimal important change; $MIC_{Predictive}$ = predictive minimal important change; Cor = correlation between the PROMIS (FROM-16) change score and the anchor and in this study r=0.40; SD_{change}= standard deviation of the PROMIS (FROM-16) change score, in this study SD_{change}=5.413; log-odds(pred)imp = log-odds of improvement = natural logarithm of [proportion improved/(1 − proportion improved)].

This method has been used in some recent studies for the estimation of MIC values ($MIC_{predict}$) (Smit et al. 2020; Ohno et al. 2021). The predictive modelling method and ROC analysis have an advantage over the average change method as they provide a threshold between improved and not improved patients (Terluin et al. 2015). However, predictive modelling is considered more precise than ROC analysis as it can be corrected for bias if the percentage of improved patients is not 50% (Terluin et al. 2017; Terwee et al. 2021).

5.2.3.2 Distribution-based approach

Distribution-based methods for detecting MID are based on statistical parameters reflecting statistical spread/variation and measurement accuracy of the PROM. The rationale for distribution-based methods is related to the inherent variability in the scoring of PROMs, which is observed both at the individual and at group levels. It is possible that a patients' score on a PROM may vary over time even when the patient does not have any important change in the outcome being measured, and this is also reflected at the group level (Sedaghat 2019). The two most widely used statistical parameters reflecting spread in the calculation of MID are standard deviation (SD) and the standard error of measurement (SEM).

The most common approach for using and interpreting the distribution-based formula for calculation of the MID of a PROM/FROM, using the SD of the PROM/FROM score at baseline, is to base the MID on 0.5 of the SD (Kvam et al. 2011; Den Oudsten et al. 2013; Le et al. 2013; Binenbaum et al. 2014; Sagberg et al. 2014; Asher et al. 2018; Chen et al. 2016; Hoehle et al. 2019). It has been demonstrated that 0.5 SD provides a good approximation of MID (Norman et al. 2004, Katz et al. 2008, Norman et al. 2003). For the purpose of this study, MID was calculated as 0.5 SD.

Another method used in this study to calculate MID was to use the standard error of mean (SEM). In this method, MID is calculated as a function of SEM: it could be 1 SEM, 1.96 SEM or 2.77 SEM (equal to 1.96√2 × SEM) (Mouelhi et al. 2020). 1.96 SEM represents 95% certainty that the smallest change is above the measurement error. This study used 1 SEM and 1.96 SEM (Den Oudsten et al. 2013; Bedard et al. 2014; Wong et al. 2015; Raman et al. 2016; Asher et al. 2018) for the estimation of MID. The advantage of using SEM is that it is not sample dependent and hence provides a more reliable MID value (Wyrwich et al. 1999).

However, in order to calculate MID using this method, it is important to first calculate SEM. SEM was calculated using the formula below:

SEM= SD*$\sqrt{1-r}$

where ‘r’ is the FROM's reliability (test-retest reliability or Cronbach alpha of the sample).

5.2.4 Data Processing and Statistical Analysis

The statistical analysis involved calculating descriptive statistics. The correlation between FROM-16 change scores and GRCQ rating was conducted prior to conducting the anchor analysis to check if the anchor analysis was valid and met the minimum requirement (r=0.3) for the anchor method.

The difference in the mean of FROM-16 scores from baseline to follow-up corresponding to anchor categories were calculated for the average change method. The GRCQ scores were categorised into no change, small, moderate, and large changes. The scores for each category of the GRCQ were compared with the mean change in FROM-16 scores from the first assessment (baseline) to the second assessment (three months’ follow-up). The scores for the small but important change (-3, -2, 2, 3) category of the GRCQ were compared with the corresponding mean change in FROM-16 scores from the first assessment (baseline) to the second assessment, and the mean of this group represented MID.

Another anchor approach was the sensitivity-specificity analysis, involving dichotomising anchor scores into 'improvement against no improvement' and 'worsening against no worsening' and running ROC analysis using the difference in

FROM-16 scores as a test variable. The cutoff score where sensitivity and specificity were maximised (known as the Youden index, J) represented the MID. Precision was indicated by the Area under Curve (AUC) value. MIC_{pred} was calculated using the logistic regression modelling approach proposed by Terluin et al. (2015). The confidence interval was calculated by substituting regression values (values for Constant, regression coefficient [B], standard errors for constant and B, correlation coefficient between constant and B) into the Excel formula sheet provided by Terluin et al. (2017).

For the calculation of MID using the distribution-based method, standard deviation (SD) assessment of FROM-16 scores at baseline and change in scores from baseline to follow-up were calculated. The MID was calculated as 0.5 times the standard deviation at baseline. The MID was also calculated as a function of the SEM. The SEM was calculated by multiplying the SD at baseline with the square root of 1- reliability of the FROM-16. The MID was calculated as 1.96 times the SEM.

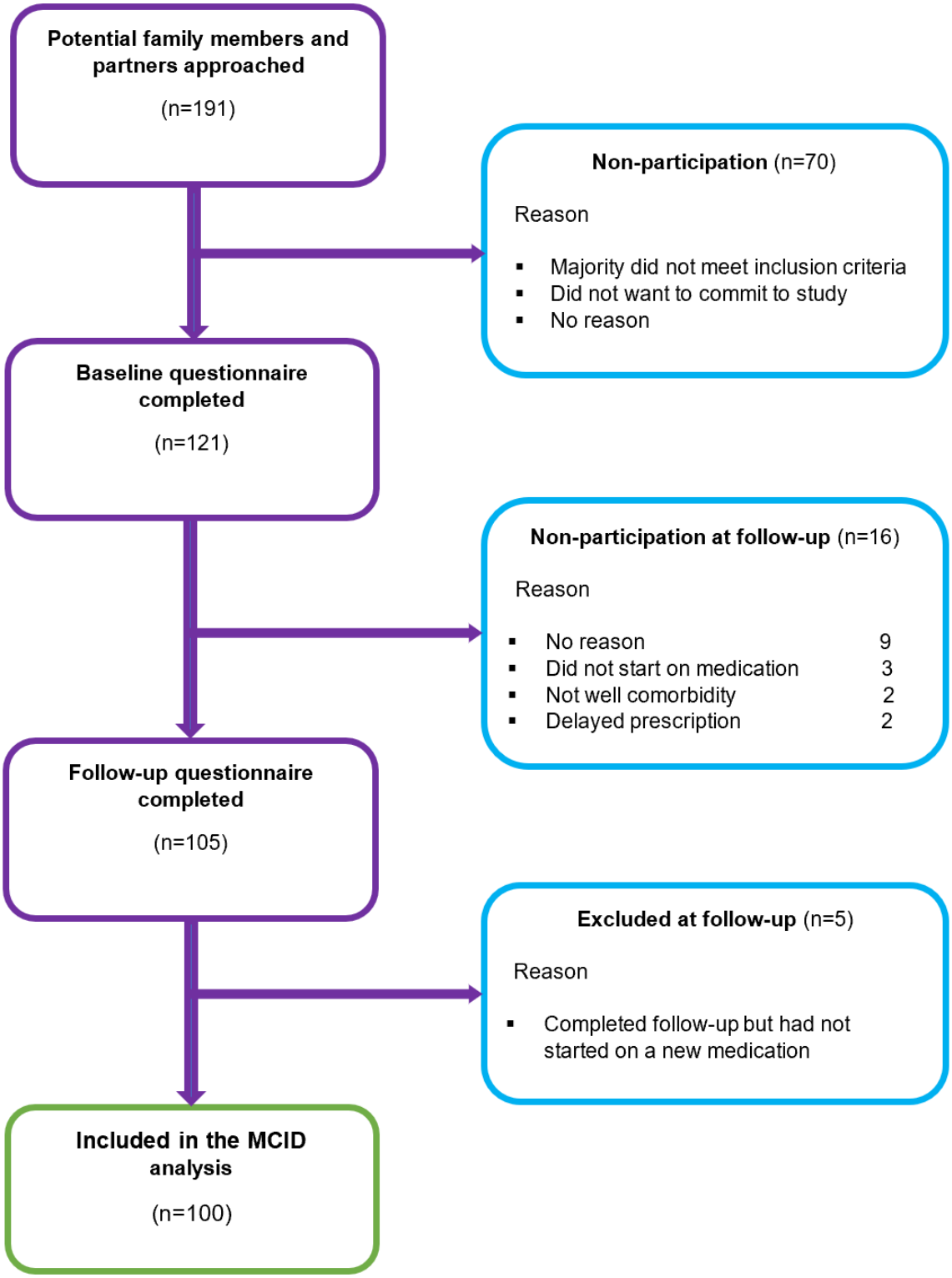
It was decided a priori that MID/MIC values obtained from using different yet complementary methods (Anchor-based approach: *Average change; ROC analysis; predictive modelling* and Distribution-based approach: *SD; SEM*) would be triangulated to arrive at one MCID value (Mouelhi et al. 2020). The decision rule used was that the MID should be based primarily on anchor-based methods in the first instance on the ROC curve and MICpred or adjusted MIC_{pred} in the case of the change group being less than 50%, and the value should be chosen that is higher than the SEM and around the 1.96 SEM value. Although MIC for improvement and deterioration was calculated, it was decided with the research team that an average of two values would be used on which to inform the MID/MIC value.

5.3 RESULTS

5.3.1 Response Rate

Of 191 patients and family members approached to participate, 121 completed the baseline study (Figure 5.1). However, only 105 (86.77%) family members completed

Figure 5.1 Flow chart of recruitment: Baseline to follow-up



the three months' follow-up. Nine family members did not respond to the follow-up invitation, three family members did not respond as the patient did not start on a new medication, another two were suffering from severe comorbidity and therefore were not eligible to participate in the follow-up, and another two family members could not complete follow-up due to delayed start of patient's new treatment. Of 105 family members who completed follow-up, five responses were discarded as the patient had not started on a new medication and hence didn't meet the inclusion criteria, leaving 100 responses to be included in the final analysis (Figure 5.1).

5.3.2 Sociodemographic Characteristics of the Study Participants

One hundred family members/partners (mean age=49.25 years, SD=14.69; range=18–83 years; male= 42; female=58) of patients (mean age=44.12 years, SD=22.94, range=1-89 years, male =47) with 15 different health conditions completed baseline and follow-up questionnaires. Concerning relationships with the patient, most family members were spouses or partners (67%), followed by parents (25%) (Table 5.1). Most family members/partners were White (84%), 13 % were Asian, and 2% were Black/African/Caribbean. Family members were mostly in paid jobs (64%), and 24 % were retired.

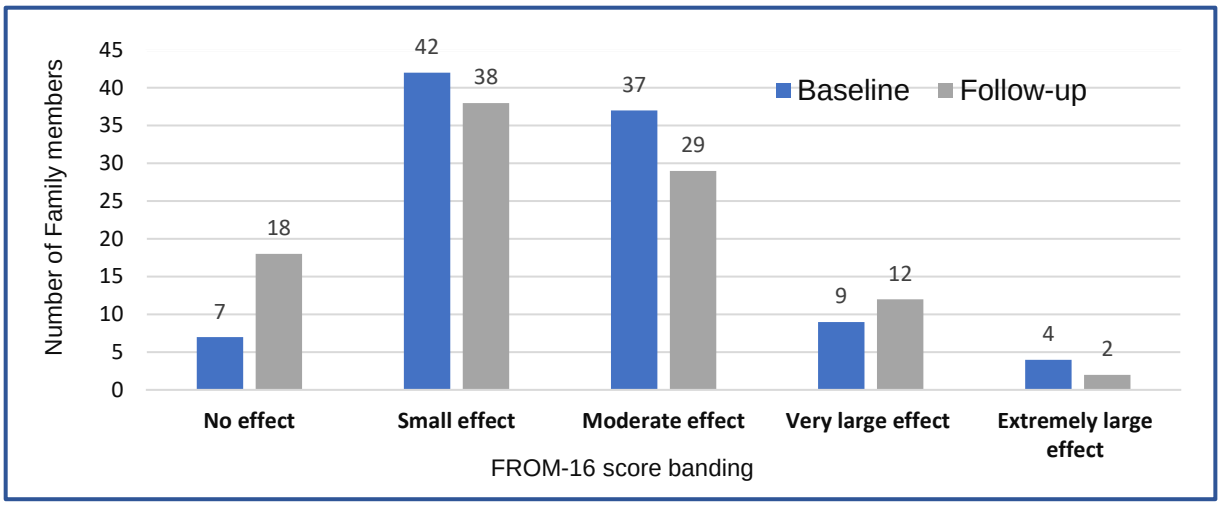
The mean FROM-16 total score at baseline was 9.52 (SD=6.57), and the mean FROM-16 total score at three months' follow-up was 8.55 (SD=7.38). The mean FROM-16 score change between baseline and follow-up was 0.970 (SD=5.41). There was a moderate correlation (r=0.42) between family members' FROM-16 scores and GRCQ scores (Table 5.1).

The severity banding of FROM-16 scores indicates that most family members were experiencing a small to moderate impact of the patient's health condition on their QoL (Figure 5.2). The visual inspection of the score bands indicates the proportion of family members experiencing 'No effect' of their relative's health condition on their QoL increased between baseline and follow-up, suggesting that the patients' new treatment had a positive impact on the QoL of some family members.

Table 5.1 Sociodemographic and descriptive characteristics of patients and their family members

Characteristic (n=100)		Number (%) or Mean (SD)
Patient		
Age (years)	Mean age	44.12 (22.94)
	Range	1-89
Gender	Male	48 (48)
	Female	52 (52)
Ethnicity	White	81 (81)
	Asian/Asian British	15 (15)
	Black/African/Caribbean/Black British	2 (2)
	Prefer not to say	2 (2)
Occupation	In paid work	44 (44)
	Unemployed	5 (5)
	Homemaker	6 (6)
	Retired	25 (25)
	Rather not say	3 (3)
	N/A	17 (17)
Heath condition	Acne	11 (11)
	Eczema	14 (14)
	Psoriasis	13 (12)
	Urticaria	1 (1)
	Rosacea	1 (1)
	Hidradenitis Suppurativa	10 (10)
	Rheumatoid Arthritis	10 (10)
	Seronegative Arthritis	1 (1)
	Psoriatic Arthritis	2 (2)
	Ankylosing Spondylitis	1 (1)
	Enteropathic Arthritis	1 (1)
	Myeloma	5 (5)
	Type 1 Diabetes	10 (10)
	Type 2 Diabetes	19 (19)
	Ulcerative Colitis	1 (1)
Family member/partner		
Age (years)	Mean age	49.25(14.69)
	Range	18-83
Gender	Male	42 (42)
	Female	58 (58)
Ethnicity	White	84 (84)
	Asian/Asian British	13 (13)
	Black/African/Caribbean/Black British	2 (2)
	Prefer not to say	1 (1)
Occupation	In paid work	64 (64)
	Unemployed	1 (1)
	Homemaker	5 (5)
	Education/training	1 (1)
	Retired	24 (24)
	Rather not say	5 (5)
Relationship to patient	Spouse/Partner	67 (67)
	Parent	25 (25)
	Son/Daughter	6 (6.1)
	Brother/Sister	1 (1.0)
	Other	1 (1.0)
FROM-16 scores		
Baseline FROM-16 score	Mean (SD)	9.52 (6.57)
Follow-up FROM-16 score	Mean (SD)	8.55 (7.38)
Mean FROM-16 score change	Mean (SD)	0.970 (5.41)
FROM correlation to GRCQ		0.418 ($p<0.001$)

Figure 5.2 Severity banding between baseline and follow-up (n=100)



No effect=0-1; Small effect=2-8; Moderate effect=9-16; Very large 17-25; Extremely large effect=26-32.

5.3.3 MCID Calculation – Anchor Method

The MID value for FROM-16 using the Average Change method was 9.5 for "smallest clinically important improvement" and -2.5 for "deterioration". MID_{mean} was estimated as 6 and calculated as the mean of improvement and deterioration (Figure 5.3 and Table 5.2).

Figure 5.3 Average change analysis for MCID calculation

Anchor-based approach-Average Change method

Small Important Change

Better (n=2)				Worse (n=4)				
SB	SF	diff	GRC	SB	SF	Sdiff	diff	GRC
15	**7**	8	3	11	**16**	5	-5	-2
12	**1**	11	3	9	**11**	2	-2	-2
		9.5		13	**13**	0	0	-2
				10	**13**	3	-3	-2
							-2.5	

MCID=9.5

MCID=-2.5

Overall MCID=(9.5+2.5)/2=6

Moderate Change

Better (n=6)				Worse (n=5)			
MB	MF	Diff	GRC	MB	MF	Diff	GRC
13	**19**	-6	4	**16**	**30**	-14	-4
17	**19**	-2	4	**6**	**16**	-10	-4
0	**0**	0	4	**12**	**14**	-2	-4
14	**11**	3	4	**26**	**25**	1	-4
15	**13**	2	4	**26**	**24**	2	-4
8	**5**	3	5			**-4.6**	
15	**5**	10	4				
		1.43					

Moderate change=(1.43+4.6)/2=3.02

Large Change

Better (n=2)				Worse (n=4)			
LB	LF	Diff	GRC	LB	LF	Diff	LGRC
11	**4**	7	6	18	**24**	-6	-6
0	**0**	0	6	27	**29**	-2	-7
27	**1**	26	6			**-4**	
12	**5**	7	6				
		10					

Large Change=(10+4)/2=7

Red-coloured cells indicate recall bias.

Table 5.2 MID calculation using the Average Change method based on family members' GRCQ responses

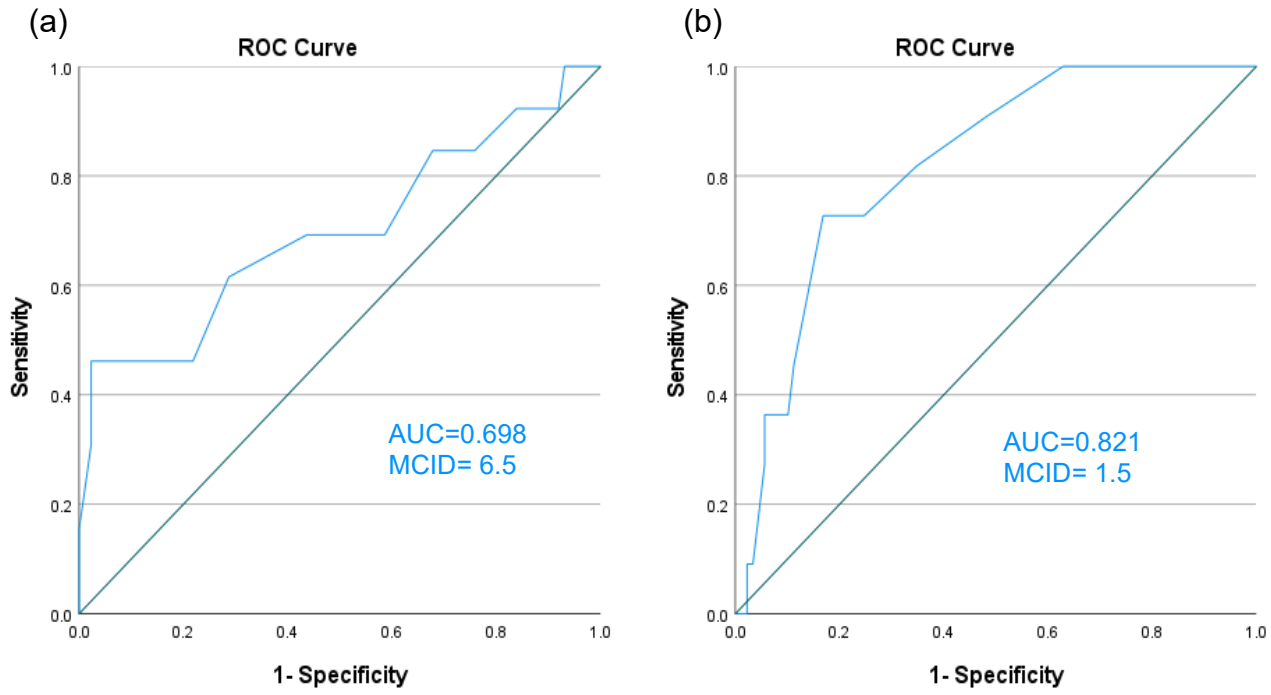
FROM-16	**Global rating of change**						
Quality of life	Better			Same	worse		
	7 & 6	5 & 4	3 & 2	1 & 0 &- 1	-2 & -3	-4 & -5	-6 & -7
Mean change Overall QoL (n=100)	10 (n=4)	1.43 (n=7)	9.5 (n=2)	0.89 (n=76)	-2.5 (n=4)	-4.6 (n=5)	-4 (n=2)

7 & 6=Large improvement in QoL; 5 & 4=Moderate improvement in QoL; 3 & 2=Small but important improvement in QoL of family member; 1 & 0 &- 1=No change in QoL; -2 & -3=Small but important deterioration in QoL; -4 & -5=Moderate deterioration in QoL; -6 & -7=large deterioration in QoL of family member.

5.3.4 ROC Curve Analysis

The MID value for FROM-16 using ROC curve analysis was estimated as 6.5 for "smallest clinically important improvement (AUC=0.698, p=0.022 CI=0.516-0.880) and 1.5 for "smallest clinically important deterioration" (AUC=0.821, p=0.01 CI=0.710-0.933) (Figure 5.4). Overall, the MID using this method was estimated as 6.5+1.5=8/2=4.

Figure 5.4 Receiver Operating Curve characteristic curve



5.3.5 Predictive Modelling

The MID value (MIC_{pred}) was calculated using the logistic regression modelling approach proposed by Terluin et al. (2015). MIC_{pred} (MID) for improvement and deterioration was calculated as 2.5 and 0.78. The calculation involved substituting values for regression coefficient of change score (B) and intercept (C) for improvement and deterioration (Tables 5.3 and 5.4) in MIC_{pred} formula for improvement and deterioration. Calculation for MIC_{pred} for improvement and deterioration is shown in respective text boxes.

Table 5.3 Results of logistic regression analysis for improvement in QoL

	B	SE.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
FROM-16 score change	0.209	0.082	0.011	1.233	1.049	1.449
Constant	-2.423	0.418	<0.001	0.089		

B, regression coefficient; SE, standard error; Sig, Significance <0.05; Exp(B), Exponential value of B. When Exp(B) is greater than 1, increasing values of the variable correspond to increasing odds of the event's occurrence.

Calculation of MIC_{pred} for improvement

MIC_{pred} for improvement was calculated using the formula below:

$$MIC_{predict} = (\log(Odds_{pre})imp - C)/B$$

C represents the intercept, and B represents the regression coefficient of the change score, (log($Odds_{pre}$)imp=log-odds of improvement=natural logarithm of [proportion improved/(1 − proportion improved)].
Substituting values of C and B from Table 5.3 into the above formula for MIC_{pred}

ln(0.13/(1-0.13))-2.423/0.209

ln(0.149)-(-2.423)/0.209

(-1.901+2.423)/0.209=**2.498=2.5**

Table 5.4 Results of logistic regression for deterioration in QoL

	B	SE.	Sig.	Exp(B)	95% CI for EXP(B)	
					Lower	Upper
FROM-16 score change	0.177	0.061	0.004	0.838	0.744	0.944
Constant	-2.229	0.365	<.001	0.108		

B, regression coefficient; SE, standard error; Sig, Significance <0.05; Exp(B); Exponential value of B. When Exp(B) is less than 1, increasing values of the variable correspond to decreasing odds of the event's occurrence.

Calculation of MIC_{pred} for deterioration

The MIC_{pred} for deterioration was calculated using the formula below:

$$MIC_{predict} = (\log(Odds_{pre})det - C)/B$$

C represents the intercept and B represents the regression coefficient of the change score, (log($Odds_{pre}$)det=log-odds of improvement=natural logarithm of [proportion deteriorated/(1 − proportion deteriorated)]. Substituting values of C and B from Table 5.4 into the formula for MIC_{pred}

ln(0.11/(1-0.11))-(-2.229)/0.177

ln(0.124)+2.229/0.177

(-2.091+2.229)/0.177= **0.779=0.78**

However, as number of family members who rated change (improvement and deterioration) on GRCQ was less than 50%, MIC_{pred} values of improvement and deterioration may be biased. Therefore, adjusted MIC_{pred} was calculated to overcome the bias of underestimation. The adjusted MIC_{pred} was calculated as 3.9 for improvement and 2.3 for deterioration**.**

The adjusted MIC_{pred} was calculated for improvement and deterioration using the formula below (Tarawee et al. 2021; Teruluin et al. 2017):

$$MIC_{predict(adjusted)} = MIC_{predict} - (0.090 + 0.103 * Cor) * SD_{change} * \log(odds_{pre})$$

Where $MIC_{Adjusted}$=adjusted minimal important change; $MIC_{Predictive}$=predictive minimal important change calculated above; Cor=correlation between the FROM-16 change score and the anchor and in this study r=0.418; SD_{change}=standard deviation of the FROM-16 change score, in this study SD_{change} =5.413; log-odds(pred)imp=log-odds of improvement = natural logarithm of [proportion improved/(1 − proportion improved)].

The calculation of adjusted MIC_{pred} for improvement and deterioration is shown in the text boxes below:

Calculation for adjusted MIC_{pred} for improvement

The adjusted MIC_{pred} for improvement was calculated using the formula below:

$$MIC_{predict(adjusted)} = MIC_{predict} - (0.090 + 0.103 * Cor) * SD_{change} * \log(odds_{pre})\text{imp}$$

Here, $MIC_{pred\ (imp)}$ =2.498; Cor r=0.418; SD_{change} =5.413; log-odds(pred)imp = -1.901 (calculated in MIC_{pred} equation for improvement)

Substituting the above values in the formula:

$MIC_{pred\ (adjusted)imp}$ =2.498 –(0.090+ 0.103*0.418)*5.413*-1.901

=2.498- 0.1331 *5.413*-1.901

*=2.498- (-1.369)=**3.867=3.9***

Calculation of adjusted $MIC_{predict}$ for deterioration

The adjusted MIC_{pred} for deterioration was calculated using the formula below:

$$MIC_{predict(adjusted)} = MIC_{predict} - (0.090 + 0.103 * Cor) * SD_{change} * \log(odds_{pre})\text{det}$$

Here, $MIC_{pred\ (det)}$ =0.781; Cor r=0.418; SD_{change}=5.413; log-odds(pred)det =-2.09074 (calculated in MIC_{pred} equation for deterioration)

Substituting above values in the formula:

, $MIC_{pred\ (det)}$ =0.781-(0.090+ 0.103*0.418)*5.413*-2.09074

=0.781-(0.1331)*5.413*-2.091=2.2867=**2.3**

5.3.6 Distribution-Based Methods

The MCID for FROM-16 was calculated using SD and SEM. The MCID was 3.3 using 0.5*SD, 2.2 as 1 SEM and 4.2 as 1.96 SEM (Table 5.5)

Table 5.5 Distribution-based methods for estimation of MID value for FROM-16

Baseline		Follow-up		MID		
Mean FROM-16	SD	Mean FROM-16	SD	**0.5*SD$_B$**	**SEM**† $= SD_b * \sqrt{1 - Reliability}$	**1.96*SEM**
9.52	6.568	8.55	7.382	3.284	2.158	4.23

† Cronbach's Alpha for FROM-16 was 0.892

5.3.7 Arriving at MID/MIC Value for FROM-16

The MID values for FROM-16 using anchor and distribution methods ranged from 2.2 to 6 (Table 5.6). SEM estimates the error associated with the measure, implying that changes below the SEM value could result from a measurement error rather than a true change. Using 1 SEM resulted in a MID of 2.2 and using 1.96 SEM resulted in a MID of 4.2.

Table 5.6 Triangulating MID/MIC values from different methods

Methods	MCID/MIC		
	Improvement	**Deterioration**	**Overall**
0.5 SD			3.3
1 SEM			2.2
1.96 SEM			4.2
Average Change score	9.5	2.5	6
ROC curve analysis (95%CI)[a]	6.5 (1, 8)	1.5 (-2, 4)	4
Predictive modelling LR MICpred (95%CI)[b]	2.5 (-3.6, 6.2)	0.78 (-5.7, 5)	
Predictive modelling LR[c] MICpred (Adjusted) (95%CI)	3.9 (-0.1, 9.5)	2.3 (-2.7, 7.6)	3.1
Mean MIC value			3.65=4

Grey coloured cells were not included in the MIC analysis; [a]CI based on 1000 bootstrap simulations; [b]CI calculated using Excel formula of Turluin et al.(2017): https://ars-els-cdn-com.abc.cardiff.ac.uk/content/image/1-s2.0-S0895435615001602-mmc2.xlsx); [c]Adjusted for the proportions improved and deteriorated.

Since 1.96 SEM is a more stringent estimation, representing 95% confidence that this figure is above the measurement error, the value of 1 SEM was excluded from the triangulation. An MIC value of 6, as calculated by the average change method, was also excluded as it was thought it could be biased due to the small number of responses in the smallest change group. MIC_{pred} was replaced with adjusted $MIC_{pred,}$ and therefore, MIC_{pred} was not included in triangulation. Based on the values shown in Table 5.6, the overall MID for FROM-16 could lie between 3.1 and 4.2. The MCID of improvement using the anchor approach ranged from 3.9 to 6.5, and for deterioration, it ranged between 1.5 to 2.3. However, it was decided to priori to arrive at one MIC value for FROM-16 using triangulation. Based on an a priori decision rule, triangulation included averaging of MIC improvement and deterioration for anchor-based methods (MIC_{ROC}=4 and adj MIC_{pred}=3.1)=3.55, rounded up to 4. Average MIC values from the anchor and distribution methods also resulted in a value of 4 (4+3.1+4.2+3.3=14.6/4 =3.65). Since the FROM-16 score is a whole number, an MID/MIC value of 4 is suggested for FROM-16. The MIC value of four assigned to FROM-16 is above the value of I SEM (2.2) and around 1.96 SEM (4.2).

5.4 DISCUSSION

This study uses both anchor-based as well as distribution methods to establish the MID of the FROM-16. Both methods have their own advantages and limitations, but together they complement each other. The anchor-based approaches are generally considered superior as they relate change scores on the instrument to an external criterion of important change, thus providing a clinically meaningful estimate of change. Distribution-based methods, on the other hand, provide statistical grounding to the MID value (Revicki et al. 2008; Terwee et al. 2021).

The primary method used in this study for calculating MCID was the anchor-based approach. In order to use this approach, there is a minimum requirement of moderate correlation (r >0.3) between the anchor and change scores of a measure (Revicki et al. 2008). This is because a patient's GRCQ may include constructs other than those assessed by specific measures, and a perfect correlation is not expected (Kamper et

al. 2009). This study demonstrated a significant correlation (r=0.418, p=0.001) between the GRCQ outcome and the FROM-16 score change.

The Average change method used in this study to calculate MID followed the approach of Juniper et al. (1994), where the mean change in score among those who reported feeling "somewhat better" and a little better" or "somewhat worse and a little worse" were used as the MID for improvement and deterioration respectively, and the mean of the two was taken as the overall MID. Using this method, the MID for improvement was 9.5, and that for deterioration was 2.5 with overall MID of 6. However, as only a few family members recorded “small” improvement and deterioration, the results may be imprecise. Furthermore, some have argued that this method does not represent a threshold for minimal improvement but rather a mean in a subgroup of patients categorised as minimally improved (Terwee et al. 2021). These authors claim that the mean change in PROM score in the group of patients studied is higher than the threshold for minimal important change. This is also relevant to this study since the mean score change for improvement was much higher than from other methods. Terluin et al. (2015) recommend using the ROC method or predictive modelling rather than the mean change method because these methods provide a threshold between improved and not improved patients from using the entire sample, leading to more reliable estimates than the $MID_{mean.}$

The ROC method in this study resulted in a MID value of 6.5 (p=0.02, AUC=0.698) for improvement and 1.5 (p=0.001, AUC=0.821) for deterioration. The ROC curves not only compare a continuous scale to a benchmark but also determine if this relationship differs from chance alone, thus combining an anchor-based approach with a distribution-based approach (Lydick 2000). Molino et al. (2022) argue that the ROC curve allows the most precise assessment of the aggregate responses by addressing the clinical and statistical aspects of the MID calculation. Although ROC has been used to calculate MIDs of PROMs, Terwee et al. (2021) claim that the predictive modelling method is more precise. However, both methods may be subject to bias if the proportion of improved and not improved is greater or smaller than 50%. These authors have recommended using the adjusted predictive modelling method ($MIC_{pred\ (adjusted)}$), which allows corrections to this bias (Terluin et al. 2017; Terwee et al. 2021). Since, in this study, proportions of improvement or deterioration were less than 50%,

adjusted MIC_{pred} was calculated using the formula given by Terluin et al. (2017). The adjusted MIC_{Pred} was 3.9 for improvement and 2.3 for deterioration.

This study used the SD for the calculation of MID using the distribution method. Although multiples of SD (0.5SD, 0.3SD, 1/3SD, 0.2SD) have been used to calculate MID (Mouelhi et al. 2020), this study used 0.5 SD as it has been shown to represent a good approximation of the MID (Norman et al. 2004; Katz et al. 2008; Norman et al. 2003). The 0.5 SD was 3.3, which could be a possible value of the MID of FROM-16. Although the use of SD for the calculation of MID is well established (Guyatt et al. 2002; Wyrwich et al. 2005), a disadvantage is that SD is a property of the group being studied so the MID calculation might be sample dependent (Altman and Bland 2005) and hence less generalisable.

Another distribution approach used to calculate MID was SEM. The SEM estimates the error associated with the measure, implying that changes below the SEM could result from a measurement error rather than being a true change. 1 SEM, 1.96 SEM and 2.77 SEM have all been suggested as the basis for calculating MID. The 1.96 represents the value with a 95% confidence interval. The 2.77 SEM value is 1.96 SEM multiplied by $\sqrt{2}$, which incorporates a multiplier of two to adjust for sampling error when using data from two samples (test and retest) versus one. As a test-retest was not carried out, analysis was based on Cronbach's alpha coefficients obtained from the sample score at baseline, $\sqrt{2}$ was not incorporated into the calculation (Shikiar et al. 2005). Although the number of SEMs needed to qualify for meaningful change is not yet fully established (Copay et al. 2007; Revicki et al. 2008), 1 SEM has been shown to refer to meaningful change (Wyrwich et al. 1999a; Wyrwich et al. 1999b). The more stringent estimation is 1.96 SEM and 2.77 SEM. A benefit of using the SEM is that it is not sample dependent because it includes the sample's reliability and variability in the SEM computational formula. This means that for repeated samples drawn from the same population, the SEM values should be the same unless particular samples have a high number of subjects at the extreme ends of the distribution. In this study, values for one SEM and 1.96 SEM were estimated as 2.16 and 4.23. Although these methods provide statistical meaning, they largely ignore the core of the concept of MID, which is to determine a clinically important change rather than a statistically significant change (Copay et al. 2007). Moreover, the authors recommended using these methods when

anchor-based calculations are not possible (Revicki et al. 2006). Nonetheless, distribution methods provide confirmatory evidence for the MID values derived using the anchor-base methods and hence are of great value in determining the quality of MID calculations.

The findings of both the anchor-based and the two distribution-based methods resulted in a range of MID values, indicating that the MID for FROM-16 is likely to be in the range of 3.1-4.2. Since the FROM score is a whole number, a value of 4 is suggested as the MIC for FROM-16. During the triangulation of results, it was considered that the MID should be based primarily on anchor-based methods in the first instance on the ROC curve and adjusted MIC_{pred} (mean of improvement and deterioration), and the value should be chosen that is higher than the SEM and around the 1.96 SEM value. After triangulation, only one of the MID values (MID_{mean}=6) fell outside the selected value range. However, as MID_{mean} was based on only a few responses, it was considered that this calculation could be imprecise. When using several methods, it is impossible to arrive at a single value, and the stability of a single MID score has not been demonstrated in the literature. Mouelhi et al. (2020), in their review of studies on MID, contend that the MID can be best estimated using a combination of anchor and distribution measures triangulating toward a single value. However, the MIC/MID value should not be seen as a deterministic cut-off point to interpret score changes but rather a probabilistic value indicating that an individual has experienced a meaningful change (Terwee et al. 2021). For the same measure, the MID for improvement may not be the same as the MID for deterioration (Cella et al. 2002; Conijn et al. 2015; Hendrikx et al. 2015). In this study, all three anchor-based methods showed lower values for deterioration than for improvement, indicating that FROM-16 might have different MCID values for improvement and deterioration. However, this warrants further research.

This study has several strengths. Although numerous studies have reported the MID/MCID of PROMS, this is the first study to report a MID/MCID value for FROM-16, a family-specific measure. Second, the study explored several distributional and anchor-based methods, including more recent methods of predictive modelling. This study has followed all recommendations of Terwee et al. (2021) for conducting and reporting high-quality MIC studies. However, the study has some limitations. Only a small number of family members reported a change in GRCQ scores. Although the number

of responses in change versus no change was less than 50%, the study used adjusted MIC_{Pred} to calculate MID to correct this bias (Terwee et al. 2021). One possible reason that fewer family members recorded change on GRCQ could be the design of the presentation online of the GRCQ question, which may have obscured the options from the family members. In order to keep the design simple, the family members were first asked to choose one option from improved, same, or deteriorated. If family members chose improved or deteriorated, only then could they see further detailed options to describe a range of magnitudes of improvement or deterioration. Nevertheless, it could also be argued that the majority of family members did not experience a noticeable change in their QoL and remained stable, which could be considered a favourable outcome of an intervention. This possibility is demonstrated by the small ES of change noticed by the patients as well as family members, indicating that future studies should be conducted on a bigger sample, in order to have a higher number of individuals in the change group. Although sample size was modest, it was within the recommended size for this type of study (Mokkink et al. 2010; Terwee et al. 2021). Another limitation is the use of GRCQ as an anchor rather than a clinical endpoint, which could be free of recall bias. Since the study included family members of patients with a number of health conditions, GRCQ provided the most suitable option as a single measure to measure change across conditions.

5.5 CONCLUSIONS

The study, for the first time, calculated the MID value for FROM-16, suggesting that a score change of four points in FROM-16 represents clinically meaningful change. The results of the study have clinical implications. The establishment of the MID for the FROM-16 provides an important reference point for clinicians and researchers interested in the effect of treatments on the QoL of patients' family members. Clinical trial researchers may use these MID values to evaluate the degree to which an intervention improves family members'/partners' QOL in a clinically significant manner.

5.6 SUMMARY

- Chapter 4 established the longitudinal validity of FROM-16, demonstrating that it can measure change over time. However, change may be statistically significant yet not clinically important and relevant to the patient (in this case family member/informal carer).

- The smallest change in scores that a patient (in this case, family member/informal carer) considers important is called minimal clinically important difference (MCID), also known as minimal important difference (MID) and 'minimal important change' (MIC).

- This study aimed to estimate MCID for FROM-16.

- One hundred family members/partners of patients with 15 different health conditions completed GRCQ and FROM-16 questionnaires at baseline and at three months' follow-up.

- MCID was estimated using the distribution-based and anchor-based methods.

- The distribution-based methods included standard deviation (SD) and standard error of the mean (SEM). This study used 0.5 SD, 1SEM and 1.96 SEM as MIC, as these values represent a good approximation of the MID based on evidence from previous studies.

- The anchor-based approaches to MIC estimation included ROC analysis and the predictive modelling method. However, results could be biased for the anchor-based approach if the change group is less than 50%.

- It is recommended to calculate adjusted MIC_{pred} if the change group is less than 50% based on responses to the anchor question, which was the case in this study. Adjusted MIC_{pred} was calculated to address this bias.

- MID value based on the distribution method was 3.3 for $MID_{0.5SD}$, 2.2 for MID_{1SEM}, and 4.2 for $MID_{1.96SEM}$.

- MIC value based on the anchor method was: 6.5 for improvement and 1.5 for deterioration on MIC_{ROC}; 2.5 for improvement and 0.78 for deterioration on MIC_{pred}; 3.9 for improvement and 2.3 for deterioration on $MIC_{pred(adjusted)}$.

- Triangulation of MID value across the anchor and the distribution-based methods resulted in a range of MID values, indicating that the MID for FROM-16 is likely to be in the range of 3.1- 4.2. Since the FROM score is a whole number, a value of 4 is suggested as the MCID for FROM-16.

CHAPTER 6

Validation of FROM-16 for Use in the Pandemic: Understanding the Impact of COVID-19 on the Quality of Life of Survivors and their Partners/Family members

6.1 INTRODUCTION

In the previous chapters, we have discussed and justified the robustness of FROM-16 as a generic tool that could be used to measure the family impact of disease in routine clinical practice, research, clinical trials and in health economic evaluation of a medical intervention. In this chapter, we will provide further evidence of the practical use of FROM-16, to measure the family impact of the COVID-19 pandemic. A pandemic is the worldwide spread of a new disease (WHO 2021b). The COVID-19 pandemic has been the biggest public health emergency of modern times, which has challenged healthcare systems and psychological resilience of healthcare professionals across the globe. The World Health Organization (WHO) declared COVID-19 as a 'health emergency of international concern' on 30th January 2020 after the first clusters of people infected by COVID-19 were diagnosed in China (WHO 2020a) and as a 'Pandemic' on 11th March 2020 when 118,000 cases and 4,291 deaths across 114 countries were recorded (WHO 2020b). Since then, the Covid-19 pandemic swept across the world, infecting billions, killing millions and paralysing healthcare systems and institutions which were ill-equipped to deal with the scale of the crisis. Three years on, WHO director-general Tedros Adhanom Ghebreyesus in his statement on 5th May 2023, said that COVID-19 is now an established and ongoing health issue and is no longer a public health emergency (WHO 2023a).

During the COVID-19 pandemic, people all over the world remained socially isolated, and strict lockdown of all businesses and institutions, including the closure of borders and airports, was imposed to contain the spread of the virus. By April 2020, when COVID-19 infection was at a peak in the UK, it became apparent that the quality of life (QoL) of both COVID-19 patients and their family members across the globe was greatly impacted by this new and emerging infection. It was, therefore, critical to measure this impact on survivors and their family members to inform healthcare providers and policymakers and to encourage them to develop support mechanisms sensitive to the needs of COVID-19 survivors and their family members. Bryson (2021) contended that COVID-19 has a far-reaching impact on the health-related QoL (HRQoL) of people and argued that:

> It is time that HRQoL researchers begin to consider the role they will play in the near future. The initial step will be to devise studies to better understand the relationships of the various factors that affect those who have been infected with COVID-19 and those who are involved in the care of these individuals (Bryson 2021).

This study addressed (in advance) the research gap identified by Bryson (2021) and, to researcher's knowledge, is the first study that not only studied the impact of COVID-19 on the QoL of survivors but also on their partners and other family members. Although this study was not part of my original PhD planning, the COVID-19 pandemic provided me with a unique opportunity to validate the FROM-16 for measuring the family impact of the pandemic and fitted well with my PhD objective of providing evidence of usability of FROM-16.

6.1.1 Background

6.1.1.1 Epidemiology of COVID-19

The COVID-19 pandemic has affected 221 countries globally since first being reported in China in December 2019, and there have been more than seven hundred and sixty-six million (**766,895,075)** confirmed cases of COVID-19 and nearly seven million (**6,935,889)** deaths reported by WHO as of 24th May 2023 (WHO 2023b).

Although people of all ages are at risk of COVID-19 infection, the probability of COVID-19 infection and severe disease was found to be greater in people aged 60 years and above, particularly those living in care homes and with pre-existing chronic health conditions. In a study conducted in the United States, the percentage of patients who died was 12 times higher (19.5% vs 1.6%), and the percentage of patients who were hospitalised was six times higher (45.4% vs 7.6%) in those with pre-existing medical conditions than in those without medical conditions (Stokes et al. 2020). The mortality rates were higher for those aged 70 years and above, irrespective of whether they had a pre-existing health condition or not (Stokes et al. 2020). In the UK, racial and ethnic minorities experienced higher rates of COVID-19 infection and subsequent hospitalisation and death (Azar et al. 2020; Gross et al. 2020). Research conducted in the UK has shown that South Asian and Black patients had respectively 1.93 and 1.47

greater odds of having suspected Covid-19 infection (Hull et al. 2020), with a lower average age, compared to White patients (Apea et al. 2021). Despite having similar disease severity at admission and being younger with fewer comorbidities, ethnic minorities in the UK (including South Asian, East Asian, Black, and other ethnic minorities) were more likely to be admitted to intensive care and to require invasive mechanical ventilation than White patients (Harrison 2020).

This increased susceptibility of these populations to COVID-19 infection could be explained on the basis of a number of factors, including over representation in work environments that pose a higher risk of COVID-19, economic inequalities that limit their protection from COVID-19, neighbourhood disadvantage, overcrowded living environment and reduced or lack of access to healthcare (Kind and Buckingham 2018; CDC 2021a). In addition, there may be structural inequalities that can lead to health disparities including higher rates of comorbid conditions such as diabetes, heart disease, hypertension, obesity, and pulmonary diseases (Price-Haywood et al. 2020).

Interestingly, COVID-19 infection rates among children were found to be much lower than among adults, with less than 10% of COVID-19 cases in the United States being reported among children and adolescents aged 5–17 years (CDC 2021b). Furthermore, children less than ten years of age were less likely to be infected than adolescents (Dong et al. 2020; Castagnoli et al. 2020; Choi et al. 2020). However, children and adolescents have been reported to be commonly asymptomatic (Dong et al. 2020) or have mild, non-specific symptoms (CDC 2020; Laws et al. 2021) and hence were likely to spread the COVID-19 infection when asymptomatic or with only mild symptoms.

6.1.1.2 Aetiology

The COVID-19 is an infectious disease caused by the coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The disease was first noticed in Wuhan, Hubei Province, China, in December 2019 (WHO 2023c). Coronaviruses derive their name from the Latin word “corona” meaning crown, referring to the unique appearance of the virus under an electron microscope as round particles with a rim of projections resembling the solar corona. Coronaviruses belong to a family of enveloped RNA viruses, some of which can cause illnesses in people such as the common cold,

severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS), and others can circulate among mammals and birds. In very rare cases, animal coronaviruses can spread to humans and then spread between people, as was the case with SARS and MERS. SARS-CoV-2 belongs to the *Sarbecovirus* subgenus of the *Coronaviridae* family and is the seventh coronavirus known to infect humans (Mitchell 2021; BMJ 2021). However, SARS-CoV2 is a unique strain of RNA viruses that had not been previously observed in humans (Zhu et al. 2020; Lu et al. 2020).

People can catch COVID-19 by coming into contact with a person who is infected with the virus. It spreads from person to person through small droplets from the nose or mouth as an infected person coughs or exhales. The incubation period of COVID-19 ranges from 1-14 days, most commonly around five days (WHO 2022). It is very common for viruses to mutate and change over time and this has happened to SARS-CoV-2. When a virus contains at least one new change to the original virus, it is called a variant. Some mutations can lead to changes in important features of the virus, including characteristics that affect its ability to spread and/or its ability to cause more severe illness and death, these variants are called “variants of concern”. From May 2021, WHO named COVID-19 variants based on letters of the Greek alphabet to make them easier to remember, and to remove the stigma associated with referring to them by the country where they were first detected (WHO 2021a). The COVID-19 variants of concern included:

Alpha (B.1.1.7): first detected in the United Kingdom, and designated a variant of concern in December 2020, it was eventually identified in 192 locations worldwide. Alpha was estimated to be around 50% more contagious than the original Wuhan strain, and thought to be associated with increased disease severity (Geddes 2021).

Beta (B.1.351): first detected in South Africa and also designated a variant of concern in December 2020. Since then, it was identified in 139 locations worldwide. Although transmissibility is around 50% more than the previous variants, it was not associated with more severe disease. The main concern about this variant was reduced neutralisation by antibodies generated through vaccination or as a result of previous infection, which could have meant that vaccines were less effective against it or that people can get reinfected. However, vaccines in 2021 provided strong protection against it (Geddes 2021).

Gamma (P.1): first detected in Brazil, and was designated a variant of concern in January, 2021. It has now been verified in 98/239 locations worldwide. The Gamma variant may be 1.7 to 2.4 times more transmissible than non-variants of concern. However, COVID-19 vaccines that existed in 2021 seemed to work well against it (Geddes 2021).

Delta (B.1.617.2): first detected in India in May 2021, was later identified in 176 locations worldwide and become the dominant variant in many countries.
The Delta variant is estimated to be 40-60% more transmissible than the Alpha variant, and roughly twice as transmissible as the original Wuhan strain of SARS-CoV-2, being associated with roughly double the risk of hospitalisation compared with Alpha. Although data suggest that vaccines available in 2021 are slightly less effective against preventing infection with the Delta variant, they still provided strong protection against severe disease (Geddes 2021).

Omicron (B.1.1.529): this variant was first detected in South African scientists in November 2021 and later verified at 22 locations worldwide, including parts of North and South America, Europe, Africa, Asia and Australia. Omicron has a large number of mutations, some of which have been of concern. The variant is associated with an increased risk of reinfection compared to other variants of concern. The nature of the mutations also prompted concerns that it could be partially resistant to existing COVID-19 vaccines (Geddes 2021). However, a recent study concluded that three doses of an mRNA vaccine gave substantial protection against death in outbreaks of omicron (78%), along with 61% protection against admission to hospital (Kundi 2023).

6.1.1.3 Pathophysiology

The most common symptoms that a person having COVID-19 can experience include fever, dry cough and tiredness. The less common symptoms include aches and pains, sore throat, diarrhoea, chills, conjunctivitis, headache, loss of taste or smell, myalgia, nausea, vomiting, a rash on the skin, and discolouration of fingers or toes (WHO 2021). Many people with COVID-19 may also experience serious symptoms such as difficulty breathing or shortness of breath, chest pain or pressure, and loss of speech or movement (WHO 2021).

The COVID-19 virus enters the body via respiratory aerosols and binds to angiotensin-converting enzyme 2 (ACE-2) receptors on nasal epithelium cells in the upper respiratory tract. Following this, the virus undergoes replication and propagation, infecting ciliated cells in conducting airways. This stage lasts for a few days and invokes a limited immune response. However, the person is highly infective and contagious in spite of a low viral load at this point. Later, the virus travels to the upper respiratory tract via the conducting airways, and the person displays symptoms such as fever, malaise and dry cough. There is a greater immune response during this phase, sufficient to contain the spread of infection, and the majority of patients do not progress beyond this phase. However, about one-fifth of all infected patients progress to the next stage involving the lower respiratory tract and progression to acute respiratory distress syndrome (ARDS) (Cevik et al. 2020). The COVID-19 infections have been grouped into the following categories based on the severity of illness:

- Asymptomatic or Pre-symptomatic Infection: Individuals who test positive for COVID-19 using a virologic test but who have no symptoms that are consistent with COVID-19.
- Mild Illness: Individuals who have any of the various signs and symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.
- Moderate Illness: Individuals who present evidence of lower respiratory disease during clinical assessment or imaging and who have a saturation of oxygen ≥94% on room air at sea level.
- Severe Illness: Individuals who have a saturation of oxygen less than 94%, 30 breaths/minute
- Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction (Mitchell 2021)

6.1.1.4 Prevention

The fact that the COVID-19 virus is highly contagious meant that those infected had to self isolate, and those around them had to quarantine, thus having a huge impact on the patient as well as those around them. Quarantine refers to separating and

restricting the movement of people who are exposed to a contagious disease to see if they become sick, thus reducing their risk of infecting others (CDC 2021), whereas isolation means separating infected people from those who have not had the infection to prevent the spread of disease. A number of prevention measures were put in place to restrict the infection, such as social distancing, the practice of increasing the space between individuals to decrease the closeness of contact, thus reducing the risk of spreading disease (CDC 2021), frequent cleaning of hands using soap and water or alcohol scrub and covering mouth and nose with masks. However, what was most challenging about COVID-19 infection in 2020 was an aspect that at first it was not realised, that the virus could be transmitted by patients without symptoms (Rothe et al. 2020), thus making it difficult to identify those infected and to control the disease spreading, especially in the absence of a specific treatment or vaccine.

A vaccine is a substance used to stimulate the production of antibodies and provide immunity against one or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without inducing the disease. Vaccination is the safest and most effective way of protecting people against harmful diseases such as COVID-19. Several vaccines were authorised for public use after December 2020, including those produced by AstraZeneca, Pfizer–BioNTech, Gamela Research Institute (Sputnik V), Sinopharm, Sinovac, Johnson & Johnson, Moderna and Convidecia. With the availability of vaccines in late 2020 and subsequent rolling out to priority risk groups and the general population in 2021, the number of infections and deaths was brought down, although the risk of new variants and subsequent need for a new, improved vaccine remained (de Courten 2021).

6.1.2 Study Rationale

While a lot of attention has been placed on the prevention of COVID-19 with efforts made to prevent deaths, the post-COVID morbidity was poorly appreciated and underestimated (Davis et al. 2021). Research was mainly focused on identifying the epidemiological and clinical characteristics of infected patients (Huang et al. 2020; Chen, N et al. 2020), the genomic characterisation of the virus (Lu et al. 2020), vaccine development (Lurie et al. 2020, Slaoui and Hepburn 2020)), therapy (Moore 2020) and the response of healthcare systems to the pandemic (Narain et al. 2020). Many

studies looked into the psychological impact of COVID-19 on healthcare professionals (Cai et al. 2020; Shanafelt et al. 2020; Godlee 2020), and some studies explored the risk and resilience in families, parents and children during the COVID-19 pandemic (Spinelli et al. 2020; Prime et al. 2020). It was not until late 2020 that some studies reported a growing number of patients with COVID-19 having persistent symptoms; however, the duration and pathophysiology of long-COVID remained uncertain (Carfì et al. 2020; Michelen et al. 2020; Mitrani et al. 2020; Assaf et al. 2020).

At the time when this study was conducted, there was little information on the physical and psychosocial impact experienced by COVID-19 survivors and their families, despite the need having been identified for information on the lived experience of infected people and of their family members (Holmes et al. 2020). It was, therefore, important to ascertain the immediate and persisting impact of COVID-19 on those affected and on their families in order to aid healthcare workers and government agencies to better support them. The understanding of how a person's health condition impacts the QoL of their partners and other family members has increased over the last decade (Golics et al. 2013a; Shah et al. 2021a).

6.1.3 Aim and Objectives

The aim of this study was to assess the impact of COVID-19 on survivors and their family members based on their lived experience of COVID-19, using validated QoL instruments administered using online social media platforms.

The primary objectives were to:

- Validate FROM-16 for measuring the impact of survivors' COVID-19 on the QoL of partners and family members
- Assess the impact of COVID-19 on the QoL of survivors.

6.1.4 Study Hypotheses

- COVID-19 impacted QoL of survivors but also the QoL of their family members/partners.
- FROM-16 could be used to measure the impact of survivor's COVID-19 on QoL of their family members/partners.

6.2 METHODS

6.2.1 Study Design

This was a cross-sectional global online study using an anonymous online questionnaire. Study participants were COVID-19 survivors and their family members/partners. Data collection took place from June to August 2020.

6.2.2 Ethical Considerations

The ethical issues considered and addressed included ethical approval, approval from Euroqol for use of electronic version of EQ-5D-3L, the GDPR compliant survey platform, informed consent, voluntary participation, anonymity and maintaining confidentiality. Ethics approval was sought from the Cardiff University School of Medicine Research Ethics Committee to conduct an online cross-sectional global survey using social media to understand the impact of COVID-19 on survivors and their family members (Appendix XVIII). The approval was granted on 28th of May 2020 (Appendix XIX). Data was collected between June and August 2020. The study was carried out using the GDPR compliant survey platform Jisc online platform https://www.onlinesurveys.ac.uk/ (Jisc 2020). Study participants were provided with information about the study via a link in the survey to a "Participant Information Sheet" where they were informed that participation was voluntary, and their data would remain anonymous (Appendix XVIII). Approval was also sought from Euroqol for the use of the electronic version of the EQ-5D-3L health status questionnaire for measuring the impact of COVID-19 on survivors (Appendix XX). As this was an anonymous study, no identifiable information was recorded. All computer files with survey data are password-protected and only the investigator has access to this data.

6.2.3 Inclusion/Exclusion criteria

6.2.3.1 Inclusion criteria

- People who have had COVID-19 and their family member or partner
- Able to understand and read English
- Adults aged 18 years or older

- Have the mental capacity to give informed written consent and complete the questionnaire using an electronic device.

6.2.3.2 Exclusion criteria

- People not affected by COVID-19
- Patient and family member or partner under 18 years of age
- Unable to read and understand English
- Unable to give written informed consent or to operate an electronic device to answer the survey.

6.2.4 Sampling

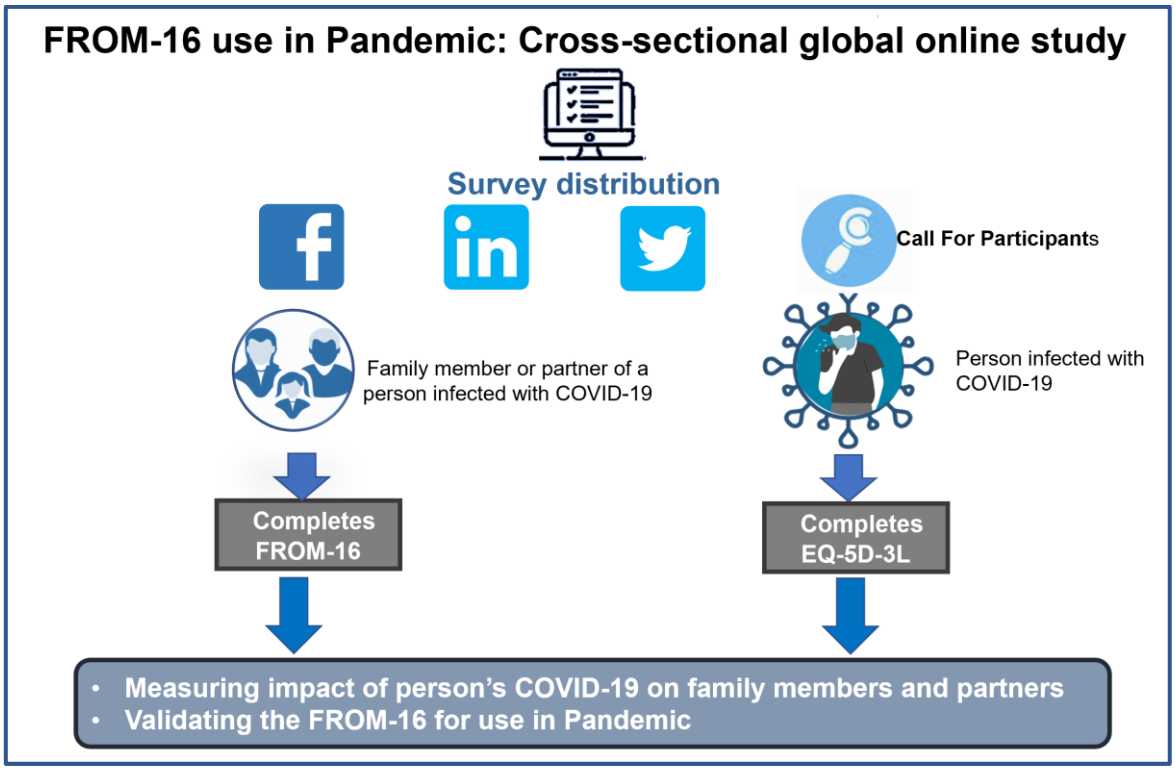
The study used a mix of convenience and “snowball” sampling (Bhardwaj 2019). Snowball sampling is a nonprobability sampling technique where existing study participants recruit other subjects from among their family, friends and colleagues. This type of sampling is termed “snowball sampling”, as the sample group is said to grow like a rolling snowball (Bhardwaj 2019). It was the nature of the pandemic that people could not be reached by many normal routes but still be reached through social media. Snowball sampling through social media was the most efficient way to reach out to a wider population globally in order to understand the impact of COVID-19 on patients and their families. Furthermore, to ensure that a diverse group of participants were recruited, the survey was widely distributed through Facebook, Twitter, and LinkedIn.

6.2.5 Survey Design

The survey had two sections. Section one was to be completed by the COVID-19 survivor. Each survivor provided responses to the EQ-5D-3L questionnaire and also answered basic health demographic questions such as age, gender, country of residence, occupation, whether the patient was admitted to a hospital because of COVID-19 and whether the patient suffered from any pre-existing health condition. Section two was completed by the partner or a close family member of the survivor. Each participating family member and partner completed FROM-16 and provided basic demographic details such as age, gender, country of residence, occupation, the relationship to the patient, weeks since their relative (the COVID-19 survivor) was

infected, and whether or not the participating family member or partner was also infected with COVID-19 (Figure 6.1).

Figure 6.1 Flow diagram: FROM-16 implementation-COVID-19 Study



Although there are a number of other generic questionnaires, such as WHOQOL, SF-36, SF-12 and EQ-5D-5L, the EQ-5D-3L was chosen to measure the impact of COVID-19 on the QoL of survivors as it is short and user-friendly, with only three response options. This was particularly important in reducing the respondent burden on already burdened COVID-19 survivors as the study was conducted during the COVID-19 pandemic. Furthermore, it was also chosen as the preferred measure by patient and family member research partners.

It is possible that some ethnic groups were more likely to get COVID-19 infection, but this study was designed at the start of the pandemic, when such issues had not become apparent. A question on ethnicity was not asked in the survey.

Since race and ethnicity do not have universally agreed scientific definitions, it was challenging to include race and ethnicity questions that would encompass all people and cultures across the globe in this international survey. Therefore, to avoid misclassification and possible offence through misunderstandings, it was decided not to

include such questions. The study participants were provided with information about the study via an approved participant information sheet embedded in the survey (Appendix XVI). The participants gave informed consent online at the start of the survey after reading the participant information sheet.

6.2.6 Participant Recruitment

The survey was distributed using various social media channels such as Facebook, Twitter and Linked-In by posting the Public URL link on these sites. The survey link was also shared with COVID-19 Facebook groups (Figure 6.1). To maximise the response rate, people were asked to share the link through social media with their friends and relatives infected with COVID-19. The survey was also published on the 'Call for Participants' platform, a simple advertising platform operated by Jisc surveys focused on bringing opportunities for taking part in academic research to the general public https://www.callforparticipants.com/researcher.

6.2.7 Patient and Public Involvement and Engagement - PPIE

Two patients and one family member were integral members of the research team. The patient/family member perspective was sought concerning every aspect of this study. All three research partners contributed from the start of the research project planning discussions. These research partners reviewed the study protocol, the survey documents, ethics application and patient/family member material (participant information sheets and study promotional materials such as blurbs/posters). They were also involved in choosing instruments for measuring survivor QoL and online survey testing. One research partner (SJN) attended weekly research meetings and contributed to all research discussions for this study. SJN was involved as a co-author and reviewed the study manuscript for publication.

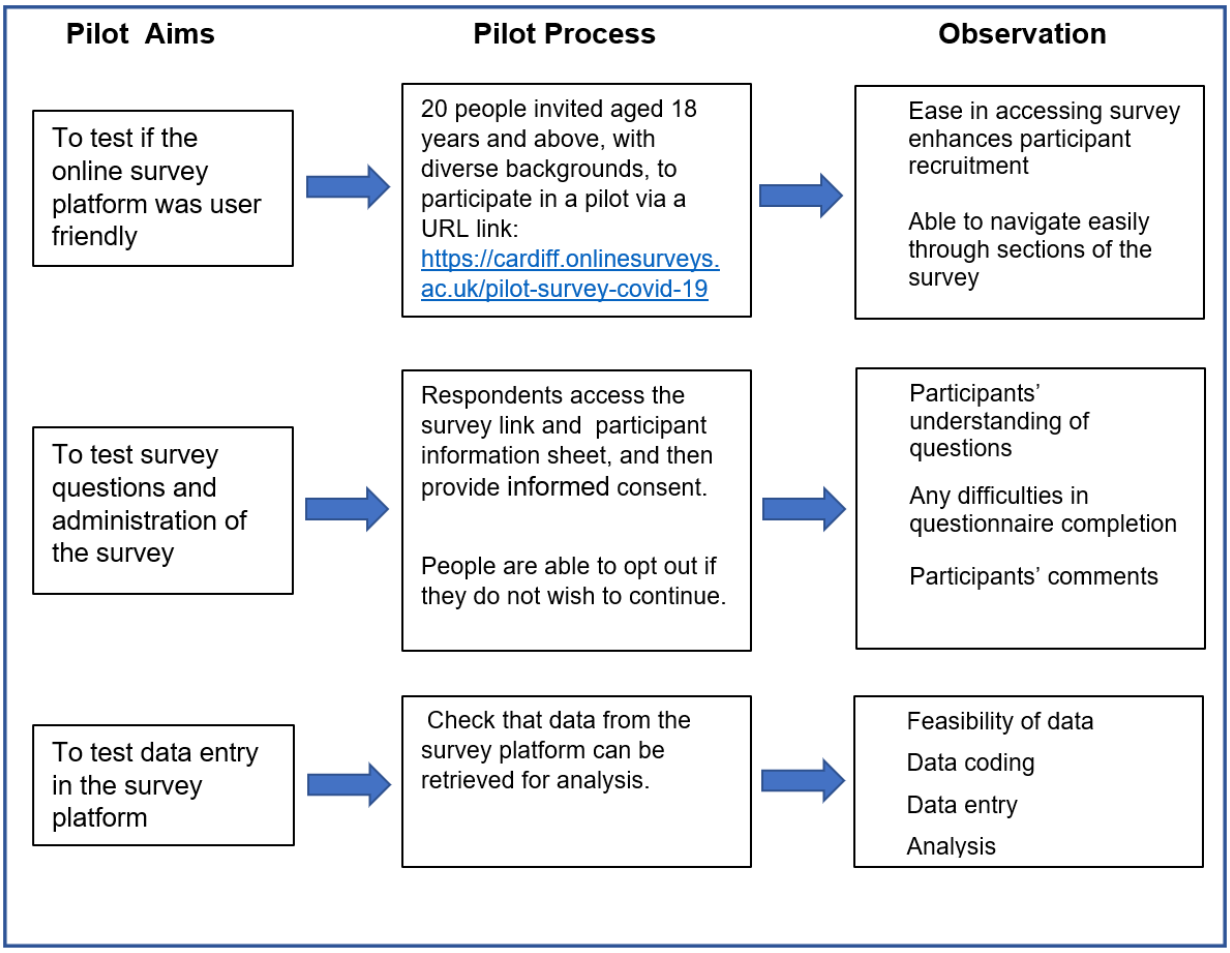
The PPIE strategy for this study also included members of the public. Twenty individuals (aged 18 years and above) not affected by COVID-19 from five countries (UK, India, Zimbabwe, Pakistan and the UAE), participated in a pilot. The feedback and insights from the PPIE were used to improve the survey. Further details about this pilot are discussed in this chapter under the "pilot study".

6.2.8 Pilot Study

A pilot study was conducted to test the draft survey between 12th May 2020 to 20th May 2020. A pilot is a 'small study to test research protocols, data collection instruments, sample recruitment strategies, and other research techniques in preparation for a larger study" (Hassan et al. 2006). The pilot survey was distributed to 20 individuals aged 18 years and above who did not have COVID-19, across the UK, India, Zimbabwe, Pakistan and the UAE. The participants were asked to imagine being family members of someone with COVID-19 when answering the survey. The aim of the pilot was:

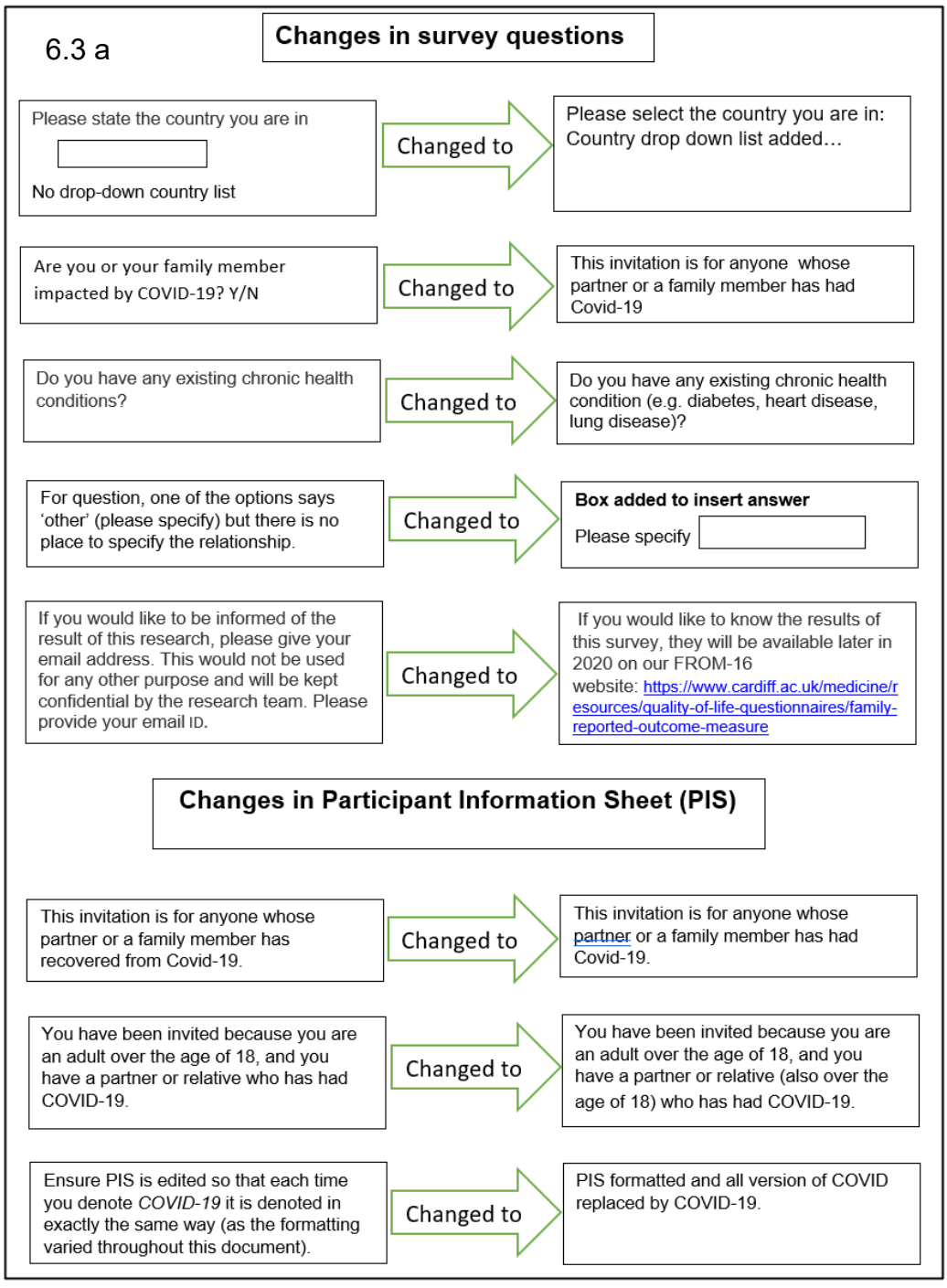
- To check if the survey was user-friendly
- To test respondents' understanding of questions and ease of navigation through the survey.
- To test data entry and retrieval of the survey platform (Figure 6.2).

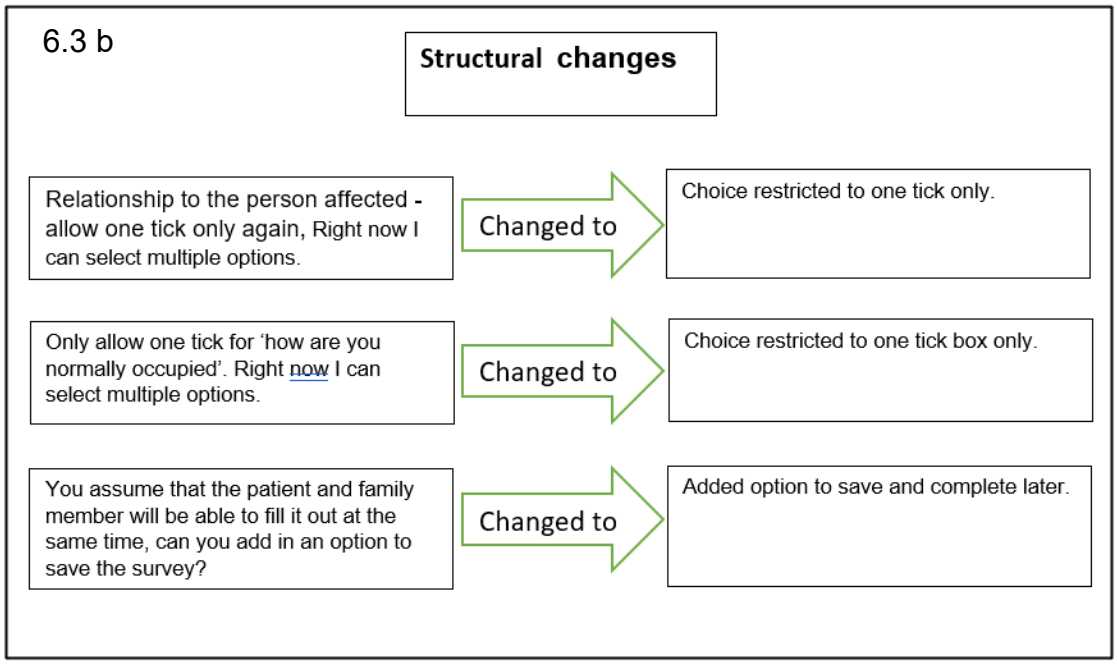
Figure 6.2 Flow chart of the pilot study



All respondents (n=20) answered the survey and provided their comments about the survey. Most of the comments were about wording of the questions that needed to be changed to make them clearer, identification of missing information, being consistent with use of COVID terminology such as COVID-19 or COVID and structural changes in the survey format. A number of changes were made in the survey following the pilot feedback (Figure 6.3 a and b).

Figure 6.3 a and b The changes made in the survey following pilot feedback





6.2.9 Data Processing and Statistical Analysis

Once the study was closed, the data was transferred and saved as Excel files. The analysis was carried out using SPSS version 25. The analysis involved descriptive statistics, non-parametric statistical tests such as the Mann-Whitney U test, and Spearman rank correlation and multiple regression using total FROM-16 and EQ-5D scores as outcome variables.

Descriptive statistics (i.e. mean, standard deviation, median, inter-quartile range) were performed for all variables. The Shapiro–Wilk test was used to examine normal distribution of continuous variables. The required assumptions for normal distribution were not met. Consequently, data analysis employed non-parametric statistical methods. Both the EQ-5D-3L and the FROM-16 scores were treated in the analysis as dependent variables. The EQ-VAS component of EQ-5D was examined separately as a dependent variable. To determine differences between groups defined by each outcome, chi-square tests (when appropriate, Fisher's exact tests) and Mann-Whitney U tests were computed. These bivariate comparisons were based on COVID-19 survivor's characteristics (gender, existing health condition, and hospitalisation) and family member characteristics (gender and whether diagnosed with COVID-19). Spearman's rank correlation coefficient and multiple regression analyses were conducted to understand the effect of independent variables (i.e., predictors: survivor

age, existing health condition, hospital stay for COVID-19, number of weeks since COVID-19 diagnosis, survivor gender) on the EQ-5D outcomes. Similarly, these analyses were conducted to understand the effect of independent variables (EQ-5D score, age of family member, number of weeks since COVID-19 diagnosis, family member gender, whether family member also had COVID-19, relationship to survivor, survivor age, survivor existing health condition, survivor hospital stay for COVID-19) on the FROM-16 outcomes. Statistical Product and Service Solutions (SPSS®) (version 25) was used, and the probability of type I error was set at $p < 0.05$.

6.3 RESULTS

6.3.1 Sociodemographic Characteristics of the Study Participants

A total of 1,254 individuals initially consented to participate in the survey. However, both sections were completed by 765 (58.6%) respondents. Thirty responses were excluded as the respondents were below the age of 18 years. The final analysis included 735 COVID-19 survivors and their 735 family members/partner from Europe (50.6%), North America (38.5%) and the rest of the World (10.9%) (Table 6.1).
Of the 735 COVID-19 survivors, 76.6% were females (mean and median age=48 years) and 73.3% were in paid employment. The mean time since COVID-19 symptoms started was 12.8 weeks (median=13 weeks). In 86.6% (n=637) > 4 weeks had elapsed since COVID-19 symptoms started and in 63.5% (n=467) >12 weeks had elapsed. Of the family members (mean age=47 years, median=48 years), 66.5% were male and 72.1% were in paid employment. Most of the family members were spouses/partners (77.7%), followed by sons and daughters (10.5%) and parents (6.5%). In addition, 48.3% of the family members had also contracted COVID-19 (Table 6.1).

6.3.2 Quality of Life Impact of COVID-19 on Survivors

The overall EQ-5D mean score was 8.65 (SD=1.97) with the ‘usual activities’ item scoring the highest (mean=2.06, max 3) followed by pain/discomfort (1.93) and anxiety/depression (1.84). The mean score of the visual analogue part of EQ-5D was 55.83 (SD=22.94) (Table 6.2).

Table 6.1 Sociodemographic characteristics of the COVID-19 survivors and family members

Variables	Categories	N (%) or N(SD)
COVID-19 Survivors (n=735)		
Gender	Male	172 (23.4%)
	Female	563 (76.6%)
Age (years)	Mean (SD)	47.77 (11.66)
	Median	48
	Range	19-85
	Range (IQR)	19-85 (16)
Number of weeks since COVID-19 diagnosis	Mean (SD)	12.76 (6.10)
	Median	13
	Range	1-36
	Range (IQR)	1-36 (8)
	≥4 weeks	98 (13.3%)
	5-11 weeks	170 (23.1%)
	≥12 weeks	467 (63.5%)
Occupation	Unemployed	19 (2.6%)
	In paid work	538 (73.2%)
	In education or training	26 (3.5%)
	In unpaid work	7 (1%)
	Work in the home/manage the family	60 (8.2%)
	Retired	66 (9%)
	Rather not say	19 (2.6%)
Existing health conditions	No	508 (69.1%)
	Yes	227 (30.9%)
Hospitalised for COVID-19	No	587 (79.9%)
	Yes	148 (20.1%)
Regions	Europe	372 (50.6%)
	North America	283 (38.5%)
	Rest of the World	80 (10.9%)
Family members (N=735)		
Gender	Male	489 (66.5%)
	Female	246 (33.5%)
Age (years)	Mean (SD)	47.43 (13.58)
	Median	48
	Range	18-87
Occupation	Unemployed	42 (5.7%)
	In paid work	530 (72.1%)
	In education or training	29 (3.9%)
	In unpaid work	18 (2.4%)
	Retired	95 (12.9%)
	Rather not say	21 (2.9%)
Relationship to the person affected with COVID-19	Spouse/Partner	571 (77.7%)
	Son/Daughter	77 (10.5%)
	Parent	48 (6.5%)
	Brother/Sister	24 (3.3%)
	Other	15 (2%)
Diagnosed with COVID-19	No	380 (51.7%)
	Yes	355 (48.3%)

Of the five dimensions of EQ-5D, ‘pain and discomfort’ was the impact most frequently reported (81.1%; 68.7 % some problems and 12.4% extreme problems), followed by usual activities (79.5%; 53.2% and 26.3%) and anxiety and depression (68.7%; 53.3% and 15.4%) (Figure 6.4). There was a significant gender difference for ‘mobility’ and for ‘pain and discomfort’ ($p \leq 0.05$) with females being more impacted than males (Table 6.3).

Although existing health conditions were self-reported and severity was not stated, the scores of survivors with existing health conditions did not appear to differ from those without such conditions except for mobility and usual activities ($p \leq 0.05$) (Table 6.3). Having an existing health condition was not a clear predictor of impact on the family member/partner’s QoL. There was a significant difference between the survivors who had been hospitalised for COVID-19 (20%) and those who had not, with the hospitalised survivors being more severely affected across mobility, self-care ($p \leq 0.001$) and usual activities ($p \leq 0.02$) (Table 6.3).

There were significant differences in overall EQ-5D mean scores between survivors with respect to number of weeks since COVID-19 diagnosis ($p<0.001$). Overall EQ-5D mean scores of survivors having COVID-19 symptoms for up to 4 weeks was 8.03 (SD=1.97), 5-11 weeks was 8.3 (SD=2.13) and 12 weeks and above was 8.9 (SD=1.86).

The survivors EQ-5D index values were calculated using the UK TTO tariff. The survivors had a mean overall EQ-5D utility value of 0.725 with North Americans having a significantly lower utility value (0.717) compared to those from Europe and rest of the World. However, all values were lower than normative value for the UK population implying that the survivors’ QoL was impacted in a similar way across the globe (Table 6.4).

6.3.3 Quality of Life Impact of Survivor’s COVID-19 on Family Members

The total FROM-16 mean score was 15, reflecting the extent of the impact of the survivors’ COVID-19 on the HRQoL of their family members (Table 6.2).

Table 6.2 Mean scores of EQ-5D and FROM-16 (n=735)

Scale	Mean (SD)	Median (interquartile range)	Range
EQ-5D-3L			
Total EQ-5D score	8.65 (1.97)	9 (3)	6-14
EQ-5D-3L domains			
Mobility	1.59 (0.54)	2 (1)	1-3
Self-Care	1.23 (0.45)	1 (0)	1-3
Usual Activities	2.06 (0.68)	2 (1)	1-3
Pain / Discomfort	1.93 (0.56)	2 (0)	1-3
Anxiety / Depression	1.84 (0.67)	2 (1)	1-3
EQ-VAS (n=733)	55.83 (22.94)	60(35)	3-100
FROM-16			
Total FROM-16 score	15.00 (8.05)	15 (13)	0-32
Emotional Domain	6.12 (3.23)	6.0 (5)	0-12
Worried	1.43 (0.61)	1 (1)	0-2
Angry	0.75 (0.73)	1(1)	0-2
Sad	1.05 (0.70)	1 (1)	0-2
Frustrated	1.24 (0.74)	1 (1)	0-2
Talking about thoughts	0.84 (0.79)	1 (1)	0-2
Difficulty caring	0.81 (0.76)	1 (1)	0-2
Personal and Social Domain	8.88 (5.51)	9.0 (9)	0-20
Time for self	0.74 (0.76)	1 (1)	0-2
Everyday travel	0.63 (0.78)	0 (1)	0-2
Eating habits	0.65 (0.73)	0 (1)	0-2
Family activities	1.26 (0.73)	1 (1)	0-2
Holiday	1.10 (0.88)	1 (2)	0-2
Sex life	1.09 (0.85)	1 (2)	0-2
Work or study	0.84 (0.79)	1 (1)	0-2
Family relationships	0.73 (0.76)	1 (1)	0-2
Family expenses	0.83 (0.82)	1 (2)	0-2
Sleep	1.01 (0.79)	1(2)	0-2

The mean score of each of the 16 items is given in Table 6.2 with ‘Feeling worried’ scoring highest (1.43) followed by family activities, frustration, holiday, and sex life (1.26, 1.24, 1.10 and 1.09, respectively) (Table 6.2). Of the FROM-16 items, the “feeling of being worried” was most frequently reported (93.6%; 44.6% a little, 49% a lot), followed by “family activities” (83.3%; 41%, 42.3%), “feeling of frustration” (81.7%; 39.7%, 42%), “feeling sad” (78.4%; 51.2%, 27.2 %), “sleep” (68.9%; 37.1%, 31.8 %) and “sex life” (68.1%; 26.7%, 41.4%) (Figure 6.5). There was a significant gender difference among family members, with females feeling sadder, experiencing more impact on everyday travel ($p \leq 0.01$) and on their sleep ($p \leq 0.05$). The impact on sex life was experienced significantly more by males than females ($p \leq 0.001$) (Table 6.5).

Those with a COVID-19 history experienced a greater impact on eating habits, work and study, family activities, holiday, sex life ($p \leq 0.05$), and sleep ($p \leq 0.001$). There were no significant differences for the remaining 10 items of FROM-16 (Table 6.5 and Figure 6.6). There were significant differences in overall FROM-16 mean scores between family members of survivors with respect to onset of COVID-19 symptoms ($p < 0.01$).

The total FROM-16 mean scores of family members of survivors having COVID-19 symptoms for up to 4 weeks was 16.11 (SD=7.35), for 5-11 weeks was 13.31 (SD=7.77) and for 12 weeks and above was 15.38 (SD=8.21). The total FROM-16 score for family members of COVID-19 survivors who had an existing condition was slightly more than for family members of survivors with no existing health condition, but this difference was not statistically significant.

The mean total FROM-16 score for family members of COVID-19 survivors who had an existing condition was slightly more than that of family members of survivors with no existing health condition, but this difference was not statistically significant. A small nonsignificant difference was also noticed in domain scores. However, significant difference was observed between total FROM-16 score and emotional domain scores of family members of survivors who were hospitalised for COVID-19 (Tables 6.6 and 6.7).

Figure 6.4 COVID-19 survivor responses to EQ-5D-3L questions (n=735)

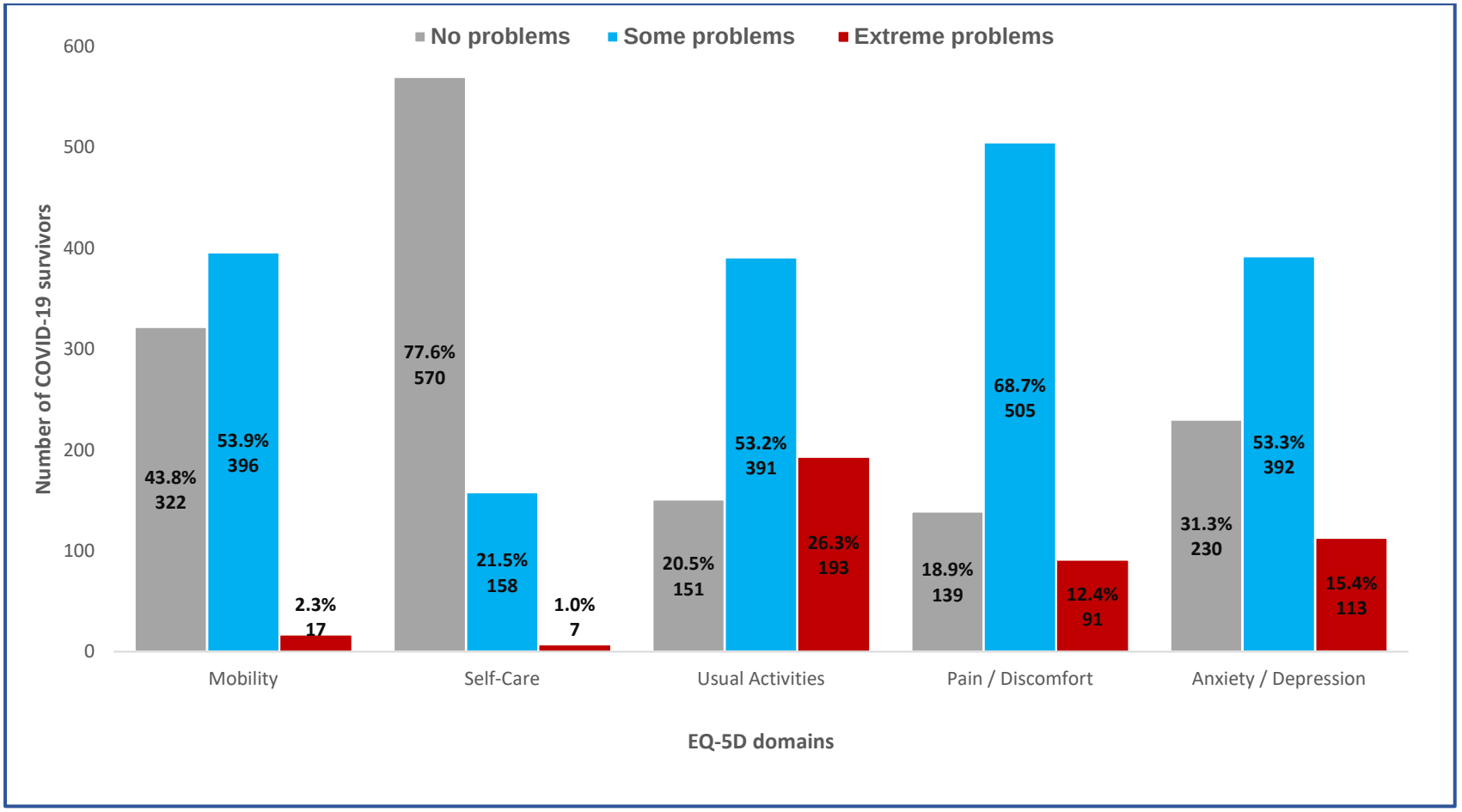


Table 6.3 Comparisons† of EQ-5D scores for gender, existing health condition and hospitalisation

EQ-5D domain	Gender Mean score		p-value	Existing health condition Mean score		p-value	Hospitalised for COVID-19 Mean score		p-value
	Male (n=172)	Female (n=563)		Yes (n=227)	No (n=508)		Yes (n=148)	No (n=587)	
Overall	8.33	8.74	0.036*	8.89	8.54	0.012*	9.17	8.51	0.001**
Mobility	1.51	1.61	0.037*	1.67	1.55	0.006**	1.75	1.54	0.0001**
Self-Care	1.22	1.24	0.602	1.28	1.21	0.053	1.36	1.20	0.0001**
Usual Activities	1.97	2.08	0.065	2.14	2.02	0.034*	2.19	2.02	0.009**
Pain / Discomfort	1.82	1.97	0.002**	1.93	1.94	0.989	1.99	1.92	0.141
Anxiety / Depression	1.81	1.85	0.611	1.88	1.82	0.289	1.88	1.83	0.427

*† Mann Whitney U test; *p ≤ 0.05, **p ≤ 0.01, 2-tailed. (p values were calculated using mean rank scores but mean scores are presented here for ease of understanding)*

Table 6.4 Comparison of COVID-19 survivor EQ-5D utility values with UK Norm† and Quality of Life Impact across three regions

Region	Mean	SD	Min	Max	Male	Female	Existing health condition		Hospitalised for COVID-19	
							Yes	No	Yes	No
Overall (n=735)	0.725	0.195	-0.040	1	0.755	0.715	0.709*	0.732	0.685**	0.735
Europe (n=372)	0.724	0.193	-0.040	1	0.737	0.720				
North America (n=283)	0.717	0.193	-0.040	1	0.769	0.707*				
Rest of the World (n=80)	0.754	0.210	0.095	1	0.792	0.730				

*†Overall = 0.86; Male=0.86; Female=0.85 (Szende and Janssen, 2014); Mann Whitney U test; *p ≤ 0.05, **p ≤ 0.01, 2-tailed*

Figure 6.5 Partner or family member responses to FROM-16 items (n=735)

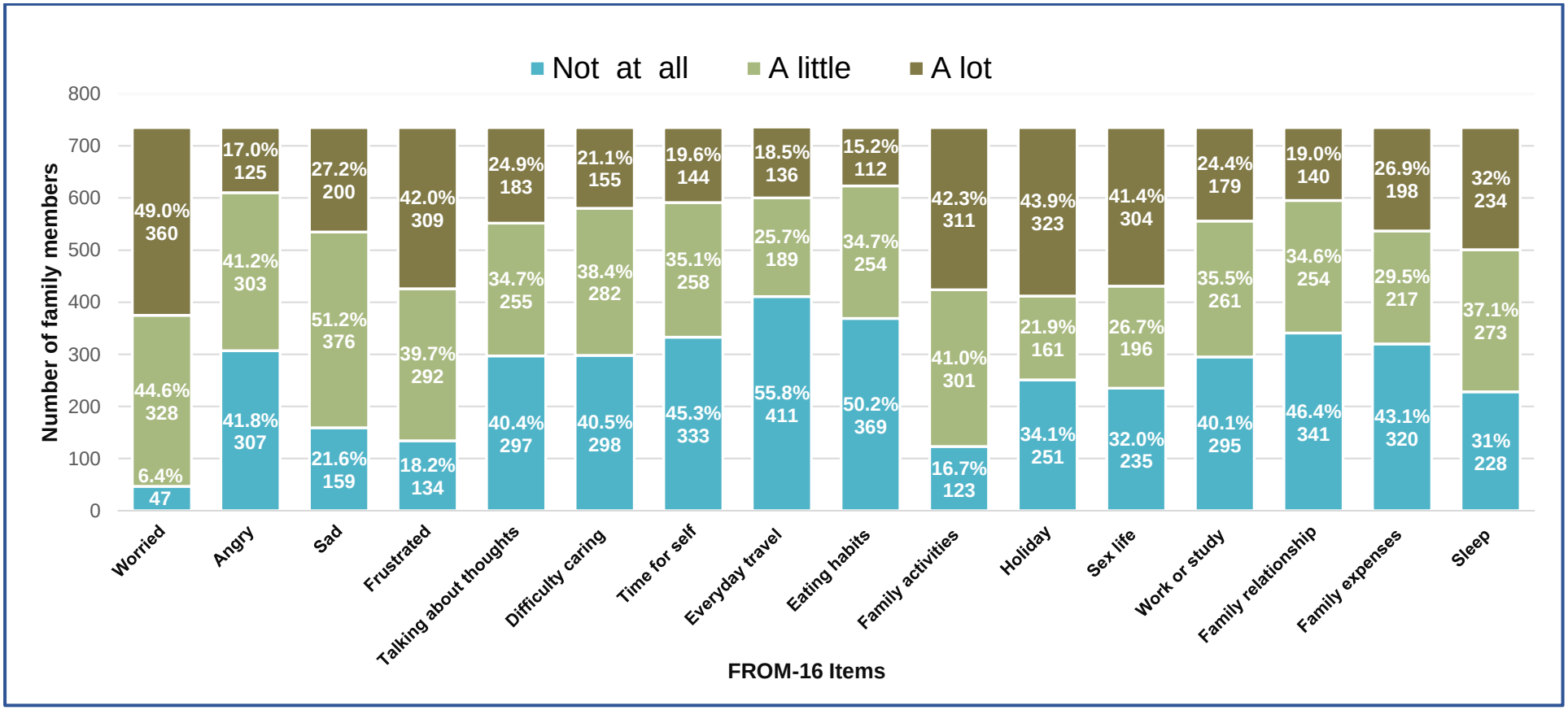
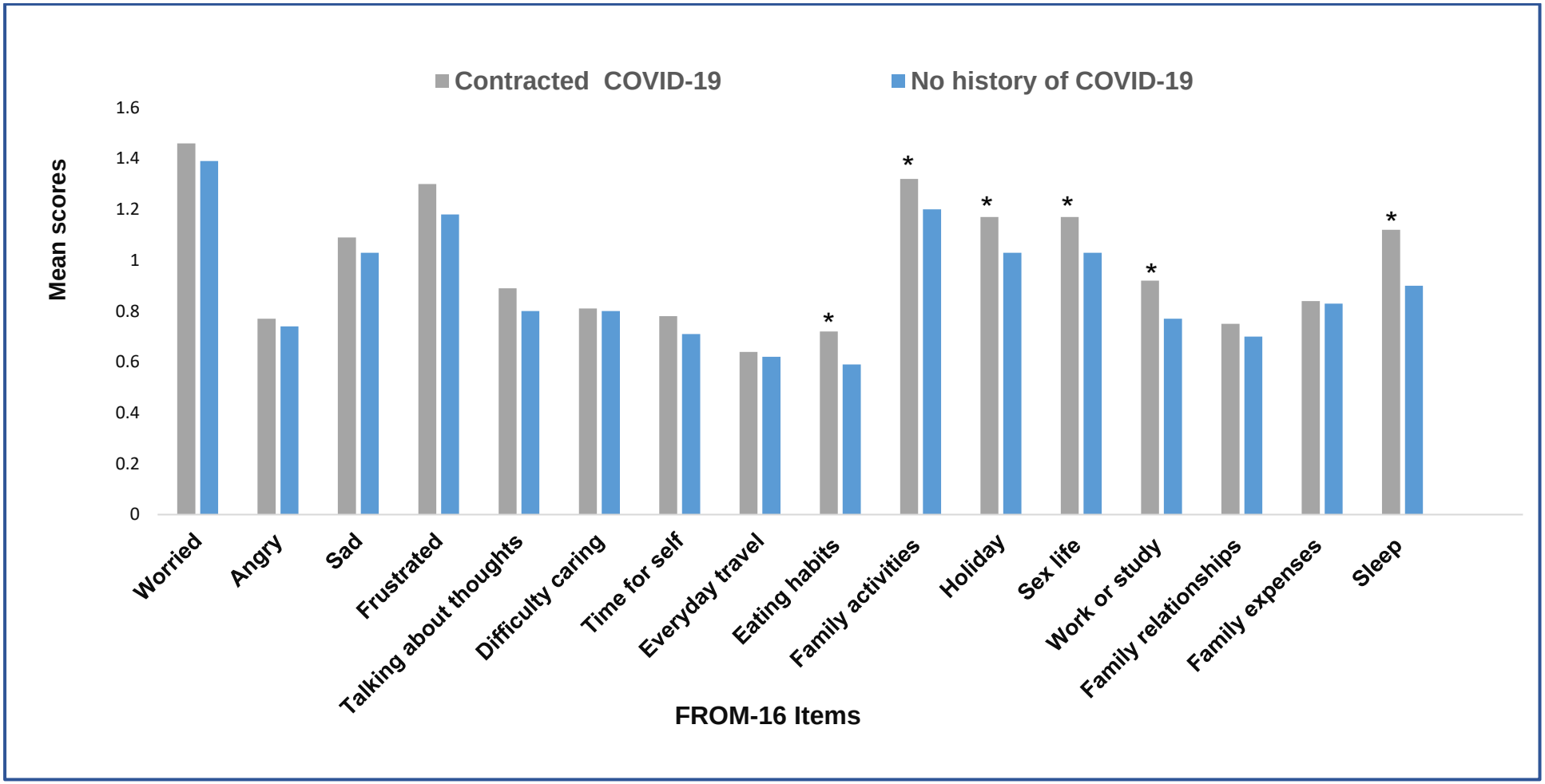


Table 6.5 Comparisons[†] of FROM-16 scores for gender and for whether partner/family member also diagnosed with COVID-19 (n=735)

FROM-16 Items	Gender Mean score Male (n=489)	Female (n=246)	p-value	Diagnosed with COVID-19 Mean score Yes (n=355)	No (n=380)	p-value
Overall	14.81	15.36	0.401	15.74	14.32	0.017*
Worried	1.40	1.48	0.068	1.46	1.39	0.135
Angry	0.73	0.79	0.332	0.77	0.74	0.519
Sad	1.00	1.16	0.004**	1.09	1.03	0.225
Frustrated	1.23	1.26	0.569	1.30	1.18	0.054
Talking about thoughts	0.83	0.87	0.651	0.89	0.80	0.132
Difficulty caring	0.79	0.85	0.324	0.81	0.80	0.847
Time for self	0.70	0.83	0.036*	0.78	0.71	0.164
Everyday travel	0.58	0.72	0.048*	0.64	0.62	0.874
Eating habits	0.64	0.67	0.565	0.72	0.59	0.015*
Family activities	1.28	1.21	0.144	1.32	1.20	0.041*
Holiday	1.10	1.10	0.992	1.17	1.03	0.030*
Sex life	1.22	0.84	0.000**	1.17	1.03	0.035*
Work or study	0.83	0.87	0.485	0.92	0.77	0.013*
Family relationships	0.69	0.79	0.109	0.75	0.70	0.281
Family expenses	0.81	0.87	0.367	0.84	0.83	0.759
Sleep	0.98	1.07	0.138	1.12	0.90	0.000**

*[†]Mann Whitney U test; *p ≤ 0.05, **p ≤ 0.01, 2-tailed. (p values were calculated using mean rank scores but mean scores are presented here for ease of understanding)*

Figure 6.6 FROM-16 item mean scores for family members diagnosed with COVID-19 and for those with no history of COVID-19



Statistically significant difference at $p < 0.05$

Table 6.6 Comparisons† of FROM-16 score between family members of survivors with and without existing health condition

FROM-16 score	FMs of survivors with existing health condition (n=227)	FMs of survivors with no existing health condition (n=508)	p-value
	Mean (SD)	Mean (SD)	
Total FROM-16 score	15.8 (8.1)	14.6 (8.0)	0.075
Emotional domain	6.4 (3.3)	6.0 (3.2)	0.201
Personal and social domain	9.4 (5.5)	8.6 (5.5)	0.07

*†Mann Whitney U test; *p ≤ 0.05, 2-tailed. (p values were calculated using mean rank scores but mean scores are presented here for ease of understanding); FMs, Family members*

Table 6.7 Comparisons† of FROM-16 score between family members of survivors hospitalised and not hospitalised for COVID-19

FROM-16 score	FMs of survivors hospitalised for COVID-19 (n=148)	FMs of survivors not hospitalised for COVID-19 (n=587)	p-value
	Mean (SD)	Mean (SD)	
Total FROM-16 score	16.3 (7.9)	14.7 (8.1)	0.048*
Emotional domain	6.7 (3.1)	6.0 (3.3)	0.010*
Personal and social domain	9.5 (5.5)	8.7 (5.5)	0.162

*†Mann Whitney U test; *p ≤ 0.05, 2-tailed. (p values were calculated using mean rank scores but mean scores are presented here for ease of understanding); FMs, Family members*

6.3.4 FROM-16 Score Banding

FROM-16 score banding (0-1=no effect on family member; 2-8=small effect; 9-16= moderate effect; 17-25=very large effect; 26-32=extremely large effect on family members) reported in Chapter 2 has been now applied retrospectively to this study. Around 44% of family members experienced a very large to extremely large impact on their QoL, whilst 4.5 % experienced no effect of their relative's COVID-19 (Table 6.8). Although male and female family members of COVID-19 survivors seem to have been impacted in almost similar ways to those who reported scores meaning ‘no effect to moderate effect’ on QoL, family members varied in the frequency of reports of impact across bands 3 and 4, representing ‘very large’ and ‘extremely large’ effects with more females experiencing ‘extremely large’ effect than males (Figure 6.7). Furthermore, analysis of FROM-16 scores across Europe, North America and the ‘Rest of the World’ showed that family members of survivors from the ‘Rest of the World’ were impacted more (47.6% in bands 3 and 4) compared to family members of survivors from Europe (46%) and North America (39.2%) (Figure 6.8).

Table 6.8 Family member's FROM-16 score banding (n=735)

Score band	FROM-16 score	Frequency	Percent (%)
0 (No effect)	0-1	33	4.5
1 (Small effect)	2-8	152	20.7
2 (Moderate effect)	9-16	230	31.3
3 (Very large effect)	17-25	232	31.6
4 (Extremely large effect)	26-32	88	12.0

Figure 6.7 Gender differences in FROM-16 score banding

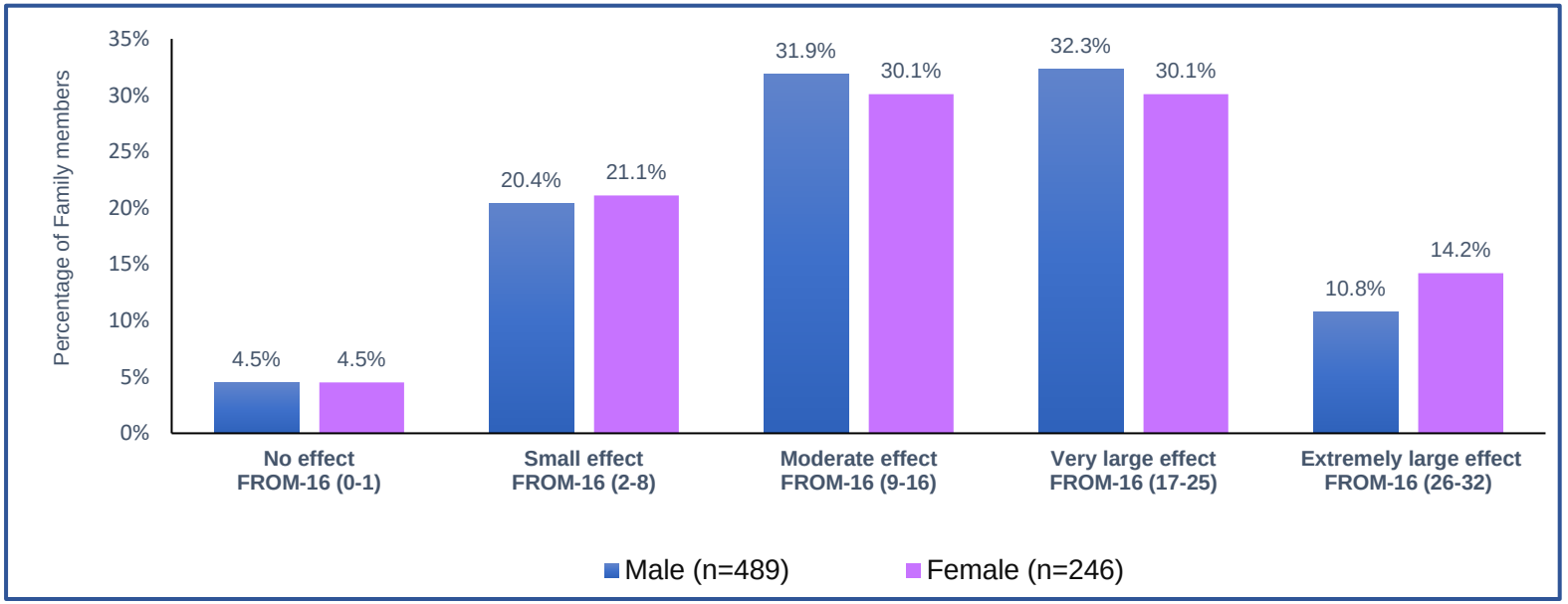
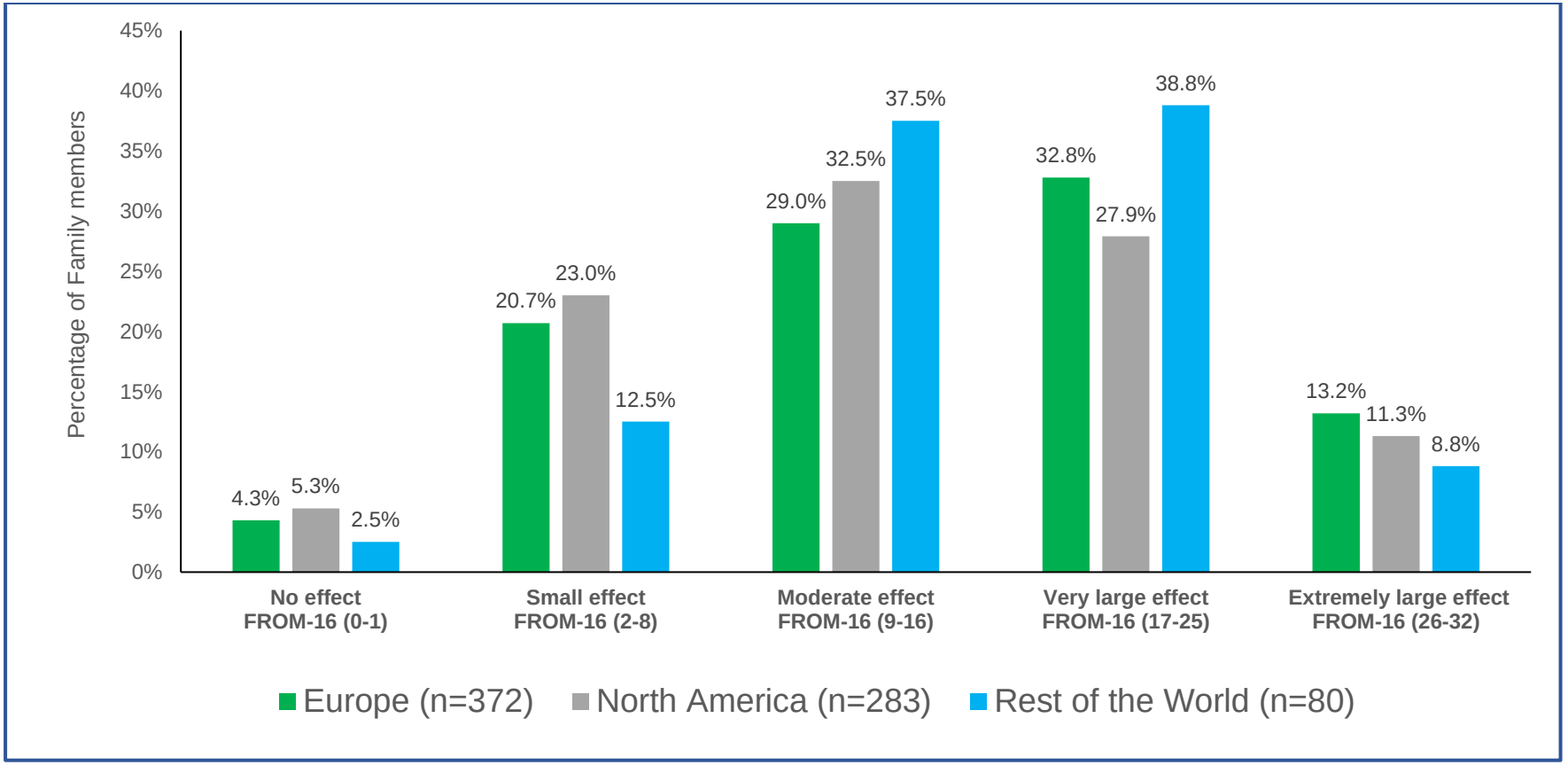


Figure 6.8 FROM-16 severity banding indicating impact of survivor's COVID-19 on family members across Europe, North America and Rest of the World



6.3.5 Relationship between the Quality of Life of Survivors and their Family Members

There were significant positive correlations between the EQ-5D score and the survivors' gender, hospital stay, existing health condition and number of weeks since COVID-19 diagnosis ($p < 0.05$, $p < 0.001$) (Table 6.9). There was a significant positive association between the family members' FROM-16 scores and the survivors' EQ-5D scores ($p < 0.001$) (Tables 6.9) and a significant negative association between FROM-16 scores and the family members' age, survivors' age and EQ-VAS scores ($p < 0.05$).

The EQ-VAS scores showed a significant ($p < 0.01$) inverse relationship with EQ-5D scores, as expected. The variables such as hospital stay, existing health condition and gender (being female) were associated with lower EQ-VAS scores ($p < 0.05$), that is, lower health status (Table 6.10).

6.3.6 Can Quality of Life Predict Outcomes?

The results of multiple regression analyses indicated that survivors' demographics, number of weeks since COVID-19 diagnosis and hospital stay, were significant predictors of the extent of the impact on QoL of the survivor ($p=0.001$) while the survivors' existing health condition was not a predictor (Tables 6.11). Inclusion in the model of variables such as EQ-5D scores, family members' COVID-19 history, family members' gender and relationship to the survivor predicted family reported outcomes ($p=0.001$) while family members' age, survivors' age, number of weeks since COVID-19 diagnosis, existing health condition and hospital stay were not significant predictors of QoL of family members (Table 6.11). The multiple regression analyses confirmed that the QoL of family members/partners was more impacted than the QoL of survivors, female family members were affected more than males, family members with a history of COVID-19 were affected more than those without a history and partners were affected substantially more than those of other relationships. In addition, the model predicted that the functional behaviour of younger survivors (both physical and psychosocial) was more impacted by COVID-19 than that of older survivors.

Table 6.9 Correlation† matrix demonstrating the relationships between EQ-5D, FROM-16 and the participant demographics (n=735)

	EQ-5D score	FROM-16 score	EQ-VAS (n=733)	Survivor age (years)	Survivor gender	Survivor hospital stay for COVID-19	Survivor existing health condition	Number of weeks since COVID-19 diagnosis	Family member age (years)	Family member gender
EQ-5D score	1									
FROM-16 score	0.467**	1								
EQ-VAS (n=733)	-0.591**	-0.346**	1							
Survivor age (years)	-0.020	-0.118*	-0.075	1						
Survivor gender	0.077*	-0.024	-0.102*	0.064	1					
Survivor hospital stay for COVID-19	0.127*	0.073	-0.097*	0.143*	-0.091*	1				
Survivor existing health condition	0.093*	0.066	-0.104*	0.201**	0.036	0.134*	1			
Number of weeks since COVID-19 diagnosis	0.164*	0.029	-0.218	0.158*	0.032	0.097*	0.042	1		
Family member age (years)	-0.015	-0.077	-0.025	0.535**	0.066	0.034	0.145*	0.108*	1	
Family member gender	-0.030	0.031	0.032	-0.008	-0.507**	0.097*	0.050	-0.034	-0.113*	1

† *Spearman's Rank*; **p ≤ 0.05, **p ≤ 0.01, 2-tailed.*

Table 6.10 Summary of survivors' characteristics predicting EQ-5D scores* (n=735)

Predictor	Unstandardised coefficients		Standardised coefficients		*95%* confidence interval levels for *B*					
	B	*Std. Error*	*Beta*	*p-value*	*Lower level*	*Upper Level*	R^2	*Adjusted* R^2	*F-test*	*p-value*
							0.058	0.051	8.907	0.0001
Survivor Age	-0.013	0.006	-0.076	0.043	-0.025	0.000				
Existing health condition	0.298	0.157	0.070	0.059	-0.011	0.607				
Hospital stay for COVID-19	0.644	0.181	0.131	0.0001	0.288	1.001				
Number of weeks since COVID-19 diagnosis	0.050	0.012	0.154	0.0001	0.027	0.073				
Male gender	-0.471	0.169	-0.101	0.005	-0.802	-0.139				

**Multiple regression; B=the slope of the line between the predictor variable and the dependent variable – the larger the number, the more spread out the points are from the regression line; F-test=degree of the linear regression model fitting the data; R^2 = how well the model fits the data; Males=1 and females=0; females are the reference group.*

Table 6.11 Summary of family member/partner and patient characteristics predicting FROM-16 scores* (n=753)

Predictor	Unstandardised coefficients *B*	*Std. Error*	Standardised coefficients *Beta*	*p-value*	*95%* confidence interval levels for *B* *Lower Level*	*Upper Level*	R^2	*Adjusted* R^2	*F-test*	*p-value*
							0.272	0.260	22.506	0.0001
EQ-5D score	2.019	0.134	0.495	0.001	1.757	2.282				
Age family member	-0.044	0.030	-0.073	0.144	-0.102	0.015				
Number of weeks since COVID-19 diagnosis	-0.064	0.043	-0.048	0.144	-0.149	0.022				
Male family member	-1.357	0.587	-0.080	0.021	-2.510	-0.204				
Family member also had COVID-19	1.138	0.524	0.071	0.030	0.109	2.167				
Relationship										
parent	-1.061	1.204	-0.033	0.379	-3.426	1.303				
sons and daughters	-3.243	1.108	-0.123	0.004	-5.419	-1.067				
brothers and sisters	-4.079	1.476	-0.090	0.006	-6.977	-1.180				
other	-2.728	1.827	-0.048	0.136	-6.314	0.859				
Survivor age	-0.040	0.032	-0.059	0.201	-0.103	0.022				
Survivor existing health condition	0.658	0.574	0.038	0.252	-0.468	1.785				
Survivor hospital stay for COVID-19	0.547	0.660	0.027	0.408	-0.749	1.842				

*Multiple regression; *B=the slope of the line between the predictor variable and the dependent variable – the larger the number, the more spread out the points are from the regression line; F-test=degree of the linear regression model fitting the data;* R^2 *=how well the model fits the data; Males=1 and females=0; females are the reference group.*

6.4 DISCUSSION

This study fills an important knowledge gap in measuring the impact of COVID-19 on the HRQoL of both the survivors and, importantly, their partners and family members. Health-related QoL is defined as a person's perception of his/her physical, mental, social and overall well-being (Papakostas et al. 2004; Ma et al. 2020). Therefore, its assessment embraces a wider view of the impact of COVID-19. Chinese survivors of COVID-19 reported lower HRQoL with significant impact on their physical and psychological health, one month after recovery (Chen, K.-Y et al. 2020). This PhD study has shown a major impact not only on the HRQoL of survivors of COVID-19 but also on their partners and family members. This is consistent with the findings of Golics et al. (Golics et al. 2013a; Golics et al. 2013b) that multiple elements of family members' lives can be affected by a relative's illness including emotional, financial, family relationships, education and work, leisure time, and social activities. Interestingly, of the patients who participated, most (76.6%) were women, as found in other surveys (Davis et al. 2021); however, there was a higher proportion of men among participating family members (66.5%). This may be because the majority of COVID-19 social media support groups have been initiated by women (patients), and the most convenient family person to ask to participate might be their partner (mostly male).

This study has revealed that the pandemic has had a major impact on the lives of those who have survived the infection. The study depended on the patient's self-report of the diagnosis of COVID-19 infection and did not specifically ask whether patients had had a COVID-19 positive test. However, further authentication of the diagnosis is given by both the patient and their relative having completed the QoL instruments. The problem most frequently reported by COVID-19 survivors was pain and discomfort, followed by impact on their usual activities, anxiety and depression, affecting females to a greater extent than males. As the majority of COVID-19 survivor respondents were in paid employment, being physically unwell might have impacted their usual activities or return to work. According to a global review on return to work after critical illness (Kamdar et al. 2020), after intensive care stays a third of previously employed survivors remained out of work after five years.

In this study 69% COVID-19 survivors reported feelings of anxiety and depression, much higher than the 43.1% reported by Ma et al. (2020) in clinically stable patients

with COVID-19. Previous studies of Severe Acute Respiratory Syndrome (SARS) revealed the persistence of depression in patients up to 30 months after discharge from hospital (Wu et al. 2005; Mak et al. 2009).

Survivors with existing health conditions did not differ significantly from those without such conditions, except for mobility and usual activities. However, survivors with existing health conditions had significantly lower HRQoL (EQ-5D utility value=0.709). The survivor's QoL was impacted greatly irrespective of having a pre-existing condition. Besides, having a pre-existing health condition was not a significant predictor of impact on the family member/partner's QoL. On the other hand, hospitalised survivors reported greater impact on mobility, self-care and usual activities compared to those who had not been hospitalised.

This study does not have a control group, but EQ-5D values of survivors were compared with UK population normative values. For healthy volunteers in the UK, mean EQ-VAS is recorded as 82.75, Mobility=0.18, Self-Care=0.04, Usual Activity=0.16, Pain/Discomfort=0.33 and Anxiety/Depression=0.20 (Szende and Janssen 2014). In contrast, COVID-19 survivors in this study (47.1 % of survey respondents were from the UK) had mean scores of EQ-VAS=55.83, mobility=1.59, Self-Care=1.23, Usual Activity=2.06, Pain/Discomfort=1.93 and Anxiety/Depression=1.84. This suggests that overall HRQoL was highly impaired in the COVID-19 survivors across all domains. The overall mean EQ-5D utility scores for survivors in this study was 0.725, which is much lower than UK norm value of 0.856 (Szende and Janssen 2014), indicating that COVID-19 had a huge impact on the QoL of survivors .

The study also revealed a major impact on the QoL of the survivors' partners and family members, with partners being most impacted. Using the FROM-16 score banding revealed that 43.6% of family members/partners of COVID-19 survivors experienced a very large or extremely large effect of their relative's COVID-19 on their QoL. The QoL of family members of survivors from the Rest of the World were impacted more than family members of COVID-19 survivors in Europe and North America. Nearly half of participating partners and family members also reported having had COVID-19. Although there were no significant differences between the family members with COVID-19 and those without across 10 of the 16 QoL items of FROM-16, eating habits, family activities, holiday, sleep, sex-life and work or study were impacted significantly

more in those partners and family members who had had COVID-19. The total FROM-16 scores were higher for partners and family members with COVID-19 after adjusting for age, gender, relationship to survivor and the overall survivors' EQ-5D scores, thus indicating poorer QoL for family members with COVID-19 than for those without, as one might predict.

Most partners and family members reported being worried and frustrated, many reported sadness, inability to talk to someone and difficulty in caring for their loved ones. This is not surprising in a situation where there was constant media coverage and an emphasis on high daily death rates, and the fear of infecting loved ones, stigma due to community or family members blaming survivors for the spread of the illness, isolation of loved ones, inability of a family member to provide support, and prolonged recovery time (Sahoo et al. 2020). Such stressors have been implicated in the poor psychological and emotional health of survivors and their family members, both in the context of COVID-19 and other conditions (Tansey et al. 2007; Li et al. 2020; Xiang et al. 2020; Sahoo et al. 2020).

Family members reported an impact on sexual life as a result of their relative's COVID-19 and this impact was greater in males and in family members who had also contracted COVID-19. Two-thirds of family members were either spouses or partners, who could have experienced these difficulties because of the contagious nature of COVID-19 and because of post survival symptoms. Moreover, physical illness in partners has a significant impact on marital relationships, contributing to marital dissatisfaction and likelihood of later divorce (Daniel et al. 2009). The study conducted by Davis et al. (2021) reported sexual dysfunction in COVID-19 survivors across genders: 14.6% of male respondents, 8.0% of female respondents and 15.9% of nonbinary respondents.

Over half of partners and family members reported impact on holidays and nearly half reported an increase in expenses due to their relative's COVID-19. However, impact on holidays was something that was experienced by the general public as well, as the pandemic restricted travel and use of holiday accommodation.

Several studies have shown the impact of COVID-19 on sleep patterns of survivors, with an increase in prevalence of insomnia (Fu et al. 2020; Marelli et al. 2020; Gualano et al. 2020). It is unknown whether the sleep patterns of survivors in this study were also impacted, since EQ-5D does not include such an item. However, in this study 69%

of partners and family members experienced problems with sleep, and 32% reported that their sleep was impacted “a lot”.

6.4.1 Evidence of Long COVID

One of the key findings of this study is the evidence that in survivors for whom the COVID-19 onset was more than 12 weeks ago, there was still a major persisting impact on QoL across all domains in both survivors and their family members. This provides a further indication of the severe impact of post-acute COVID-19 (“Long COVID”) and “Chronic COVID” (Greenhalgh et al. 2020). According to NICE, the term ‘long COVID’ *“*is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)*”* (NICE 2020). In this context the term ‘persisting’ refers to the continuity of the impact of COVID-19 on survivor’s health since the onset of COVID-19 infection.

In this study most (87%) survivors had had COVID-19 for more than 4 weeks, and 64% for more than 12 weeks, indicating that the participant survivors continued to remain unwell for long periods of time, due to post-viral symptoms or ‘long COVID’. This is in contrast to a UK COVID-19 symptom study (COVID Symptom Study 2020), where only 10% of COVID-19 positive survivors remained unwell at three weeks, and a small proportion (2.3%) for more than three months. It is possible that these differences between these studies may be explained by the different recruitment methods used. In another Italian study 87.4% reported persistence of at least one symptom, particularly fatigue and dyspnoea at 60 days from the onset of COVID-19 (Carfì 2020). Arnold et al (2020) reported that at 8-12 weeks post admission 74% of COVID-19 patients experienced persistent symptoms (notably breathlessness and excessive fatigue) with reduced HRQoL. An online survey of British doctors in August 2020 revealed that many were being treated for long term COVID-19 symptoms such as chronic fatigue, muscle weakness, loss of sense of smell, and concentration difficulties (Rimmer 2020). In the study carried out by Davis et al. (2021), 65.2% respondents experienced symptoms for at least 6 months and nearly half of study participants reported being diagnosed with at least one condition following COVID-19 infection.

6.4.2 Comparison With Other COVID-19 Studies

This study has revealed that most survivors and their family members/partners experienced poor HRQoL. The survivors had a mean EQ-5D index value of 0.725 which is lower than the UK norm (0.856) for a healthy population. Hospitalised survivors and those with existing health conditions had significantly lower HRQoL and females experienced more impact than males. The results from this study are in line with other studies. Kaso et al. (2021) found that COVID-19 infection had persistent impact on physical and psychosocial health of survivors with existing health conditions and a history of hospital admission was associated with a lower EQ-5 index and lower VAS scores. In another Belgian study on long COVID survivors, both index scores and VAS scores were significantly lower in comparison to normative persons (Moens et al. 2022).

Furthermore, in this study the majority (81%) of survivors reported moderate to extreme pain and discomfort following COVID-19 infection, 79% experienced problems with their daily activities and 69% experienced moderate to severe anxiety and depression. However, only 20.1% of the survivors were hospitalised, indicating that these long COVID symptoms were experienced by non-hospitalised survivors as well. These findings are in agreement with recent studies on long COVID. In the study conducted on post-discharge survivors, a high proportion of survivors still reported pain (41.3%) and fatigue (55.1%) three months after the disease onset (Demirhan et al. 2022): similar findings were reported by other studies. Denis et al. (2023) reported extreme breathlessness (38% at 6 months and 30% at 12 months), cognitive dysfunction (48% at 6 months and 38% at 12 months) and poor health-related quality of life (EQ-5D-5L < 0.7; 57% at 6 months and 45% at 12 months), and these were associated with female gender, younger age and single-organ impairment (Dennis et al. 2023). In an Italian cohort study at six months follow-up, about a half of ICU survivors experienced problems with mobility and daily activities, 2-3 times higher than a normative Italian population (Umbrello et al. 2022). Another Italian study which evaluated HRQoL of ICU survivors at three months and one year reported improvement in physical health but no change in survivors' dyspnoea and measures of mental function (Gamberini et al. 2021). A six-month follow-up cohort study in non-hospitalised COVID-19 infected people in England showed that survivors experienced physical

symptoms at six months with cases reporting more problems with usual activities compared to controls (Sandmann et al. 2022). Almost half of the affected subjects reported spending an average of £18.10 on prescription drugs and 10% reported a prolonged loss of function compared to the pre-COVID baseline. This established that long COVIID was not unique to hospitalised survivors (Sandmann et al. 2022). This information is important in understanding the extent of impact and the resources needed to support these people. Further studies have indicated that there is evidence of an estimated 10–30% incidence of long COVID in non-hospitalized patients, 50–70% of hospitalized patients (Bull-Otterson et al. 2022; Ceban et al. 2022) and 10–12% of vaccinated patients. However, a recent study by FAIR Health USA has reported that long COVID occurs across all ages, with the highest prevalence being among those aged 36 and 50 years and in non-hospitalized patients with a mild acute illness (FAIR Health 2022). While research is undergoing to understand long COVID and treatment options, a recent review conducted by Davis et al. (2023) has shown that long COVID is a multisystemic illness that exhibits similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (Davis et al. 2023). Therefore, many management strategies for ME/CFS might be effective for individuals with long COVID. While much research was focused on the post-COVID impact on survivors and the general impact on families, no other studies have been identified that explore the impact of survivors' long COVID on the QoL of their family members.

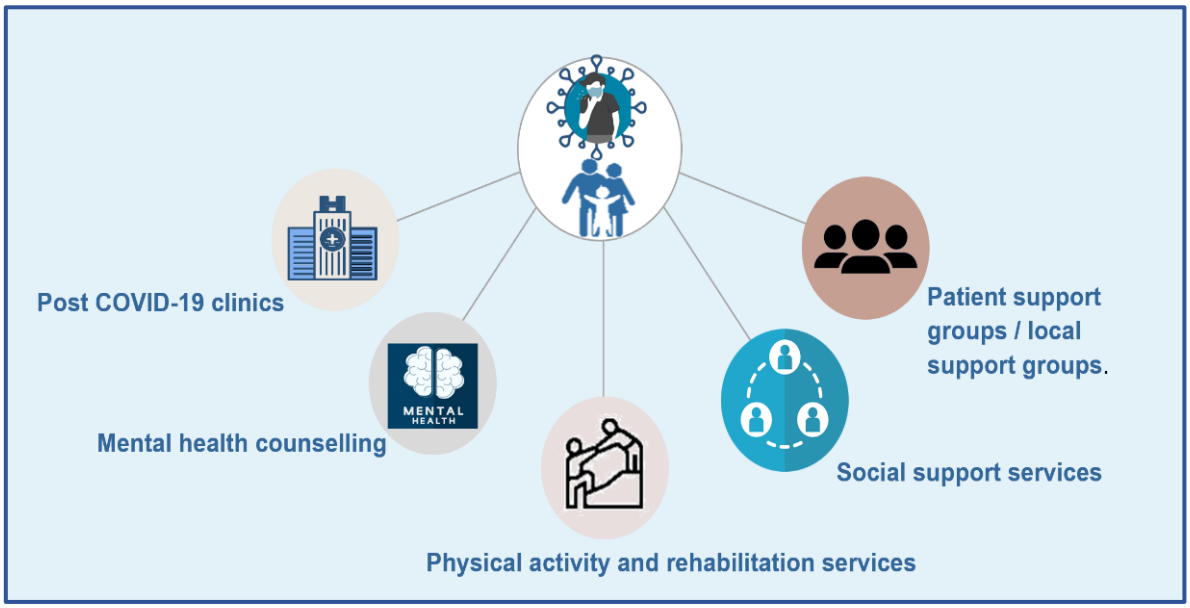
6.4.3 Comparison of FROM-16 Scores of Family Members of COVID-19 Survivors With That of Survivors of Other Diseases

The mean domain scores for FROM-16 in this study were 6.1 (Emotional) and 8.9 (Personal and Social Life) which are higher than the mean domain scores reported by Golics et al. (2014) (Emotional=5.6; Personal and Social Life=6.7) on the impact of patients' chronic disease on family members across 26 medical specialties. Another study (Chantarasap et al. 2019) reported the mean domain scores of family members of patients with cancer as Emotional=4.7 and Personal and Social Life=7.1. In a FROM-16 study on family members of patients with urinary stone disease, family members were not impacted much by their relative's disease, however they reported a slightly greater degree of change in the 'emotional' domain compared with the 'personal

and social life' domain (Raja et al. 2020). This indicates that the family members of COVID-19 survivors who responded to this study suffered more than family members of patients with these severe chronic diseases. However, a study by Britain et al. (2021) reported the mean domain score of family members of people with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) as Emotional=8.8, Personal and social=11.1, with a mean total score of 19.9 (Brittain et al. 2021). Another global study on ME/CFS reported Emotional=7.62 and Personal and social life=10.31, and total mean FROM-16 score as 17.93, indicating that a person having MS/CFS has a huge emotional and psychological impact on their family members (Vyas et al. 2022).

6.4.4 Implications for Clinicians and Policymakers

Figure 6.9 Support services needed for COVID-19 survivors, their partner and family members



This study is one of the earliest publications describing the impact of COVID-19 on survivors, providing evidence of long COVID, and its impact on survivors and their family members. Since then, three years on, long-COVID is now recognized as an important health issue and has been taken seriously by governments and clinicians across the world. According to one conservative estimate, nearly 65 million individuals worldwide have long COVID, with cases increasing daily (Davis et al. 2023), indicating that support services for this group of people and their families will need to continue

and expand. This study has shown how the impact of COVID-19 on one family member could have a domino effect on other family members, especially those close to them such as partners, parents and children. Based on the findings of this study, policymakers should consider developing and commissioning the following support services for people affected by long COVID and their family members (Figure 6.9):

- *Post COVID-19 clinics:* Survivors reported pain and discomfort even after 12 weeks of COVID-19, indicating that tailored services to deal with such symptoms are important to help survivors suffering with long term sequelae. Survivors with post-COVID-19 complications should be heard and treated. Although such clinics have been started in the UK and other western countries, there is a considerable need for such initiatives globally.

- *Needs-based mental health counselling*: Most family members and survivors reported being depressed and worried. It is imperative to further develop care services to ensure the mental wellbeing of survivors and their family members.

- *Physical activity and rehabilitation services*: Most survivors have reported pain and discomfort and an inability to carry out their normal activities. Rehabilitation clinics could provide emotional and physical support to physically and emotionally drained survivors and their family members to enable their return to normal routines. However, it should be noted that exercise/physical activity could be harmful for patients with long COVID who exhibit ME/CFS or post exertional malaise (Heerdt et al. 2022; NICE 2021) and might worsen the condition (Wright et al. 2022).

- *Social support services:* Patients with COVID-19 come from diverse backgrounds and therefore will benefit from culturally and socially appropriate support. Financial assistance is particularly important for those for whom COVID-19 has both reduced earning capacity and increased expenditure.

- *Patient support groups/local support groups for COVID-19 survivors and family members:* The creation of local support groups could be encouraged in primary

care settings. Such groups can help by significantly combating isolation and the disability identified by this study that occurs in COVID-19 survivors and their family members/partners. This could in turn have health economic benefits by possibly reducing long-term utilisation of mental health services. Although long-COVID patient support groups have been created in the UK and western countries, developing countries might also benefit from such initiatives. Similar approaches have been successful, for example in supporting people with myalgic encephalitis.

6.5 CONCLUSIONS

Survivors of COVID-19 report a major persisting impact on their QoL, with many feeling unwell beyond 12 weeks. This indicates the importance of developing a holistic support system that is sensitive to their needs. Moreover, the QoL of partners and family members is also severely impacted, demonstrating the importance of investigating disease impact on family QoL. The establishment of services to provide support to long COVID survivors and their family members in general is therefore a key consideration in the future management of COVID-19. While this research has shown that FROM-16 can be used to measure the impact of the pandemic on partners and family members of those infected, it has also highlighted the importance of measuring the impact of a patient's disease on partners and family members who bear substantial secondary impact.

6.6 SUMMARY

- The COVID-19 pandemic has been a major public health concern of modern times.
- The study aimed to measure the impact of the COVID-19 pandemic on survivors and their family members/partners.

- COVID-19 survivors and their family members/partners were recruited into an online global cross-sectional study between June–August 2020 through social media such as Facebook, Twitter and Linked-in.

- Inclusion criteria were people (≥18 years) infected with COVID-19 and their family members (≥18 years).

- Seven hundred and thirty-five survivors and their family members completed the online study. The COVID-19 survivors completed the EQ-5D-3L and family members/partners the FROM-16 questionnaire in addition to some basic demographic details. Fifty-one per cent of participants were from Europe, 38% from North America and 11% from the rest of the World.

- The results of this study revealed that the HRQoL of COVID-19 survivors were greatly impacted by COVID-19. The EQ-5D-3L index value was 0.725, which was lower than the UK norm of 0.856 for a healthy population.

- Eighty-one per cent of survivors reported moderate to severe pain and discomfort, and 79.5% reported moderate to severe impact on their usual activities. 69% reported anxiety and depression, 56% reported moderate to severe impact on their mobility while 22% reported moderate to severe impact on their selfcare.

- Hospitalised survivors and those with existing health conditions were severely impacted across mobility and usual activities with hospitalised survivors also being severely impacted across selfcare.

- Eighty-seven per cent of survivors were more than four weeks into COVID, and 64% were more than 12 weeks into COVID at the time of completing the survey, indicating that a majority of COVID-19 survivors who contributed to this study were suffering from what is now called ‘long COVID’.

- Family members/partners of survivors have experienced a major impact on their QoL with 43.6 % of family members having a FROM-16 score of 17 or over, meaning a “Very large effect on their quality of life.

- Family members reported a huge emotional impact of their relative having COVID-19, with 94% reporting being worried and 82% reporting being frustrated. Most family members (83%) reported an impact on family activities due to their relatives' COVID-19. Many family members/partners reported an impact on their sleep (69%) and sex life (68%).

- Nearly half of the family members/partners reported contracting COVID-19, however, there was no significant difference across 10 of the 16 FROM-16 items between those who contracted COVID-19 and those who were not infected with COVID-19, indicating that family members were impacted by their relative's COVID-19 irrespective of their own COVID history.

- This study has many strengths, which included being the first study to measure the impact on survivors as well their family members. Other strengths included the large sample size and the heterogeneous population.

- To conclude, COVID-19 had a major impact on the QoL of survivors and a substantial impact on the QoL of their family members/partners, indicating the importance of measuring the family impact of disease and holistic clinical practice.

CHAPTER 7

General Discussion

The impact of illness on family members is a huge secondary burden (Golics et al. 2013a; Golics et al. 2013b; Shah et al. 2021a), that has been largely unnoticed up to now. Although a recent surge in publications related to the family impact of disease demonstrates increased research activity and awareness of the impact, there is a need to measure this impact on a routine basis to provide the needed support to families. Golics and colleagues (2014) created a generic tool, the Family Reported Outcome Measure (FROM-16), which can be used across all areas of medicine to assess the impact of a person's health condition on the QoL of family members and partners (Golics et al. 2014). The FROM-16 is a short and simple tool with a maximum score of 32 and a minimum score 0, a higher score meaning a greater negative impact on family members/partners. The beauty of FROM-16 lies in its brevity and comprehensiveness to include all key family QoL aspects making it suitable for use in both clinical settings and research. Although high-quality initial validation of FROM-16 was carried out during its development, FROM-16 needed further aspects of validation to emerge as a robust generic Family QoL (FQoL) tool for use in clinical practice, research, and health economics. This PhD project is about further validation of FROM-16.

A literature review was initially carried out to update the knowledge base about the family impact of a disease, identify available FQoL instruments, and appraise their psychometric properties (Shah et al. 2021a). Following this publication, the review has been updated for inclusion in this thesis. The initial review was carried out to ensure that no new generic family quality of life tool had been created since 2014 which could have replaced FROM-16: the review established that FROM-16 is the only generic tool that could be used across all areas of medicine to measure the impact of the health condition of a person (of any age) on their family members. Although a systematic review would have better suited this type of topic area, this was not possible due to the time and other resource constraints (Jones 2004). Therefore, a high-quality structured review following PRISMA guidelines was undertaken, including a detailed study selection process and quality assessment for selected studies (Shah et al. 2021a). This review has confirmed the huge physical and psychosocial impact of a person's health condition on their family members/partners, which is in agreement with earlier findings by Golics et al. (2013a). While the exponential rise in the literature on the family impact of a disease over the past decade demonstrates growing awareness about this impact

and the importance of measuring it, this review showed that research is still focused on only a few medical specialities, such as neurology, oncology and dermatology. During the literature review, fifty-two FQoL instruments were identified. Of these instruments, only six were generic instruments and all, except the FROM-16, were generic but with restrictions with respect to certain health conditions or patient populations (Chapter 1, Tables 1.9 to 1.12). This evidence demonstrates that the FROM-16 is the only generic tool that could be used with family members of patients across all disease areas and patient ages. Although it could be argued that disease-specific instruments could provide more explicit details related to the impact of a disease, family members of patients across all disease areas are impacted in similar ways (Golics et al. 2013b). Therefore, a generic tool that is brief yet comprehensive and allows measuring this impact across all disease areas, and that is based on family members/partner perception, could be a more practical option to use in clinical settings. Furthermore, using a generic tool allows the measurement of trends in family impact across different medical specialities and can be used as a single measure to include the family impact of different health conditions in health economic analyses. The appraisal of psychometric properties of fifty-two FQoL tools revealed that most instruments reported content validity, test-retest reliability and construct validity, however only 11 reported responsiveness and only one the minimal clinically important difference (MCID), also known as minimal important change (MIC), (Chapter 1, Tables 1.10 and 1.12). This suggests that most of these instruments do not yet have evidence of sensitivity to change in family members over time, an essential characteristic if being considered for monitoring.

Furthermore, none of the fifty-two instruments reported interpretability, a severity banding of instrument scores to provide meaning to scores. Although this is not a requirement set by the FDA for using PROMs (FDA 2009), it is emerging as an important requirement for their use, particularly if a measure is to be used in clinical practice (Singh and Finlay 2020). The severity banding of QoL scores allows rapid and simple clinical interpretation of scores, leading to better-informed clinical decisions. The review also highlighted that none of the 52 identified FQoL tools could be used in health economic evaluation. Although some carer burden tools have been created to measure this impact, these cannot be used to estimate utility values for family members and

hence are not relevant to evaluations based on EQ-5D, such as those recommended by NICE in the UK. Besides, longitudinal validity for these measures has not yet been established (McLoughlin et al. 2020). Based on the findings of the review, it was clear that if FROM-16 is to become widely established in clinical practice and health economics, further validation is required, including the development of clinically meaningful score bands, evidence of longitudinal validity of FROM-16, estimation of MIC/MCID, and development of an algorithm to convert FROM-16 scores to utility values for economic appraisal of interventions and demonstration of the use of FROM-16 across different areas of medicine. The subsequent psychometric validation of these properties for FROM-16 described in this thesis has transformed FROM-16 into a robust clinical and research tool. It can now be used with confidence across all areas of medicine to measure the family impact of a disease and in health economic evaluation of a medical intervention to measure the wider family impact of the disease.

7.1 ESTABLISHMENT OF THE MEASUREMENT PROPERTIES AND CLINICAL INTERPRETATION OF FROM-16

The development of score banding in this PhD has transformed FROM-16 from a research tool to a clinically useful instrument, providing new information to clinicians to interpret scores and score changes, thus allowing better-informed decision taking for patients and their families (Chapter 2). This development is important because measuring the QoL of family members/partners can help determine the wider burden of disease, can help identify individuals and subgroups who experience major impact, and can allow interventions to alleviate this burden to be assessed meaningfully. These all ultimately support holistic clinical practice. The score banding calculated for FROM-16 (0–1, 2–8, 9–16, 17–25, 26–32) is pragmatic and easy to remember, as the “half-way” score of 16 out of a maximum of 32 represents a key cut-off between mild and very large impact on QoL. These aspects make the measure particularly suited to routine use in clinical settings. There was a strong correlation between the anchor (Global question) and FROM-16 scores (r=0.79), indicating the robustness and accuracy of the proposed score banding. It could be argued that with such a high correlation, the anchor question alone would be sufficient to measure the impact on family members. However, it should be noted that, unlike FROM-16, an anchor question is a single item

measuring the overall perception of the impact of the patient's condition on the QoL of the family member and, therefore, does not provide any information about what aspects of QoL are impacted. This information is vital in tailoring support to impacted family members. The sub-group analysis of the proposed banding in the cohort of 4,413 family members, based on gender, revealed a higher proportion of females in band 4 "very large effect" and band 5 "extremely large effect" categories. This indicated that females were impacted more by their relative's health condition than males and this finding is consistent with other studies (Marks et al. 2002; Pinquart and Sörensen 2006; Penning and Wu 2016). Women caring for their spouses tend to be impacted more than their male counterparts (Penning and Wu 2016; Swinkels et al. 2019) and in this study the majority (78%) of family members were spouses/partners.

Furthermore, family members aged under 60 years had a higher mean FROM-16 score than older respondents but a similar score on the Global question. This could be explained on the basis that the family members caring for their relatives were mostly in paid employment and possibly overburdened by work, family duties and caring responsibilities. As the FROM-16 questions allowed family members to express this impact, this may have contributed to the mean FROM-16 scores being higher for those under the age of 60 years than for those over the age of 60. One of the interesting findings that emerged from having a FROM-16 score banding explanatory system is the importance of being able to measure the secondary impact of disease. By applying the proposed banding retrospectively to the cohort of partners/relatives who contributed to the banding study, it is clear that only 3% of the 4,413 family members experienced "no impact" of their relative's health condition on their QoL, while 42% experienced "a very high" or "extremely high" impact. Although the figure of 42% may have been inflated because the study was conducted during the COVID pandemic and because of some selection bias, the results suggest that the secondary burden of disease is very great indeed and needs to be taken seriously. Unidentified partners and other family members suffering alone or "in silence" need to be reached out to and supported. It is hoped that the ability to interpret scores with the score bands will encourage clinical use of FROM-16 in routine care, in the same way as the score banding of the Dermatology Life Quality Index (DLQI) and that of other similar patient QoL instruments

influenced their use, thus facilitating appropriate support to be given to impacted family members.

Economic evaluations are becoming an increasingly important way to inform decisions as to how to improve the efficiency of publicly funded healthcare systems in the face of the emergence of new and expensive health technologies. New treatments that improve patients' health can also positively impact the QoL of their family members/partners, but to date, in most instances, only patient QoL impact is included in economic evaluation. Although the inclusion of measurement of the impact on family members is encouraged in the estimation of benefits of new interventions by decision-makers and economists, such assessment is often omitted due to the lack of suitable family-specific measures. In the UK, NICE informs resource allocation decisions with patient health utility state data derived from EQ-5D-3L. As there is no carer equivalent to EQ-5D, NICE has been using the EQ-5D directly to measure carer utility. Therefore, in order to most conveniently allow the inclusion of the secondary burden, it would be useful to be able to also derive health utility state data from a generic family measure such as FROM-16. The development of the algorithm to convert FROM-16 scores to EQ-5D-3L utility values in this PhD project has filled this research gap and provided a way to include family members' impact in the health economic evaluation of medical interventions, such as new advanced therapies (Chapter 3).

The model developed in this study reliably predicts EQ-5D scores, in particular at a group level. The mean difference between observed and predicted utility across ten validation sets was 0.015, indicating a slight overestimate of poor health, but this difference is so small that it is not clinically important (Coretti et al. 2014). The study used a response mapping approach that closely follows the logic of the EQ-5D instrument by predicting health states and then attaching the utility tariff values to these. This means that predicted response values can be used in different countries using country-specific tariffs. The study results were based on a large sample of 4,228 UK family members of patients with a wide range of health conditions, hence generalisable to the UK population of family members/partners of patients.

Although, in most cases, it is preferable to collect utility data directly rather than having to estimate it based on responses to other measures, NICE has been using mapping

algorithms to account for utilities where EQ-5D data is missing (Kearns et al. 2013). Furthermore, as EQ-5D was created with patients in mind, the questions asked might not be relevant to family members. For example, the EQ-5D question on 'mobility as a moderate effect' may mean to family members/informal carers an inability to go out to meet people or travel for work/ study, while 'mobility as an extreme effect' may confuse family caregivers as to why they should be 'confined to bed'. However, there is emerging evidence that EQ-5D can still reliably be used to assess family member/informal carer utility with some validity (McLoughlin et al. 2020).

Interestingly, the mean observed utility across the ten validation sets was 0.67 (SD=0.33), and the mean predicted utility was 0.66 (SD=0.28), both of these values are considerably lower than the utility value of 0.83 (SD=0.32) (Kind et al. 1999) for the UK general population. Since the sample was taken from family members of patients with more than 200 different health conditions, this predicted utility already indicates the considerable QoL impact experienced by family members/partners of the patients. However, it is important to note that this study was conducted just after the second wave of COVID-19, therefore, the lower utility values in family members might be due to the impact of COVID-19, as many studies have shown that informal caregivers (compared to non-caregivers) felt more anxious and depressed, and experienced increased burden during the pandemic (Bergmann and Wagner 2021; Pitchik et al. 2021; Viny et al. 2023).

In order to use FROM-16 in economic evaluation to measure the impact of a new intervention on family members/partners of patients, FROM-16 needs to demonstrate that it can measure change over time. This is known as "responsiveness", an important property of any QoL instrument. This thesis demonstrated that FROM-16 could measure change in family outcomes, including both improvement and deterioration over time. In this study, these changes were parallel to changes in patients' HRQoL (Chapter 4). This means that FROM-16 can now be used in routine clinical practice alongside PROMs to measure a change in HRQoL outcomes (Pennington 2020), facilitating routine inclusion of family member/informal carer HRQoL in economic evaluation, allowing consistency in decision-making (Brouwer 2019; McCabe 2019; Wittenberg et al. 2019). Although there is evidence that family members/informal carers of patients with more severe diseases have worse HRQoL (Black et al. 2018; Xu

et al. 2021), there is no current information on how changing a patient's disease severity would impact a family member's or informal carer's HRQoL (Pennington and Wong 2019). A report by the NICE Decision Support Unit has identified this as a research gap and recommended a longitudinal study to address this gap (Pennington and Wong 2019). The responsiveness study in this PhD demonstrated that FROM-16 is not only sensitive to changes in patient HRQoL but also to changes in patients' disease severity. This provides information about how family members' QoL changed in response to changes in patients' disease severity, addressing the research gap highlighted by NICE (Pennington and Wong 2019). However, establishing the responsiveness of an instrument is not enough in itself unless it is possible to demonstrate that the instrument can respond appropriately to clinically important change, referred to as the "minimal clinically important difference" (MCID) or minimal important change (MIC). This would be the smallest change in the FROM-16 score that family members/partners of the patient perceive as either beneficial or detrimental. The MIC value for FROM-16 has been estimated in this thesis (Chapter 5) as a score change of 4 points, following triangulation of MIC values from distribution- and anchor-based approaches (Chapter 5). A score change of four points could, for example, arise from a change in score of two FROM-16 items from "a lot" to "not at all", or as another example, a change in score of four items from "a little" to "not at all". From a "common sense" or "face value" perspective, such a change in the scoring would seem to be appropriate as a minimally important change.

The strength of the FROM-16 responsiveness and MIC studies is that multiple methods were used to evaluate responsiveness and estimate the MIC value. These included distribution-based methods with strong statistical grounding to anchor-based approaches, using high-precision ROC analysis and predictive modelling. Only 24% of family members reported any change on the anchor, the Global rating of change question. It therefore could be argued that the MIC estimate using the anchor approach could be biased because of the small number of subjects that reported change. However, the study used adjusted predictive modelling which corrects biases that may be induced when the subjects that record change on the anchor question are less than 50% of the total group (Terwee et al. 2021). Furthermore, the MIC value calculated from the anchor approach using adjusted predictive modelling was consistent with the

MIC value calculated by using the distribution-based approach. The responsiveness analysis revealed that overall, patients and their family members only noticed a small change in their HRQoL, and so it could be argued that if a longer follow-up period had been chosen, a bigger change might have been detected. Even though the three-month follow-up chosen for these studies could be considered insufficient, the study only included relatives of patients with health conditions and interventions where clinicians thought change in patient HRQoL was likely within three months. Furthermore, longer follow-up periods might not necessarily result in the detection of greater change. A responsiveness study conducted on instruments designed to measure carer QoL concluded that none of the measures examined exhibited clear responsiveness to change within a year (McLoughlin et al. 2020). There could also be other factors which could explain why only a small number of patients and family members experienced change. The patients involved in the responsiveness study were from five different specialities and had 15 different health conditions. Presumably, the treatments and therapies they received were different, and hence one could expect varying efficacy experienced by the patients and hence variability in score changes. For example, patients with diabetes included not only those with poor glycaemic control starting on insulin treatment but also those having dose adjustment for better glucose control. Although dose adjustment changes can have a major effect in controlling patients' glycaemic levels, they may only have a subtle effect on the QoL of patients and family members because most of these patients and family members have been living with diabetes for a long time. In contrast, myeloma patients starting on biologics or having transfusions may take longer to see a beneficial qualitative change, as many patients with myeloma experience treatment side effects when starting therapy. While this variability in the patient’s responses to treatment may have resulted in an overall average small change, it is important for a study testing a generic tool to include a range of conditions, from mild to severe.

Apart from the above mentioned psychometric validation of FROM-16, this PhD work also included validating FROM-16 for use in the COVID-19 pandemic to measure the impact of having a family member with COVID-19 on the QoL of family members/ partners. The study measured the impact of COVID-19 on the survivors and their family members in an international study using social media. This study was the first global

study to explore the impact of COVID-19 on both survivors and their family members/partners, as most studies in those early stages of COVID-19 were focused on epidemiological and clinical aspects of disease, vaccine development and the response of healthcare systems to the pandemic (Huang et al. 2020; Chen, N et al. 2020; Lurie et al. 2020; Slaoui and Hepburn 2020; Narain et al. 2020). The study demonstrated that COVID-19 has a major persisting impact on the QoL of survivors and also a substantial impact on the QoL of partners and family members. One of the key outcomes of the study was establishing evidence of the existence of long-COVID and its impact on both survivors and their family members/partners. Most (87%) survivors experienced COVID-19 symptoms for more than four weeks, and 64% continued to be unwell for more than 12 weeks. These results were substantiated by an online survey of British doctors and numerous other studies internationally (Rimmer 2020). The results of this study were published in BMJ Open in June 2021 (Shah et al. 2021b) and created huge media attention across more than 200 news outlets in the UK (Appendix XXI) and internationally. This study was one of the earliest to examine QoL issues in COVID-19 and the first and only study to measure QoL impact on partners and family members. After publication in May 2021, within 24 months it has been cited 68 times (Google Scholar 2023).

7.1.1 Comparison Across Studies in This PhD

The average FROM-16 scores varied across the five different studies. The total FROM-16 mean score was 15.00 (SD=8.05, range=0-32; Emotional=6.12; Personal and social=8.88) for family members of patients in the FROM-16 implementation-COVID-19 study (Chapter 6), 15.02 (SD=8.08, range=0-32; Emotional=6.69; Personal and social=8.33) in the FROM-16 score banding study (Chapter 2) and 14.79 (SD=8.12, range=0-32; Emotional=6.62; Personal and social=8.17) in the FROM-16 mapping study (Chapter 3). Although total FROM-16 scores seem to be similar, family members of patient with chronic diseases were more emotionally impacted by their relative's health condition than family members of people with COVID-19 infection. This may be explained as family members of patients with chronic conditions found it incredibly difficult to manage their affected relatives during the COVID-19 restrictions, with frequent cancellation of hospital appointments and procedures, leading to a higher emotional burden (Bergmann and Wagner 2021; Pitchik et al. 2021; Viny et al. 2023).

On the other hand, the higher score for the personal and social domain in COVID-19 survivors could be explained by family members being isolated from others while having to look after COVID survivors, juggling with family responsibilities, complying with COVID-19 protocols, home schooling their children and possibly having reduced income. A smaller total FROM-16 mean score was observed in the responsiveness (baseline=9.54, SD=6.83; follow-up=8.11, SD=6.92) and in the MIC (baseline=9.52, SD=6.57; follow-up=8.55, SD=7.38) studies.

High FROM-16 scores were expected to be seen in the COVID-19 study since the pandemic was a major public health calamity that impacted everyone's lives, particularly those for whom a family member was infected by COVID-19. Concerning the banding and mapping studies, the data for these studies were collected during the second wave of COVID-19, so all family members of patients could have been impacted in a similar way. Furthermore, the data was based on a cohort of more than 4000 family members with a wide range of health conditions and severities. In contrast, the responsiveness (Chapter 4) and MIC (Chapter 5) studies were based on a small sample of 83 and 100 family members who were recruited when COVID-19 restrictions in the UK were lifted from public places, so family members might have felt relieved and better in themselves, possibly explaining the lower FROM-16 scores. The fact that the total FROM-16 mean scores reported from other studies conducted before the COVID-19 pandemic are higher than the scores in the responsiveness and MIC studies further support this hypothesis (Chantarasap et al. 2019; Golics et al. 2013b).

Most family members recruited were female, except in FROM-16 implementation-COVID-19 study (Chapter 6), where the majority (67%) of family members were male. This may be because most COVID-19 social media support groups were initiated by women (patients), and the most convenient family person to ask to participate might have been their partner (mostly male). Regarding the relationship of the family members to the patient across all five studies, spouses/partners were the largest group of family members, followed by parents in FROM-16 MCID study, and sons and daughters in all other studies.

FROM-16 score banding and FROM-16 mapping studies (Chapters 2 and 3) were conducted online with the UK patient support groups (PSGs). The PSGs used different

channels such as Facebook, newsletters, Twitter, websites, patient blogs, and patient and carer meetings to promote participant recruitment into the study. However, maintaining continuous communication with PSGs about the number of participants recruited was vital in order to ensure that new channels were explored in those cases where there was a poor response. Working with and getting to know so many PSGs and research platforms, representing a wide range of health conditions, has been a unique experience for the researcher. To ensure the researcher's engagement with the participants, she attended PSGs' monthly carer meetings to present the study to family members of patients. This not only helped to increase family members' participation in the study but also enabled the researcher (RS) to have closer contact with and experience of the population being investigated.

A major benefit of organising recruitment through PSGs was that this provided access to family members of patients with more than two hundred health conditions with a wide range of severities from 'no effect' to 'extremely large effect'. This was crucial for developing severity bands and generalisability of the study findings.

7.1.2 The Digital Aspect of This PhD Study

The COVID-19 pandemic drastically transformed people's lives across the world. In the UK "stay at home" and "social distancing" regulations were enforced on 23 March 2020 and continued during the pandemic. Digital technology was a crucial lifeline during those times. The movement restrictions meant that all supervisory meetings were conducted online, including presenting work at conferences. In addition, it also meant that the original plan to have face-to-face patient and family recruitment for this PhD study was no longer viable and there was a need to rapidly rethink new ways to achieve the study objectives. The use of mobile devices became more critical during the pandemic to foster and strengthen social connections and overall well-being (Jonnatan et al. 2022). All public health instructions about COVID-19 were delivered via social media as well as by traditional media, and connecting to people online became the 'new norm'. Therefore, depending on the study objective, recruitment of participants online was seen as the best alternative, using different approaches such as through PSGs or research support groups, using social media, or contacting NHS patients online. Moreover, this plan provided an opportunity for researcher to learn new digital

skills in the course of adapting to new research methods, such as creating online surveys and using social media to recruit participants positively, developing the potential of using them in future. Conducting studies online had its own advantages. Using an online survey platform meant data was retrieved directly to an Excel© spreadsheet and was thus ready for analysis and less prone to human error.

Furthermore, using a digital platform allowed tracking of recruitment numbers, identifying obstacles to recruitment early, taking action, and applying timely changes. One of the major advantages of the online recruitment was being able to allow participants to contact the researcher through email if they had any questions. This added a human touch to an online study and demonstrated the commitment of the participants who were involved in the study.

7.1.3 Impact of COVID-19 on This PhD Project

The COVID-19 pandemic impacted every aspect of this planned PhD research. Although ethics approval (Ref: REC Reference: 20/EE/0242, IRAS Project ID: 281134) was obtained for conducting all PhD studies with NHS patients and their family members within Cardiff and Vale University Health Board, COVID-19 restrictions meant that the original plan was no longer viable, and that researcher had to explore new ways of recruiting patients and family members. Two major studies (FROM-16 score banding study and FROM-16 mapping study), which needed a large sample size and were planned to involve 26 disease specialities across the Cardiff and Vale University Health Board, could no longer go ahead because of COVID-19 restrictions. It was decided with the supervisory team to conduct these planned studies online by involving members of UK patient support groups instead of the original planned postal survey of NHS patients. However, this meant developing a new protocol for the online study and seeking additional new ethics approval from the School of Medicine Ethics Committee. This was because the initial ethical submission and approval was specifically for recruitment within the NHS, and the new proposed online recruitment process was planned to be entirely outside the NHS structure, even though of course most patients were being cared for within the NHS. On a positive note, conducting studies with UK patient support groups meant that study results were generalisable to the UK population and not just Wales. Besides, it would have been impossible to gather data

from 4,400 family members through a postal study of family members of NHS patients within Cardiff and Vale University Health board within the limited time of this PhD project.

The final two studies (the responsiveness and the MCID studies) were longitudinal, with a three month follow-up and tightly restricted recruitment criteria (Chapters 4 and 5). The participants were originally to be recruited face-to-face from five outpatient clinics: dermatology, rheumatology, diabetology, haematology and gastroenterology at the University Hospital Wales and at University Hospital Llandough and would have involved family members completing the questionnaire in the outpatient clinic during their visit accompanying a patient. However, with the continuing pressures on NHS staff post-COVID, there were significant obstacles to staff being able to divert any time or energy to supporting research projects. Owing to the COVID-19 restrictions still being in place within hospital settings and keeping in view the time limitation of the PhD projects, amendments were made to the study protocol, which was approved by the ethics committee (Appendices XV and XVI). These allowed participants to complete the questionnaire at home following their recruitment from the outpatient clinics and once the patient had given their consent to their clinician to be contacted by the researcher with further information. This restricted face-to-face contact with participants, considered at the time to be of benefit as Covid infections remained prevalent. Also, the sample size was recalculated to a more realistic estimation. Despite these protocol changes, the study recruitment could not be started at the same time in all the clinics as planned, firstly because some clinicians and nurses had contracted COVID-19 and were off from work. Secondly, most clinics were still operating online, meaning only restricted face-to-face clinics were operating at the time of recruitment. This resulted in only a small number of participants being recruited from haematology (n=5) and gastroenterology (n=1), although the expectation had been to recruit 30-40 participants from each of the five departments.

One of the PhD objectives was to show evidence of the use of FROM-16 within the NHS. There was an informal agreement between FROM-16 research team in Cardiff University and physicians at the Aneurin Bevan University Health Board, Newport to pilot routine clinical use of FROM-16 to inform clinical decision taking, and the data from this proposed pilot was to be used by the investigator (RS) to show evidence of

the clinical use of FROM-16. However, despite great initial interest from both teams, the proposed pilot was disrupted due to the COVID-19 pandemic. This negative impact of the pandemic was offset by researcher using the pandemic as an opportunity to demonstrate the use of FROM-16 to measure the family impact of COVID-19, thus successfully and very rapidly generating evidence of the use of FROM-16 in the pandemic scenario.

7.1.4 Patient and Public Involvement and Engagement

The degree of participation and engagement of patients may vary depending on their role and involvement in the research project (Schipper et al. 2010; Abma et al. 2009), with patients/families who act as study participants having the lowest engagement compared to those acting as collaborators/partners (Hewlett et al. 2006; Kirwan et al. 2007) or moderators of focus groups (Balch and Mertens 1999). However, the highest level of engagement and participation occurs when patients/families act as research partners in a team of research professionals (Abma et al. 2009). Patient and public involvement and engagement in this PhD project occurred at two levels:

- **Patient and public involvement and engagement in pilot studies**

  Twenty people not infected with COVID-19 across five countries participated in an international pilot. In addition, a pilot study was carried out with leukaemia patients registered with the patient support group ALAN. These pilots aimed to test the understanding of survey questions and whether online surveys were respondent friendly. The feedback from pilots was used to improve these surveys.

- **Patient and public involvement and engagement as patient research partners**

  Although, traditionally, patients and their families served simply as participants in research, the last decade has seen an increasing trend in medical and health research to actively involve patients more intimately in the planning, design and execution of research projects (McCarron et al. 2021).The role of patients and family carers as members of the research team is increasingly being considered important and ethically desirable in medical research and clinical trials, in order to increase the effectiveness of research by making research aims appropriate and relevant to patients/family members, ensuring that study materials are easy to understand by study participants,

advising on appropriate recruitment strategies, and suggesting implementation and dissemination strategies (Brett et al. 2014; Domecq et al. 2014; Miah et al. 2019). This PhD study engaged two patients (HA and SJN) and one family member (MN) as research partners to provide patient and family member perspectives. The research partners were identified through the 'Cardiff University patient and public involvement group' operated by the School of Health Sciences. These research partners were active PPIE members who had already contributed to research projects elsewhere. The research partners were included at the beginning of this PhD project, with roles and responsibilities clearly explained and where necessary training provided (van Schelven et al. 2020; Haywood et al. 2017). The involvement of patient and family member research partners in this PhD was evaluated using GRIPP guidance (GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research) (Staniszewska et al. 2017) and weekly supervisory meeting logs between June 2020-July 2023.

7.1.4.1 Evaluation of involvement of patient and family member research partners in this PhD

All three research partners were actively involved in the study, however, one (SJN) participated in all weekly supervisory meetings (except for a period when he was unwell), contributing to in-depth discussion on the research topics. Research partners played an active role in all study research activities, from reviewing study design and protocols, discussing how the research project was going to be conducted, designing recruitment strategies, supporting ethical and effective enrolment among different populations (including vulnerable people) and ensuring clearer communication and a better understanding of study material (reviewing promotional material, surveys, participant information sheets). Their feedback led to changes in the text of lay summaries, lay abstracts, participant information sheets, survey text and manuscripts, which ultimately had a positive facilitating impact on the execution of the PhD project as well as on the quality of the outcomes.

Patient and family member research partners also engaged in the interpretation of results, advising the investigator on designing knowledge translation such as writing plain language summaries to ensure accessibility of research to patients and families. For example, they suggested patient-friendly graphs and illustrations and checked that

the language was simple, free of scientific jargon and relevant to the audience. Thus, involvement of patient/family member research partners in this PhD project has not only increased the quality and applicability of research to the intended audience but also has helped the research team members to gain new skills such as drafting patient-friendly material and lay summaries. This is because patients are experts in themselves, having experiential, cultural, and circumstantial knowledge that academic researchers often lack (Lauzon-Schnittka et al. 2022).

Research partners played an important role in the dissemination of the PhD research findings, for example, SJN contributed to the content of the lay study report for the FROM-16 banding/mapping study (which was distributed to 58 patient support groups and three research platforms), and the press release for the COVID-19 study, ensuring they were patient friendly. The contributions of these research partners working alongside the academic team were recognised by including them as co-authors of publications that resulted from this PhD project, confirming and promoting the profound advantages of patient-centred research.

In this PhD project, patient and family member/partners had previous experience working with Cardiff University research projects, which meant that after the initial discussion about the project with them, explaining their roles and responsibilities, the research partners were all set to contribute to the project, leading to early successful collaboration. This is consistent with the findings of Smith et al. (2023), who argue that patient research partners with an established track record of working collaboratively with researchers and who have previous training and experience require less support and guidance in successfully fulfilling the patient partner role. This was particularly important for this PhD research programme, which was limited by time and resource constraints in our training of the lay public research partners.

The pressured timeline of this PhD project meant that research partners had to review study documents within a limited time. However, flexibility in terms of giving them the option of contributing as a group in research meetings and/or on a one-to-one basis and communicating via emails ensured that those who were not able to attend meetings due to health or work demands or personal preference were still able to contribute substantially to the study. This helped to maximise their involvement in the

study within the overall constraints of the study timeline. Insights from the research partners were incorporated into the projects, though at times this generated challenging, but creative, issues. For example, one patient research partner suggested extending recruitment through the social services departments in Wales for the FROM-16 banding and mapping studies; we had originally planned that family members of patients would be recruited only through Patient Support Groups (PSGs). Although this suggestion was seen as very useful and was appreciated by the research team as a way to meet the requirement for a large sample size for these studies, the suggestion resulted in a need for an amendment to the original ethics application, which had sought approval for subject recruitment only through UK-based patient support groups. However, the amendment was approved, and recruitment was extended to social services departments in Wales.

This PhD research project included two patients and one family member as research partners. However, given that the focus of the study was on family members of patients, one might have expected that more family members than patients would have been invited as research partners. Although originally the study only planned to include one patient and one family member/partner as research partners, it was thought that having two patients might be useful in case one was unavailable due to health reasons. In the event, this was a very appropriate decision as during the FROM-16 responsiveness study, one of the patient research partners was unable to contribute to the project due to health reasons, but the project was able to continue to be supported by the other patient who then worked closely with the investigator reviewing all patient documents.

7.2 IMPLICATION FOR RESEARCH AND PRACTICE

7.2.1 Clinical Practice

The simplicity and brevity of FROM-16, together with high-quality extensive validation (McLeod et al. 2011), including the development of score descriptive bands and the establishment of the MIC value, makes it a suitable tool for use in routine clinical practice alongside PROMs. Descriptive score bands will assist clinicians to interpret scores and score changes, allowing better-informed decisions for patients and their

family members. It is hoped that the use of FROM-16 in routine practice will have similar benefits to that of PROMs, leading to improved levels of shared decision-making and a delivery of care more responsive to individual needs (Basch et al. 2018; Calvert et al. 2019).

PROMs play an integral role in value-based healthcare (VBHC), which attempts to maximise the value of care provided to patients within the constraints of available resources (Withers et al. 2021). One of the important components included in VBHC is societal value, a key element of which is to measure the impact of a condition (and the gains from treating or controlling the condition) on a person's family (Atun et al. 2019; European Commission 2019), and FROM-16 seems to be the most appropriate tool for this measurement. Therefore, using FROM-16 alongside PROMs could enhance the accuracy of data underpinning VBHC by providing a wider information base.

Apart from these potential benefits, FROM-16 can be used to improve communication among healthcare professionals (HCPs) in multidisciplinary team meetings to improve patient care, encouraging HCPs to discuss and act on patient care and treatment decisions, taking into account the impact on family members. Finally, for FROM-16 to be used alongside PROMs, the proposed pilot of routine clinical use by clinicians at Newport, disrupted due to the COVID-19 outbreak, should still be conducted when conditions allow. The learning and recommendations from this pilot will help to understand ways to overcome clinical and system challenges raised in implementing FROM-16 in clinical practice.

7.2.2 Support Services

Another major impact of the outcomes of this PhD project will be on the groups and services that collaborated with the recruitment of the study participants. A summary of the results will be provided to these patient support groups and research platforms. Publications that have resulted from this thesis will also be made available on the Cardiff University FROM-16 website. It is hoped that, by having access to the study's findings, patients' family members will be encouraged to participate in future research and "patient support groups (PSGs)" and "healthcare professionals" may feel encouraged to assist in the recruitment of future studies. Furthermore, since these

PSGs provide support to carers, the PSGs might be interested in using FROM-16 to measure the family impact of the condition specific to their group using FROM-16 and identify gaps in support needed for their carer groups.

7.2.3 Research

The literature review (Chapter 1) of this thesis has tabulated the psychometric properties of FQoL tools. This review showed that most of the tools lacked full psychometric validation, such as missing responsiveness to change, MCID estimation, test-retest, criterion validity, and cross-cultural validation and therefore, the review will help to signpost future researchers to work on identified research gaps.

The longitudinal validity of FROM-16 established in this PhD project will now allow researchers to assess the long-term impact of a person's medical conditions on the QoL of their family members/partner and compare trends across diseases, identifying the most impacted disease areas, thus allowing decision makers to allocate resources where most needed. Researchers interested in calculating EQ-5D-3L utility values for family members from FROM-16 scores will be able to download the FROM-16 scores conversion algorithm to EQ-5D-3L utility values developed in this study from the Cardiff University FROM-16 website (https://www.cardiff.ac.uk/family-reported-outcome-measure) once the study results are published.

Recruiting participants for research studies can be a challenging task that often requires more effort than anticipated. This study has shown how digital recruitment through patient support groups can help researchers recruit patients meeting inclusion criteria and ensure quick and easy retrieval of data for analysis while reducing the strain caused by research projects on already pressured health services.

7.2.4 Clinical Trials

With further validation of FROM-16, including responsiveness to change over time and establishment of the MIC value, the measure has the potential to be used as a secondary outcome measure in pharmaceutical company-sponsored clinical trials. Pharmaceutical companies can now investigate whether a new drug treatment or other intervention can benefit not only the patient in terms of symptom control or QoL

improvement but also improve the QoL of their family members/partner. Despite being a new concept within clinical trials, family quality of life could have a potential role in assessing treatments that can have a major impact on family members. For example, a potential treatment for Alzheimer's disease has been shown to also have an impact on a family member's QoL, given the huge impact of this condition on families (Patrícia et al. 2020; Vu et al. 2022). The recently approved treatment for Alzheimer's disease refers to 'caregivers' in the label: "Advise the patient and/or caregiver to read the FDA-approved patient labelling (Medication Guide)" (Leqembi™ 2023). The pharmaceutical company mentions in its release report, "The approval of LEQEMBI provides new hope to patients with Alzheimer's disease. Patients at an early stage of the disease and their caregivers can now consider a new treatment option with their doctors" (Biogen 2023). The mention of caregivers is the recognition of the fact that new medicines can impact both patients and family members. Although current FDA and EMA guidelines do not mention the measurement of the impact on family members in trials of new therapies (FDA 2009; EMA 2005), FROM-16 meets all of the specifications that are set in the guidelines for PROMs to be used in clinical trials (FDA 2009; FDA 2022; EMA 2005). There is a possibility that the use and interest in the FROM-16 in the commercial and industrial world could, in the future, influence regulatory agencies to issue specific guidance regarding the use of family reported outcome measures in clinical trials.

7.2.5 Economic Evaluation

Unpaid family members/partner carers make a colossal contribution to the economy of many countries around the globe, which by and large has gone un-noticed. Thus, one of the important contributions of this PhD is the development of an algorithm to convert FROM-16 scores into EQ-5D utility values. This means that the family impact of disease burden can now be accounted for and included in health economic evaluation alongside patient utility, leading to a fairer and broader evaluation of the impact of medical interventions. Currently, family members/informal carers are seldom included in economic evaluation, and where they are included, EQ-5D-3L has been mostly used for utility measurement (Wittenberg et al. 2019). The EQ-5D does not include all aspects of QoL of family members and hence is not considered adequate (Al-Janabi et al. 2011). However, a recent study comparing five QoL instruments for carers across four conditions has shown that the EQ-5D has some validity and may be appropriate for use

in health technology evaluations (McLoughlin et al. 2020). Although it could be argued that measuring family members' utility as well as the patient's utility might result in double counting, the impact on family members constitutes a separate impact from that experienced by the patient, as is evident from the FROM-16 items.

7.3 LIMITATIONS

Although all studies in this PhD project were designed to the highest possible standards (McLeod et al. 2011; Prinsen et al. 2018), there were still a number of limitations:

- Although the literature review at the beginning of this PhD followed rigorous methodology and fulfilled 19 of the 27 relevant PRISMA checklist items (Moher et al. 2009), it did not employ a systematic review technique because of time constraints and other resources that would have been required. The lack of using a full systematic review technique could mean that some studies might have been missed during the search. Though the review was updated at the end of PhD project, it is difficult to assess the likelihood of this having happened.
- All studies conducted were online, this could have introduced a selection bias. For example, only those people who could use electronic devices would participate in the study. Furthermore, the study used a specific population based on the requirement of the study, for example, family members of patients registered with PSGs (FROM-16 score banding and mapping studies) or those using social media (FROM-16 implementation-COVID-19 study). This could have further introduced bias as only those people who were registered with PSGs or who were active on social media participated in these studies. However, using social media was the only way to reach people between June 2020 and 2021 when the studies were conducted. This may have resulted in recruiting more severely impacted or more motivated family members of people with health conditions. However, for FROM-16 score banding and mapping studies, as the family members of patients were recruited across a wide range of health conditions and severities, the family members who were recruited had experienced a wide range of impacts from 'no effect' to 'extremely large effect'.

This wide range of experiences was critical for this type of study because there needed to be sufficient data linked to each potential GQ score FROM-16 banding. Recruiting via social media meant that for the FROM-16 implementation-COVID-19 study, researcher was able to reach out to recruit appropriate subjects from across the globe. As this survey was disseminated by social media, rather than being administered by research team members, there is a possibility that it might have been inappropriately completed or completed by individuals who do not conform to the inclusion and exclusion criteria. Such inappropriate responses could adversely affect the results. However, the motivation required to complete the questionnaires makes the likelihood of this low. Furthermore, for the later studies (FROM-16 responsiveness and MCID studies), respondents were given a choice of a postal questionnaire if they were unable to use an electronic device, however, only one out of 121 patients requested a postal questionnaire. Although the questionnaire was posted to that patient, he returned the questionnaire not fully completed as he had not started a new medication and so was no longer eligible to participate.

- In the case of the mapping study (Chapter 3), no external sample dataset was available to perform external validation. This is because, unlike patient-reported outcomes (Meadows 2011), family/informal carer outcomes are not regularly measured. However, the repeated split-half cross-validation method used in this study demonstrates how well the mapping model is likely to perform outside of the sample.
- Although the mapping model (FROM-16 mapping study, Chapter 3) did include age and gender information, the inclusion of other socio-demographic variables might have further improved the model's predictive performance. However, the possible resulting marginal improvements would probably not outweigh the complexity of running such a model (Gray et al. 2006).
- In order to keep the questionnaire simple and minimise respondent burden, the studies conducted during the COVID-19 pandemic (FROM-16 score banding, FROM-16 mapping and FROM-16 implementation-COVID-19) did not collect data about participants' race or ethnicity and therefore cannot provide any information on the diversity of participants. Furthermore, race and ethnicity do not have standard scientific definitions, and therefore, it was challenging to

include race and ethnicity questions that would incorporate all people and cultures across the globe, as would have been required for this international study. It was thought that including them could have introduced a risk of misclassification. Nonetheless, a race and ethnicity question was asked in the post-COVID studies (FROM-16 responsiveness and FROM-16 MCID).

- In the drafting of an online questionnaire, simplicity of wording and administration was kept in mind. However, sometimes simplicity can hinder meaning and lead to confusion. For example, the global rating of change question (GRCQ) in FROM-16 responsiveness and MCID studies was a 15-point Likert scale asking respondents about change in their QoL since they first completed the questionnaire. The simplified version meant respondents initially had to choose from three options online, “Improved”, “The same” or “Deteriorated”. If they chose “Improved” or “Deteriorated” they were then given seven further options to choose from degrees of ‘Improvement’ or ‘Deterioration’. As the study results showed, only 24% of family members recorded observed change. This indicates that the majority of family members/partner were stable which could be one of the possible outcomes of an intervention, in particular in non-inferiority trials. It is possible that the on-line formatting of this question, which initially obscured the multiple detailed options from respondents, may have introduced bias. Although it could be argued this might have biased results if the analysis had been based on the anchor method, the study actually used adjusted predictive modelling, which makes appropriate corrections if a score change is less than 50%. Reassuringly, the results calculated using anchor methodology were consistent with the results from using distribution-based methods.
- FROM-16 responsiveness and MCID studies, (Chapters 4 and 5) were conducted with patients and their family members from outpatient clinics at the departments of dermatology, rheumatology, diabetology, haematology and gastroenterology at the University Hospital Wales and the University Hospital Llandough. The expectation was to recruit 30-40 participants from each of the five departments. However, only a small number of participants from haematology and gastroenterology were recruited because clinicians in these departments had contracted COVID-19 and were off from work. In addition, only

restricted face-to-face clinics were operating at that time. Although it had been expected that there would be similar levels of recruitment from all five selected specialities, this variation in recruitment levels was not important to fulfil the objectives of the study.

7.4 FUTURE WORK

- An implementation study in routine care should be conducted to test the use of FROM-16 in routine clinical practice, understand what challenges clinicians could face if using it and to experience the reality of how the measure could be integrated into clinical practice. The learning and recommendations from such an implementation study could support the future use of the FROM-16 in clinical practice.
- Although a MIC value of “four” points has been suggested for FROM-16, based on the triangulation of values from the anchor and distribution-based approaches, a future similar study with a larger sample size should investigate the reproducibility of this finding. This possibly could be conducted as part of a clinical trial.
- The estimation of the MIC value for FROM-16 in this PhD study resulted in different values of MIC for improvement and deterioration. It would be of great interest to explore further this phenomenon, which is not unique to FROM-16 (Conijn et al. 2015; Singer et al. 2022). Therefore, a future study, using a large sample, should establish whether there is a need for separate MIC values for improvement and deterioration.
- Further studies of FROM-16 should establish population normative values (“norms”) for the measure, which could be used as benchmarks for scores and for comparison between different disease areas. This could include norm values for family members of a healthy population or norm values for family members of stable patients.
- In all five studies of this PhD, only one family member from each patient was sampled. There is, therefore, no information concerning the overall levels of impact across different family members of the same patient. Future studies could investigate more than one family member. This is particularly important in

the case of children where only one parent is measured, although both parents are impacted. As highlighted in Chapter 1, there is a dearth of published research on the impact of children's diseases on fathers. Perhaps future research could compare the impact between mother and father: areas of impact could differ and the ways of dealing with stressors could vary.

- Although FROM-16 implementation-COVID-19 study provided an overview of the impact of COVID-19 on the lives of survivors' partners and family members, it was not designed to identify causal relationships. Future longitudinal studies are needed to understand the long-term impact of long COVID-19. Since long COVID had a huge impact on COVID-19 survivors and their families, and still is impacting families as is evident from a recent large scale study (Taquet et al. 2022), it would be interesting to explore the long term impact of long COVID on survivors and families. Future research should focus on understanding the impact of long COVID on the QoL of survivors living alone or away from their families, in order to identify the special needs of this group of patients. Moreover, many families have been hit hard by the death from COVID-19 of loved ones, and so it would be of interest to measure the bereavement impact of COVID-19 on family members and partners. Another aspect that could be explored concerns the impact of intervention, including vaccination, on the QoL of survivors and family members.
- The FROM-16 questions were designed and validated for completion by adults, even though the patient could be of any age. Future studies could conduct separate content validation for children and siblings, from which it might be possible to develop a separate version of FROM-16 to be completed by children who have another member of their family (of any age) affected by a health condition. This would mean that in the future, a different version of FROM-16 could be used to measure the impact on siblings or the impact of an unwell parent on their children.
- Although a web-based version of FROM-16 has been used in this PhD, for this measure to be accessible and easy to use, a FROM-16 App should be developed. This would be important to facilitate the use of FROM-16 in routine practice, where electronic versions of PROMs are already used.

7.5 CONCLUSIONS

This study has transformed FROM-16 from being a purely research tool to being a robust, sophisticated clinical and analytical tool for use in clinical practice, interventional trials and economic evaluation of medical interventions. The study has successfully developed score descriptor bands which let clinicians and researchers understand the meanings of the scores and score changes. It will now be possible for clinicians to identify at-risk and high-risk family members and direct them to the right kind of support services. Furthermore, by establishing longitudinal validity and the MIC value for FROM-16, the measure can now be used not only in clinical trials but also in health economic assessment to measure the impact of new treatment on family members of patients. Moreover, the development of an algorithm allowing conversion of FROM-16 scores to EQ-5D utility values will ensure that family impact is included alongside patient impact in the health economic evaluation of medical interventions. The study also provides further evidence that the patient's QoL is related to the QoL of their family member, including when the patient's disease severity improves or worsens. Therefore, clinicians should consider this family perspective when making decisions about patient care, thereby enhancing family involvement in routine care and encouraging shared decision-making. FROM-16 has the distinction of being the only FQoL tool that was used to measure the impact of COVID-19 on families across the globe and is now validated for use in the pandemic and for similar public health emergencies. As a result of this PhD study, FROM-16 has emerged as a robust and strong tool which can be used in clinical practice, research, and economic analysis to measure the impact of disease on family members/partners of patients, leading to better clinical and economic decisions, supporting holistic care.

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AND PRESENTATIONS

CONFERENCES-ORAL PRESENTATIONS

- Shah, R., Salek, S.M., Andrew Y Finlay., Kay, R., Nixon, S.J., Otwombe, K., Ali, F.M., Ingram, J.R. 2023. Mapping of Family Reported Outcome Measure (FROM-16) scores to EQ-5D: Algorithm for incorporating family members' utility values into health economic evaluation. Presented at the ISOQOL 30th Annual Conference in Calgary, Alberta, Canada 18-21.

- Shah, R., Salek, M.S., Finlay, Kay, R., Nixon, S.J., Otwombe, K., Ali, F.M., Ingram, J.R . 2023. Mapping of Family Reported Outcome Measure (FROM-16) scores to EQ-5D: Algorithm for incorporating family members' Utility Values into health economic evaluation. Presented at the 7th National Patient Reported Outcome Measures (PROMs) Annual Conference. Sheffield, UK, 21-June.

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- Shah, R. A., F.M., Nixon, S.J., Otwombe, K., Ingram, J.R., Salek, S.M., Finlay, A.Y 2022. The Clinical Meaning of Family Reported Outcome Measure (FROM-16) Scores: Translational Research to Support Holistic Clinical Practice. Presented at the 6th National Patient Reported Outcome Measures (PROMs) Annual UK Research Virtual Conference. Wales, UK, 15-16 June.

- Shah, R., Ali, F.M., Nixon, S.J., Ingram, J.R., Salek, S.M., Finlay, A.Y. 2022. The Clinical Meaning of Family Reported Outcome Measure (FROM-16) Scores: Translational Research Allowing Family Quality of Life into Clinical Practice. Presented at 115 Annual Meeting of the Association of Physicians of Great Britain & Ireland, Dublin, Ireland, 15-16 March.

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- Shah, R., Andrew Y Finlay., Salek, S.M., Nixon, S.J., Otwombe, K., Ali, F.M., Ingram, J.R. 2023. Responsiveness to Change of the Family Reported Outcome Measure (FROM-16). Poster presented at ISOQOL 30th Annual Conference in Calgary, Alberta, Canada 18-21.

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Co-authored Publications

- Brilliant C, Finlay AY, Salek S, Shah R, Laing H, 2022 (rep.). *Family Reported Outcomes in the Estimation of the Societal Value of Advanced Therapy Medicinal Products (ATMPs)* (pp. 1–53). Swansea, Wales, UK: 2022.

- Brilliant C, Finlay AY, Salek S, Shah R, Laing H. Feasibility Study Protocol: Investigating Family Reported Outcome Measures (FROMs) in the Estimation of Societal Value of Advanced Therapeutic Medicinal Products (ATMPs), 29 March 2022, PREPRINT (Version 1) available at Research Square https://doi.org/10.21203/rs.3.rs-1474778/v1

SUBMITTED MANUSCRIPTS UNDER REVIEW

- Manuscript titled "*Responsiveness and Minimal Important Change of the Family Reported Outcome Measure (FROM-16)"* submitted to ***Journal of Patient-Reported Outcomes.***

- Manuscript titled *"Mapping of Family Reported Outcome Measure (FROM-16) scores to EQ-5D: Algorithm to calculate Utility Values"* submitted to ***Quality of Life Research Journal.***

AWARDS

- ISOQOL Travel Scholarship 2023
- William Morgan Thomas Fund: 2023-2024

APPENDICES

Appendix I: Family Reported Outcome Measure (FROM-16)

Family Reported Outcome Measure (FROM-16)©

Confidential

The following questions are about how **your** life is being affected by your family member's condition **at the moment**.

Please mark one box for each of the 16 questions.

Please answer the following questions:

Your age:_____

Your gender: Male / Female

Your relationship to the patient:_____

Patient's diagnosis:_____

Part 1: Emotional

Because of my family member's condition...		**Not at all**	**A little**	**A lot**
1.	I feel worried	☐	☐	☐
2.	I feel angry	☐	☐	☐
3.	I feel sad	☐	☐	☐
4.	I feel frustrated	☐	☐	☐
5.	It is difficult to find someone to talk to about my thoughts	☐	☐	☐
6.	Caring for my family member is difficult	☐	☐	☐

Part 2: Personal and Social Life

Because of my family member's condition...		**Not at all**	**A little**	**A lot**
7.	It is hard to find time for myself	☐	☐	☐
8.	My every day travel is affected	☐	☐	☐
9.	My eating habits are affected	☐	☐	☐
10.	My family activities are affected	☐	☐	☐
11.	I experience problems with going on holiday	☐	☐	☐
12.	My sex life is affected	☐	☐	☐
13.	My work or study is affected	☐	☐	☐
14.	My relationships with other family members are affected	☐	☐	☐
15.	My family expenses are increased	☐	☐	☐
16.	My sleep is affected	☐	☐	☐

Please check that you have answered every question. Thank you.

For office use only Score for part 1 (out of 12): ___ Score for part 2 (out of 20):___ Total score (out of 32):___

Appendix II: Original Study Protocol- IRAS 281134

PROTOCOL

Validation of the Family Reported Outcome Measure (FROM-16)

Prof Andrew Y Finlay , Prof Sam Salek, Dr John Ingram and Rubina Shah

Glamorgan House, Cardiff University School of Medicine, Heath Park, Cardiff, CF14 4XN

Appendix II: Original Study Protocol- IRAS 281134

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PROTOCOL SUMMARY

Validation of FROM-16 Questionnaire

INVESTIGATORS

Ms Rubina Shah, PhD postgraduate student, Cardiff University School of Medicine, Cardiff

Prof Andrew Y Finlay, Professor of Dermatology, Cardiff University School of Medicine, Cardiff

Prof Sam Salek, Professor of Pharmacoepidemiology, University of Hertfordshire, Hatfield

Dr John Ingram, Senior Lecturer & Consultant Dermatologist, Division of Infection & Immunity, Cardiff University, Cardiff

SUMMARY

The Family Reported Outcome Measure (FROM-16), created by our research team at Cardiff University in 2009-2014, is the first generic questionnaire designed to measure the impact of any chronic disease, across all medicine, on the quality of life (QoL) of family members or partners of patients with a health condition. The impact of having a person in a family with a disease on other family members is a major secondary burden of disease that has often in the past been ignored. Although high-quality initial validation has been carried out, there is a need for further robust validation, such as for easy interpretability of scores, to enhance the usability of FROM-16 by clinicians, researchers and healthcare policymakers.

PRIMARY OBJECTIVE

To validate aspects of FROM-16, including sensitivity to change, correlation with other measures, development of score interpretation bands, calculation of Minimal Important Difference (MID) in scores and creation of a methodology to convert FROM-16 scores to utility values to enable calculation of QALYs.

STUDY POPULATION

Patients with chronic disease and their family members. . (Please note no children are involved in the study. The involvement of the family member of children in completing the questionnaires does not involve paediatric patients themselves).

STUDY SITE

University Hospital of Wales and University Hospital Llandough, Cardiff & Vale University Health Board

STUDY DURATION

The overall duration of the studies will be approximately three years and will begin when relevant approvals are obtained.

NUMBER OF VISITS

In most of the planned studies, primary data collection will be carried out during patients' regular clinic appointments or while an inpatient. A relative of the patient will be asked to complete FROM -16 (and other measures). In some studies, follow-up questionnaires will be posted or emailed (depending upon the participants' preference).

STUDY DESIGN

Observational studies (longitudinal cohort and cross-sectional).

METHOD

The patients and the family members who are eligible to participate in the studies shall be approached by their regular clinician. The study details will be discussed, and consent will be sought from patient and family member. The participant information leaflet will be given, and the patient and family member will have time to decide whether or not to participate in the study. The family members, and for some studies the consented patients, will be asked to complete FROM-16, and other questionnaires such as EQ-5D or GRCQ, depending on the type of study. The data generated will be processed and analysed using SPSS version 25.

The data analysis will involve descriptive statistics as well as hypothesis testing using both parametric and non-parametric methods.

INTRODUCTION

BACKGROUND AND RATIONALE

Chronic health conditions can have a major impact on the quality of life (QoL) of patients, but also on their family members. "Quality of life" in medical context refers to "patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be

possible or ideal" (Cella and Cherin,1988). While the popularity of the term "QoL" has grown exponentially over the last few decades, an understanding of the impact of the disease on the QoL of the partners and other family members of those affected is a relatively new and emerging field.

The WHO defines "health" as "a state of complete physical and social well-being and not merely the absence of disease or infirmity" (WHO, 1947). It is this definition of health which revolutionised thinking concerning medical care and transferred healthcare attitudes from the traditional disease-centred model to a patient-centric holistic model. For today's clinicians, in many situations, QoL discussion may be central to disease treatment and management, while for pharmaceutical companies, it has become a regulatory requirement to consider QoL issues. Although family members caring for or living with the patient with a disease may suffer equally (Basra and Finlay 2007) or sometimes even more than the patient themselves (Weitzenkamp et al. 1997; das Chagas Medeiros et al. 2000; Rees et al. 2001), the family burden of disease has been largely unrecognised. Caring for a family member/partner with chronic disease disrupts normal family life and can trigger feelings of anxiety, depression, anger, fear and helplessness. Often a family member, who may be the primary caregiver, finds it challenging to deal with their own stress exacerbated by their family member's condition and feels emotionally drained and tired. Parents of children with chronic disease may become very consumed with their child's illness, leaving no time for themselves, resulting in social isolation, family conflicts and strained relationships and giving other children less attention. It is, therefore, critical to recognise the impact of the disease on family QoL and to understand the needs of these silent and invisible members of the "Greater Patient" (Basra & Finlay, 2007) to ensure that they receive the appropriate support services.

Most of the research on the impact of the disease on family quality of life (FQoL) has been focused on a few individual medical fields such as mental health, oncology and dermatology (Poston et al. 2003; Cohen et al. 2007; Basra and Finlay 2007), using disease-specific or speciality-specific questionnaires. In contrast, the study by Golics et al. (2013) explored the family impact across many different specialities as a generic approach. That study revealed that the family impact of a disease is often unnoticed by health care providers and has also been largely ignored by researchers. The study by Golics et al. (2014) carried out in Cardiff University in 2013 involved 26 medical specialities. It demonstrated that families of patients suffering from a wide range of different diseases are impacted in similar ways across the areas of psychological, emotional, personal and social wellbeing (Golics et al.; 2013). This key finding led to the development of the first, and so far only, generic family quality of life measure (Golics et al.; 2014), the Family Reported Outcome Measure (FROM-16).

The FROM-16 is a family quality of life questionnaire which measures the impact of any disease, across all medical specialities, on the QoL of family members or partners of patients. The FROM-16 comprises 16 items with three response options for each: Not at All (scoring 0), A Little (scoring 1) and A Lot (scoring 2). The lowest possible score of the FROM-16 is 0, and the highest is 32. The higher the total score, the greater the negative impact on the family member's QoL. The 16 items are divided into two categories (domains): Emotional (comprising 6 items, maximum score of 12) and Personal and Social Life (comprising 10 items, maximum score of 20). One of the useful features of the FROM-16 is

that it is a user-friendly and relatively simple questionnaire with a two-minute completion time, making it a practical tool for family members/partners.

The FROM-16 is reliable, and several aspects of its validity have been demonstrated. The FROM-16 has shown high internal consistency (Cronbach's $\alpha = 0.80–0.89$), high reproducibility (intraclass correlation = 0.85–0.92) and construct validity. There is excellent correlation both between the FROM-16 and the WHOQOL-BREF total scores ($p < 0.001$), and the patient's overall health score ($p < 0.001$) (Golics et al., 2014).

Although initial validation of FROM-16 has been undertaken, further validation of the measure is necessary to enhance its usability across all disease areas of medicine including research/clinical trials; clinical practice; and to inform health economic evaluations of interventions. Further research will include determination of construct validity (correlation with other measures); establishment of sensitivity to small but clinically important change over time; development of score interpretation bands; calculation of Minimal Important Difference (MID); creation of formulae to convert FROM-16 scores to utility values; and provide evidence of FROM-16's applicability in various conditions across medicine.

Although a higher score of FROM-16 indicates a greater impact on family members' QoL, descriptive banding gives meanings to absolute scores. The cut-off points that result from the development of score bands make it easier for clinicians to identify at-risk and high-risk family members and direct them to the right kind of support. According to Roger et al. (2012), the utility of QoL questionnaires can be maximised if a clinical meaning is assigned to the questionnaire scores. This is important as in the absence of such interpretation, scores are just arbitrary numbers, leaving clinicians to guess the magnitude of effect or importance of score change in response to treatment. The ability to interpret questionnaire scores is essential if the questionnaire is to be of value in clinical decision making or monitoring clinical change, as well as for cost-effectiveness analysis (Roger et al., 2012).

Delong & Chen (2012) state that the use of score descriptor bands is the first important step for interpretation of scores but point out that this does not provide information on MID (the smallest change in the QoL scores that patients perceive to be important). This "smallest change" may be within a single score band descriptor or may straddle across two bands. Hence calculating the MID for FROM-16 will make it a more robust measure for clinical assessment of family QoL and has the potential of being used as a secondary endpoint for clinical trials.

One of the important psychometric properties of any measure is its sensitivity to change and its ability to detect change over time (Lohr, 2002). It is essential to formally demonstrate that FROM-16 is appropriately sensitive to change. Without such evidence, it could not be used to measure change over time. The National Institute for Health and Care Excellence (NICE) has recommended that future research should explore how family/carer health-related quality of life (HRQoL) changes over time (including when the patient's health improves or worsens, or if the patient dies) (Pennington & Wong, 2019). Demonstrating the sensitivity of FROM-16 to change will, therefore, meet the research gap highlighted by the NICE decision unit in the 2019 NICE technology appraisal (Pennington & Wong, 2019).

Although the development of ways to calculate carer and/or family member utility values is encouraged by NICE, the gap in the availability of utility measures is a significant limitation to the inclusion of disease impact on carers and family members in economic evaluations (Basarir et al., 2019). Our proposed mapping study aims to allow conversion of FROM-16 scores to EQ-5D utility scores and hence calculate QALYs. This will help health technology assessment (HTA) agencies and other decision-makers to compare the cost-effectiveness of health interventions across multiple disease areas, also taking into account the impact on family QoL.

We hope that our study will encourage clinicians to use FROM-16 alongside patient-reported outcome measures (PROMs) to inform treatment choices that are in the best interests of the patient as well as the patient's partner or family.

RESEARCH QUESTION/AIM(S)

AIM: To validate the FROM-16 questionnaire for its robustness as a family quality of life measure to be used across all disease specialities.

OBJECTIVES AND OUTCOME

Primary Objectives

1. To assess FROM-16 sensitivity to change by ascertaining whether the mean scores of FROM-16 in family members are changed over time (i.e. improved or deteriorated QoL) in parallel with the patients' QoL scores based on the intervention's hypothesised outcome.

Outcome: Ability of FROM-16 to detect change over time in parallel with the patients' QoL scores

2. To develop FROM -16 score descriptor interpretation bands using the anchor-based technique

Outcome: FROM-16 score bands to facilitate interpretation of scores in clinical practice

3. To calculate the minimal important difference (MID) for FROM–16

Outcome: Minimal important Difference to facilitate interpretation of scores in research/clinical trials and in clinical practice

4. To map the FROM-16 to the EQ-5D and to develop a methodology to convert FROM-16 scores to utility values for economic appraisal of interventions

Outcome: FROM-16 scores converted to QALYs

STUDY DESIGN / METHODS

Single-arm interventional studies - studies 1& 3

Cross-sectional studies - studies 2 & 4

SUMMARY

Study-1 -Sensitivity to change over time

AIM: To assess the ability of the FROM -16 instrument to detect a change in family members' QoL over a three months period, in parallel with patient improvement or deterioration.

This will be a one-arm interventional study with patients acting as their own control, which will involve following a cohort of 375 patients and their relatives. It is observational in that we are observing the change in QoL, but the clinical reason for this change is the use of different therapy, taken for clinical reasons, not for the purpose of this study. The research team will seek permission from the consultants of the respective departments for their patients to be involved in the study. The patients will be recruited from the Dermatology, Rheumatology, Endocrinology, Cardiology and Haematology outpatient clinics at the University Hospital of Wales, Cardiff. To test FROM-16 for sensitivity to change over time, a criterion for patient/relatives to be recruited is that the patient should be being placed on a new therapy, where a change in QoL is reasonably expected within two or three months. The complete eligibility criteria and recruitment procedure for the patient and their relatives are given in detail under separate sections of this protocol.

This study will involve patients and family members completing questionnaires at two points of time. At the first point of contact, the patient's and identified family member's demographic details (age, gender, ethnicity), the patient's disease details (diagnosis, disease duration, previous treatment, and any new prescribed treatment) and the family member's relationship to the patient will be recorded. The patient will be asked to complete a generic QoL measure, the EQ-5D, and the relative will be asked to complete FROM-16.

At 12 weeks, the patient will again complete the EQ-5D, and the relative will complete FROM-16, either in person at routine follow-up appointments or by postal or emailed questionnaires. To maximise the response rate, either a phone call, letter or email will be sent as a reminder.

The EQ-5D is a standardised generic instrument that is able to evaluate QoL across all areas of medicine. The EQ-5D descriptive system is a preference-based HRQoL measure with one question for each of the five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems (scored 1–3). The patient is asked to indicate his / her health state by checking the box against the most appropriate statement in each of the five dimensions.

The FROM-16 comprises 16 items with three response options for each, i.e. Not at All (scoring 0), A Little (scoring 1) and A Lot (scoring 2). The lowest possible score for the

FROM-16 is 0 and the highest is 32. The higher the total score, the greater the negative impact on the family member's QoL.

The mean difference in the scores for FROM-16 (before and after intervention) and EQ-5D (before and after intervention) will be calculated using SPSS version 25. The participants in each group (family members and patients) will be divided into two groups- "improved" (where the QoL score had decreased) or "worsened" (where the QoL score had increased). If the scores have not changed, that subject's score data will not be used further. The two groups will be compared using the Wilcoxon signed-rank test to assess the within-group difference, and the Mann-Whitney U test will be used to assess differences between the groups. The association between FROM-16 and EQ-5D changes over time will be determined using Spearman's rank correlation coefficient. The aim will be to ascertain whether the mean score of FROM-16 changes over time (improves or deteriorates) in parallel with the patients' QoL scores.

Study 2- Development of score interpretation bands

AIM: To develop descriptor bands for the FROM-16 scores using the anchor-based technique to facilitate interpretation of scores in clinical practice.

This will be a large cross-sectional postal study. This study will be involving 4,680 relatives of patients from 26 medical specialties. This study will only include family members, and the patient's role is solely to give permission for her/ his relative to participate in the study. The patients who attended the outpatient clinics at the University Hospital of Wales and Llandough Hospital, Cardiff and Vale University Health Board over past two months at the start of the study will be recruited to the study. The research team will seek permission from at least one consultant from each of 26 disease specialties for their patients to be involved in the study. The consultants with responsibility for the patients will write to the patients to seek their consent to allow their family member to be contacted. One hundred and eighty relatives of patients from each of the 26 disease specialties (i.e. 180x26=4,680) who meet the eligibility criteria will be recruited into the study.

These same subjects will also be asked to complete the European Quality of Life -5 Dimension (EQ-5D) questionnaire, as part of Study 4 (see details in study 4)

Study 2 aims at developing descriptor bands for the FROM-16 scores using the anchor-based technique (Hongbo et al.,2005). The anchor-based approach will be used as it is most appropriate for short and relatively simple questionnaires, such as FROM -16.

The consented relatives will complete the FROM-16 and state, on a single scale, a description of the severity of their QoL impairment by answering a global question (GQ).

"Over the last week, how much has your family member's or partner's health condition affected your life?"

The five possible response categories will be:

0	1	2	3	4
No effect on my life	Small effect on my life	Moderate effect on my life	Very large effect on my life	Extremely large effect on my life

The relative will be asked to tick one of these five responses.

The FROM-16 comprises 16 items with three response options for each, ranging from 'Not at All (scoring 0)', 'A Little (scoring 1)' and 'A Lot (scoring 2)'. The lowest possible score for the FROM is 0, and the highest is 32. The higher the total score, the greater the negative impact on the family member's QoL.

While the global question (GQ) records the family member's overall assessment of the severity of their QoL impairment due to their family member/partner's disease, FROM -16 measures this impact in a structured way. The responses to the GQ will be mapped against the FROM-16 scores, which will allow calculation of the score bands.

The technique involves relating overall scores of FROM-16 to GQ scores. Each score of the FROM-16 from 0-32, will be tabulated against the corresponding GQ score. The mode, mean and median of the GQ scores for each FROM-16 score will be calculated, and these will be then used as the basis of mapping the FROM-16 scores into a set of five discrete bands, each band representing a single GQ score.

Gender differences in the responses will be compared with the Mann Whitney U test. A separate set of bands will be developed if there are significant differences between gender and age groups responses. Correlation between FROM-16 and GQ will be examined using the Spearman rank correlation coefficient. For each combination of cut-off FROM-16 values coefficient of the agreement will be calculated (Leshem et al., 2015).

Study 3

A. Comparison of the FROM-16 scores with Global Severity Question (GSQ)

Aim: To compare FROM-16 scores with the severity of patients' condition assessed by their family member/partner using the GSQ

Anchor based technique

This will be a longitudinal observational study that will involve following five cohorts with 375 relatives of patients (75x5=375) who have a similar condition (for example an inflammatory condition) and who are placed on what is expected to be an effective therapy. No patients will be recruited into this study, only relatives. There will be no separate recruitment for

Study 3. These will be the same group of relatives who participated in study 1, but who will also complete additional information needed for Study 3.

Study 3 aims to compare the FROM-16 scores to a Global Severity Question (GSQ) and from this data, to calculate the MID for FROM-16 using the anchor-based technique (Basra. et al., 2015). This will involve measuring the relative's FROM-16 scores at two times, between which some score change may be expected because of the expected change in the patient's clinical condition.

This study will involve family members completing questionnaires at two points of time. At the first point of contact, the family member/partner will complete FROM-16 and answer a GSQ to rate the patient's disease severity.

The FROM-16 comprises 16 items with three response options for each, i.e. Not at All (scoring 0), A Little (scoring 1) and A Lot (scoring 2). The lowest possible score for the FROM is 0, and the highest is 32. The higher the total score, the greater the negative impact on the family member's quality of life.

The GSQ gives the family member's self-assessment of the overall severity of the patient's disease on a 0-10 visual analogue scale; 0 indicating no symptoms and 10 that the condition was the worst possible.

The GSQ question posed will be: "Thinking of your affected partner/family member, how severe do you consider that their disease is now?

At 12 weeks the family member/ partner, in addition to completing the FROM-16 and the GSQ, will also score a Global Rating of Change Questionnaire (GRCQ) to indicate how much (if any) they perceive their QoL has changed.

The GRCQ (Jaeschke., et al. 1989), used as an anchor, allows family members to give a self-assessment of the change since baseline assessment in, for example, overall QoL, whether it has improved, remained the same or deteriorated.

The GRCQ question posed will be: *"Thinking about the effect on you of your family member/partner's condition, how much has your quality of life changed since you previously answered this questionnaire."* The GRCQ has a 15-point scoring system with responses ranging from "a very great deal better" (+7) to "no change" (0) to "a very great deal worse" (-7). Respondents with scores of 0, -1 or 1 are classified as unchanged or having a small but unimportant change. Respondents whose scores are 2, 3, –2 or –3 are considered to have experienced a small change equivalent to the minimal important difference. Those with scores of 4, 5, –4 or –5 are considered to have experienced a moderate change, and those with scores of 6, 7, –6 or –7 are considered to have experienced a large change (Juniper et al., 1994, Jaeschke et al 1989).

The scores for each category of the GRCQ will be compared with the mean change in FROM-16 scores from the first assessment at the initial clinic visit to the second assessment, for each family member.

B. Minimal Important Différence (MID)

AIM: To calculate the MID for FROM-16 to facilitate interpretation of scores in research/clinical trials

Distribution based technique

A distribution-based approach will be used to understand the responsiveness of the FROM-16 to change by correlating the magnitude of difference in the FROM-16 score between Week 1 and Week 12 with the GRCQ scores. A paired-samples t-test will be used to assess whether the FROM-16 could detect changes identified by the GRCQ that occurred between Week 1 and Week 12. The effect size will be calculated to detect the magnitude of that change in the FROM-16 scores.

Effect size (ES) is calculated as a ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation of the scores at the first assessment. An ES of 0.2 is considered small, 0.5 moderate and 0.8 large [23]. The standardised response mean (SRM) will be calculated as the ratio of the raw FROM-16 score difference from the first to the second assessment to the standard deviation of that difference.

Distribution of scores of the FROM-16 will be assessed to identify the MID. One-third standard deviation (SD) and one-half SD will be calculated as a representative of 0.33 and 0.5 ES, respectively (Yost and Eton, 2005). Since the reliability and SDs may vary across samples, standard error of measurement (SEM) will also be calculated for identifying MCID. One SEM is equivalent to 0.5 ES when the reliability is 0.75 and 0.33 ES when the reliability is 0.9 (Yost and Eton, 2005)

Study 4- Creation of a methodology to map FROM-16 scores to utility values

AIM: To develop a methodology to convert FROM-16 scores to EQ-5D based utility values for economic appraisal of interventions

The methodology will be based on the recommendations set down in Longworth L, Yang Y, Young T, Mulhern B, Hernández Alavuse, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18 (9).

The current thinking, however, with regard to the most suitable methodology is set out below. It is recognised that this methodology could change in light of recommendations detailed in Longworth, Yang et al., (2014)

The methodology for this will follow the method used to convert DLQI scores into utility values (Ali et al., 2017). It will be a cross-sectional observational postal study and will include 4,680 relatives completing both the Family Reported Outcome Measure, (FROM-16) and European Quality of Life -5 Dimension (EQ-5D) questionnaire at the same time. The patient's family member will also be asked to provide some basic information such as your

ages, ethnicity and gender and also for some information about your health history and current condition(s).

Please note that there will be no separate recruitment of either patients or their family members/partner for study 4. The relatives participating in Study 4 are the same subjects who will be participating in Study 2. These relatives will provide data for Study 2 and Study 4 at the same time.

FROM-16 and the EQ-5D are separate generic measures that may be used to gather health-related quality of life (HRQoL) information from respondents. HRQoL data can be used to derive 'Quality-Adjusted Life Years' (QALYs), which can then be used for the economic evaluation of the intervention. While FROM-16 measures HRQoL of family members of the patient, EQ-5D can be used to measure HRQoL of patients as well as that of their family members.

The EQ-5D-3L asks respondents to describe their health using five domains (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety). In each domain, respondents indicate whether they have 1) no problems, 2) some problems, or 3) extreme problems on the day of EQ-5D-3L completion. The study will use the UK tariff to produce values between −0.594 and 1, where 1 represents "full health," 0 represents death, and negative values represent health states valued as worse than death (Dolan, 1997).

The FROM-16 consists of 16 items and covers two domains (Emotional and Personal & social life) (Golics et al. 2014). The questionnaire asks respondents how they are currently being affected by their family members' condition. Each item is scored from 0 to 2, and items are summed to produce FROM-16 scores between 0 and 32, where a lower score indicates better HRQoL.

This study aims to create a mapping model using OLR to predict EQ-5D health utility estimates from the FROM-16 scores. This mapping study will involve the following steps:

Conceptual correlations

This will involve an assessment of conceptual overlap between the EQ-5D-3L and FROM-16. The FROM-16 and EQ-5D scores will be entered in Excel, and the correlation between the two will be studied using Spearman rank correlation coefficients.

The ordinal regression modelling algorithm

Using all data, a series of ordinal logistic regressions will be fitted for each of the five EQ-5D dimensions against the sixteen individual items of the FROM-16, and also age and sex, using SPSS version 25. All sixteen FROM-16 items will be included for each domain model to capture all the correlations induced by each FROM-16 item. Regressions will be run with age and sex alone, FROM-16 items alone, as well as age and sex combined with FROM-16 items to evaluate the contribution of age and sex, and collectively the sixteen FROM-16 items. Model comparisons will be undertaken by comparing twice the absolute difference in the maximised log-likelihoods with the Chi-square distribution with degrees of freedom equal to the difference in the number of model terms being evaluated. Additional variables such as

age and sex will be used in the analysis as such data have a great impact on QoL (Sampogna et al. 2006).

Model Validation

Split-half cross-validation will be employed (Steyerberg et al. 2001) whereby the dataset will be randomly split five times into separate estimation and validation sets using the random number generator in SPSS version 25. The estimation set will be used to derive the mapping models, whilst the out-of-sample validation set will be used for validating the fitted models. This process will be repeated with each of the five estimations/validation sets after which the sets will be reversed, resulting in a total of 10 complete models.

SAMPLING AND RECRUITMENT

SAMPLE SIZE

The sample size will vary for different studies. For studies 1 and 3, the sample size will be around 375 participants for each study. The studies 1and 3 will be carried out using the same sample of 375 participants. The sample size was based on our sample size calculation shown below:

$$n = 2\left(Z_{\alpha} + Z_{1-\beta}\right)^2 \left(\frac{\sigma}{\delta}\right)^2$$

Where *n* is the required sample size. For Z_{α}, *Z* is a constant (set by convention according to the accepted α error (type I) and whether it is a one-sided or two-sided effect. For our purposes, it will be two-sided. Therefore, setting α at 5% the Z_{α} would be 1.96.

For Z1-β, Z is a constant set by convention according to the power of the study. We decided to define the power to be 95%, for which the Z is 1.6449. Based on this, Z1-β would be 0.6449.

σ is the standard deviation (estimated - based on the data in the published paper) while δ is the difference between the treatment means. The ratio $\frac{\delta}{\sigma}$ is termed the effect size

We have decided to target an effect size of 0.2.

The sample size required for an effect size of 0.2 is n=340. Assuming a 10% withdrawal rate, we would need to recruit approximately 375 patients.

For the large observational studies, studies 2 and 4, the sample size will be 4,680 (180 patients from each of the 26 specialities. These studies (2 and 4) will be carried out with the same sample of 4,680 participants. We have based our considerations of sample size for

these studies on similar studies carried out by our team previously. As 40% response rate is a rule of thumb for the postal studies, we have taken this in to account while calculating the sample size for studies 2 and 4.

SAMPLING TECHNIQUE

The study will use the Purposive Sampling technique. For studies 1 and 3, there is a requirement to recruit those patients who are being placed on a new therapy, where change in QoL is reasonably expected within two or three months. In the studies 2 and 4, patients' relatives will be recruited across 26 specialties so that the sample is representative of family members of patients with a wide range of diseases and conditions. This is an important requirement when validating a generic instrument.

RECRUITMENT

1. The patients and their family members/partners will be recruited from outpatient clinics and inpatients at the University Hospital of Wales and Llandough Hospital, Cardiff and Vale University Health Board.

2. For studies 1 and 3, the clinician will first approach the patients and their family members to gain permission for the investigator to approach them and explain the study to them. If the patient agrees to participate in the study and involve his family member in the study, then the investigator will approach them with study information. Both the patient and the family member will be asked to complete consent forms after reading the patient and family member participants information sheets. The patient and family member will have a choice as to whether or not to participate in the study. The patient and family members who give written consent will be allowed to participate in the studies. The data for studies 1 and 3 will be collected at the same time. There will be no separate recruitment for Study 3. These will be the same group of relatives who participated in study 1, but who will also complete additional information needed for Study 3. The family member will be asked to complete the FROM-16 questionnaire and Global severity Question(GSQ) while the patient will be asked to complete the EQ-5D questionnaire in the beginning. The patient and family members will be given the option to be followed by post or by email. This information will be embedded in the main consent form with a tick box choice and with space to write down their email and/or postal address.

At 12 weeks follow-up, the family member will complete FROM -16, GSQ and Global rating of change questionnaire while the patient will complete EQ-5D for the second time. An introductory follow-up letter will be posted to participants of studies along with an explanation of the importance and wider benefit arising from completing the questionnaires.

All questionnaires will be coded before they are sent out so that data from individual patients and their family members can be matched up. The patients and family members who opt for follow-up via email will be sent a covering email with the same wording as the cover letter and a link to an online version of the questionnaires and questionnaire code to link patient and family member's data. At 12 weeks follow-up, the family member will complete FROM -

16, GSQ and Global rating of change questionnaire while the patient will complete EQ-5D for the second time.

3. Studies 2 and 4 will be postal studies, and data for both studies will be collected at the same time. Prior permission will be obtained from all the consultants/ clinicians across 26 disease specialities in outpatient clinics at the University Hospital of Wales and Llandough Hospital, Cardiff and Vale University Health Board to approach their patients' relatives to participate in the study. (Please note no Children are involved in the study). The involvement of the family member of children in completing the questionnaires does not involve paediatric patients themselves).

These studies will only include family members, and the patient's role is solely to give permission for her/ his relative to participate in the study. The consultants with responsibility for the patients will write to the patients to seek their consent to allow their family member to be contacted. We plan to recruit 4,680 (180 patients from each of the 26 specialities) by checking the records of patients who have attended outpatient clinics over the past two months. This sample size has been calculated, considering 40% response rate for the postal studies.

The patients who meet the inclusion criteria will be posted a study pack for the patient and the family member. The patient study pack will contain a personalised invitation letter to the patient to seek her/his permission to involve a family member in the study, a patient information sheet and patient consent form. The family member study pack will contain a family member information sheet, family member consent form, questionnaires to be completed by a family member, and a Freepost envelope. Two weeks after the first mailing, a follow-up reminder letter will be sent to the non-responders. Six weeks after the first mailing, the second reminder with follow-up study pack will be sent to the non-responders. The questionnaires will be printed on a light coloured glossy paper to enhance the response rate (Eiseman, 2000).

4. All consented family members and patients participating in the study will be provided with contact details of the investigators in case they need any further information or clarification.

STUDY POPULATION

Patients with chronic disease and their family members attending the outpatient clinics or as inpatients at the University Hospital of Wales, and Llandough University Hospital, Cardiff. For the large observation studies, study participants will be chosen across 26 disease specialties. Please note no Children are involved in the study. The involvement of the family member of children in completing the questionnaires does not involve paediatric patients themselves.

For the studies testing FROM-16 sensitivity to change and calculation of MID, the study population will include patients starting on a new therapy and where change is expected after a certain period.

INCLUSION CRITERIA

Inclusion criteria for patients

- Adult patients aged 18 years or older
- Able to give written informed consent
- Attending a clinic with a family member, or currently a hospital inpatient.
- Have the mental capacity to give informed written consent and complete the questionnaire.
- Patient starting a new treatment and follow-up patients who had changed treatment following therapy failure (study 1 & 3 only)

Inclusion criteria for family members

- Adult family members aged 18 years or older.
- An immediate family member or partner living with, or caring for, a patient diagnosed with one or more medical conditions under one of the selected specialities.
- Have the mental capacity to give informed written consent and complete the questionnaires

EXCLUSION CRITERIA

Exclusion criteria for patients

- Aged under 18 years.
- Unable to give written informed consent.
- Having a severe handicap or disability which prevents them from completing a questionnaire
- Patients suffering from significant comorbidity, if they have a non-inflammatory skin condition (studies 1 and 3 only)

Exclusion criteria for family members

- Age under 18 years
- Not considered by the patient as a family member
- Unable to give written informed consent
- Having a severe handicap or disability which prevents them from completing a questionnaire.

  Currently there are no language translations available. However if requested we will engage in the Welsh Language.

ASSESSMENTS

The family members will be asked to complete the FROM-16, EQ-5D, GQ and GRCQ questionnaires. The patients will be asked to complete the EQ-5D.

MONITORING AND DATA HANDLING

Personal data collected in paper form (the FROM-16 questionnaire and other completed questionnaires) will be stored in a locked cabinet and locked room within the hospital premises (Glamorgan House, Heath Park, University Hospital of Wales). The patients' and family members' responses to the questionnaires will be transferred to electronic files and stored anonymously using a coding system. Only the research team will have access to the data.

The data published from the study shall preserve patient anonymity and will be published in aggregate form. Any data shared with other researchers as part of FROM-16 validation shall be anonymous.

The data collection and storage shall comply with the Data Protection Act and GDPR.

STATISTICAL ANALYSIS

A range of statistical methods will be used that will link directly with the four primary objectives and ultimately provide a mapping from FORM-16 through the EQ-5D to QALYs. These methods will be developed and detailed in a Statistical Analysis Plan.

ETHICAL CONSIDERATIONS

All participants will have the right not to participate in the study or to withdraw at any point during the study. The questionnaire forms shall be stored securely on the hospital premises. The data transferred to Excel shall not include any patient identifiable information. The study shall be conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation: Good Clinical Practice guidelines.

ETHICS COMMITTEES APPROVAL

An application will be submitted for full ethical permission to the R&D Department of Cardiff and Vale UHB and the South East Wales Research Ethics Committee after favourable independent expert scientific review. Approval from a Research Ethics Committee (REC) and from local R&D committees shall be obtained before starting the study.

Detailed participant Information sheets, introductory letter and consent forms are being submitted for ethical approval along with the study protocol.

INFORMED CONSENT

All eligible patients and participating family members shall receive a verbal and written explanation of the study with a copy of the questionnaire/s to review. It will be explained to the patients, and family members that their participation is optional and declining to participate will have no impact on the patient's care. The participants will be informed that they may withdraw from the study at any time

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Appendix III: HRA/HCRW approval of original protocol

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Prof Andrew Y Finlay
3rd Floor, Glamorgan House
Department of Dermatology
Cardiff University, School of Medicine, Heath Park,
Cardiff
CF14 4XN

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

23 October 2020

Dear Professor Finlay,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Validation of Family Reported Outcome Measure (FROM-16)**
IRAS project ID:	**281134**
REC reference:	**20/EE/0242**
Sponsor	**Cardiff University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **281134**. Please quote this on all correspondence.

Yours sincerely,
Laura Greenfield

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Helen Falconer*

Appendix III: HRA/HCRW approval of original protocol

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Cardiff University Insurance / Indemnity]	1	21 August 2020
GP/consultant information sheets or letters [Consultant Email FROM-16 (studies 1 & 3)]	4	12 October 2020
GP/consultant information sheets or letters [Consultant letter FROM-16 (studies 2 and 4)]	2	12 October 2020
IRAS Application Form [IRAS_Form_17092020]		17 September 2020
IRAS Application Form XML file [IRAS_Form_17092020]		17 September 2020
IRAS Checklist XML [Checklist_17092020]		17 September 2020
Letter from sponsor [Sponsor Letter]	1	21 August 2020
Letter from statistician [Letter from Statistician]	1	20 June 2020
Letters of invitation to participant [patient personalized letter (studies 2 and 4)]	2	12 October 2020
Letters of invitation to participant [Family member follow-up email (studies1 and 3)]	3	12 October 2020
Non-validated questionnaire [FROM-16 Questionnaire]	NA	24 July 2020
Organisation Information Document		
Other [Applicant's response to the queries]		20 October 2020
Participant consent form [Patient Consent Form (study 1)]	1	03 April 2020
Participant consent form [Patient Consent Form (studies 2,3 and 4)1)]	1	03 April 2020
Participant consent form [Family member Consent form (studies 1 and 3)]	2	19 October 2020
Participant consent form [Family member Consent form (studies 2 and 4)]	2	19 October 2020
Participant information sheet (PIS) [Participant Information sheet-patient (studies 1and 3)]	4	21 October 2020
Participant information sheet (PIS) [Participant Information Sheet - Patient (studies 2 and 4)]	4	21 October 2020
Participant information sheet (PIS) [Participant Information Sheet-Family member (studies 1 and 3)]	3	21 October 2020
Participant information sheet (PIS) [Participant Information Sheet-Family member (studies 2 and 4)]	4	21 October 2020
Referee's report or other scientific critique report [Independent Reviewer report]	version 1	24 June 2020
Research protocol or project proposal [FROM-16 Study Protocol]	ver1	03 September 2020
Schedule of Events or SoECAT		
Summary CV for Chief Investigator (CI) [CV (Chief investigator)]	version 1	05 June 2020
Summary CV for student [Student CV-Rubina Shah]	version 1	06 May 2020
Summary CV for supervisor (student research) [Supervisor CV-Prof Salek]	ver1	30 June 2020
Summary CV for supervisor (student research) [Supervisor CV-John Ingram]	version 1	28 June 2020
Validated questionnaire [Global Severity Questionnaire]		
Validated questionnaire [Global Rating of Change Questionnaire]		
Validated questionnaire [Global Questionnaire]		
Validated questionnaire [EQ-5D-3L]		

IRAS project ID	281134

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
All sites will perform the same research activities therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No application for external study funding has been made.	A Principal Investigator should be appointed at study sites of this type	As a non-commercial study undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable. Where arrangements are not already in place, researchers undertaking any of the research activities listed in A18 of the IRAS form would be expected to obtain a Letter of Access. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). It is expected that the researcher is working under supervision with a memorandum of understanding in place in which case no HR Good Practice arrangements are required

Appendix IV: SMREC ethics application-Interpretation of FROM-16 scores

SCHOOL OF MEDICINE

APPLICATION FOR ETHICAL REVIEW

For Office Use Only	
SREC Reference: [x]	Meeting/Review Date: [x]
SECTION 1. GENERAL INFORMATION	
Application Type:	☐ Staff ☑ PGR student ☐ PGT/Masters Student ☐ Undergraduate
Research Project Title:	Development of score interpretation bands for the Family Reported Outcome Measure (FROM-16) and mapping of the FROM-16 scores to EQ-5D utility values
Short Title (where applicable):	Interpretation of FROM-16 scores
For Staff Projects	
Name of Chief/Principal Investigator:	
Contact details:	
Other members of research team:	
For Student Projects	
Name of Student:	Rubina Shah
Contact details:	Third floor, Glamorgan House Division of Infection and Immunity Cardiff University School of Medicine Heath Park Cardiff CF14 4XN Email: [redacted] Telephone: [redacted]
Course name:	PhD
Name of Supervisor(s):	Prof Andrew Y Finlay Prof Sam Salek (University of Hertfordshire) Dr John R Ingram

	'Research' means any project which attempts to derive generalisable new knowledge or apply existing knowledge, including studies that aim to generate hypotheses, as well as studies that aim to test them. 'Service Evaluation' is an activity which seeks to assess how well an existing service is performing. The activity is designed and conducted with the sole purpose of defining or judging a current service. 'Audit' is an activity which usually involves a quality improvement cycle that measures performance against predetermined standards and recommends specific actions to improve performance. *If your project is classed as a service evaluation or audit, it will not require ethical review by the School of Medicine Research Ethics Committee. If you are unsure as to whether your project is a service evaluation, then please send a copy of the project proposal to the Committee Secretary, Mrs Claire Evans (EvansCR9@cardiff.ac.uk) for review by the Chair.*		
2.2	Does the research project involve human participants, human material or human data (as defined in the Cardiff University Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data)? *If **no**, you are not required to submit the research proposal to this Committee. **Please do not continue with this application.***	Yes	
2.3	Does the research project require review by an external ethics committee (refer to Appendix 1 of the Cardiff University Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data)? Please note that this includes all research projects involving participants who lack the capacity to consent. *If **yes**, the research project should be submitted to the relevant external ethics committee for review and does not fall within the remit of this Committee. Please contact the Research Governance Team for further advice. **Please do not continue with this application.***		No
2.4	Has the research project been ethically reviewed by another university or research institution (for example, where the Chief/Principal Investigator for the research project is based at another institution)? *If **yes,** please provide evidence of the review conducted (such as an outcome letter or communication) and the ethical review policy of the relevant institution or committee. **Please do not continue with this application.***		No
2.5	Does the research project only involve the use of information that is publicly and lawfully available e.g. census data, population statistics		No

	published by government departments and personal letters/diaries in public libraries. Note: research projects involving the use of Human Data obtained from social media (or similar internet forums) do not fall within this category. *If **yes**, you are not required to submit the research proposal to this Committee.* ***Please do not continue with this application.***		
2.6	Does the research project fall within the scope of the UK Policy Framework for Health and Social Care Research? This Framework broadly applies to research taking place within, or involving, the health and social care systems. If you intend to recruit research participants or obtain patient data through the NHS, then you will require NHS LREC approval. Your application will fall outside of the School's remit to review so please do not continue with this application. *If **yes**, you will need to apply to the Research Governance Team for Sponsorship using the Advanced Project Information Proforma (APIP) (available on the Cardiff University intranet). The Research Governance Team will advise you on the approvals that are required for the research project after it has conducted a review of the APIP and supporting documentation.* ***Please do not continue with this application until you have sought advice from the Research Governance Team.***		No
2.7	Does the research project involve the collection or use of Human Tissue (including, but not limited to, blood, saliva and bodily waste fluids)? *If **yes**, the research project should be submitted to the Human Tissue Act Compliance Team (HTACT) prior to submission to an ethics committee.* ***Please do not continue with this application until you have sought advice from HTACT.***		No
2.8	Does the research project fall within the scope of the University's Security-sensitive Research Policy? This Policy broadly applies to research involving terrorism, extremism or radicalisation (or access to materials of such a nature). *If **yes**, you must register the research in accordance with the Policy and comply with the IT and security arrangements contained in the Policy.*		No
2.9	Has the research project received scientific review? (For student research projects, review by the research project supervisor is an acceptable form of scientific review) *If **no**, please obtain appropriate scientific review before submitting the application to this Committee.*	Yes	

If the research project involves the use of animals, please contact the Cardiff University Biological Standards Office bso@cardiff.ac.uk to seek further advice.

SECTION 3. PROJECT SUMMARY

3.1	Summarise the research project (including the purpose and its methodology) using language that would be understood by a lay person. (500 word maximum)

People's health conditions can have a major impact on the quality of life (QoL) of patients, but also on their family members, affecting their physical, social and psychological wellbeing. This impact of a disease on the QoL of partner or other family members is mostly ignored, but is a huge unmet need. The Family Reported Outcome Measure (FROM-16) created by Golics et al., (2014) at Cardiff University is the only generic instrument that can be used to measure this impact across all disease areas. Although initial validation of FROM-16 has been carried out, there is need for further validation to:

- develop descriptive bands for FROM -16 scores to aid clinicians in the interpretation of FROM-16 scores, to identify at risk and family members and direct them to appropriate support services
- develop an algorithm to convert FROM-16 scores to European Quality of Life 5-Dimension (EQ-5D) utility values which could then be used to calculate Quality Adjusted Life Years (QALYs) for use in economic appraisals.

This study aims to gather information about the impact of having someone in the family with a disease on the QoL of family members or partner of the patient, using the FROM -16, EQ-5D and a Global question. The information from this research will allow clinicians to understand what different FROM-16 scores mean in terms of the impact on QoL being experienced by family members and to enable the questionnaire information to be used as part of the assessment of new therapies and treatment decisions. The creation of a formula to calculate QALYs from FROM-16 scores will allow policy makers and health technology assessment (HTA) agencies to incorporate partner/family impact information when comparing the cost-effectiveness of health interventions across multiple disease areas, in addition to patient-centred QoL data.
We hope that eventually, this information will facilitate improved patient and family care and that clinicians will be better able to choose treatments that are in the best interests of the patient and his/her family members.

3.2	Describe the research question(s).

- Can score descriptor bands be developed for the FROM-16 questionnaire to enable easy interpretation of FROM-16 scores in clinical practice and in clinical research?
- Can methodology be created to map FROM-16 scores to utility values?

3.3	Estimated start date.

February 2021	
3.4	Estimated end date (usually the end of data collection).
September 2021	
3.5	Is the research project funded? *If **yes**, please name the funding body.*
No	
3.6	Are there any potential conflicts of interest? *If **yes**, please confirm the action you propose to take to address such conflicts.*
AYF and MSS are joint copyright owners with Cardiff University of FROM-16	

SECTION 4. FULL REVIEW CRITERIA				
		Yes		**No**
4.1	Will the research project be performed without the participants' prior consent?			No
4.2	Does the research design include an element of deception, including covert research?			No
4.3	Will the research project involve children under the age of 18 or 'at risk' (vulnerable) adults or groups? *The Cardiff University Safeguarding Children and Adults at Risk: Policy and Guidance sets out examples of 'at risk' or 'vulnerable' adults.*			No
4.4	Does the research project include topics which may be considered highly sensitive for participants? *This includes sexual behaviour, illegal activities, political, religious or spiritual beliefs, race or ethnicity, experience of violence, abuse or exploitation, and mental health.*			No
4.5	Does the research project require access to records of a sensitive or confidential nature, including Special Category Data, for the purposes of the General Data Protection Regulation and Data Protection Act 2018?			No
4.6	Is permission of a gatekeeper required for initial or continued access to participants? *This includes participants in custody and care settings, or research in communities where access to research participants is not possible without the permission of*			No

	another adult, such as another family member or a community leader.			
4.7	Does the research project involve intrusive or invasive procedures? *This includes the administration of substances, vigorous physical exercise, procedures involving pain or more than mild discomfort to participants (including the risk of psychological distress, discomfort or anxiety to participants).*			No
4.8	Does the research project involve visual or audio recordings where participants may be identified?			No
4.9	Does the research project involve the collection or use of human tissue?			No
4.10	Is there a risk to the safety and wellbeing of the Researchers?			No

PROCEDURE TO FOLLOW, BASED ON RESPONSES IN SECTION 4:

- If any 'Yes' box applies, the research project should follow a full ethics review.
- If all 'No' boxes apply, the research project may be considered for proportionate review.

SECTION 5. RECRUITMENT

5.1	How will you recruit participants to the research project? *If appropriate, please include sampling criteria.*

Through an online survey using patient and carer social media sites, such as Patient Forums and Blogs

5.2	How many participants are you aiming to recruit? *If applicable, please include a breakdown of participants by type and number.*

Participants type : Patients with any disease condition and their family members
Number: 3000 participants

5.3	What are the inclusion and exclusion criteria for participants?

Inclusion criteria

- Family members of patients with all condition.
- Able to read and understand English
- Family members aged 18 years or older
- Have the mental capacity to give informed written consent and complete the questionnaire using an electronic device.

Exclusion criteria • Family members under age 18 years • Unable to read and understand English • Unable to give written informed consent or operate an electronic device to complete the survey	
5.4	How will the research project address recruitment of participants who are not fluent in the English/Welsh language?
The survey is written in the English language. If we are asked by any participant to supply the survey in the Welsh language we will endeavour to do so. The survey is being distributed by patient organisations in the UK through their web portal in the English language and so it will not normally reach individuals who do not understand English. The nature of the research questions being asked require that the study is carried out in English, as we are only developing score descriptor bands and carrying out the mapping exercise for usage in English. Creation of descriptor bands and mapping in other languages/cultures would require separate studies and we therefore do not intend to make this survey available in other languages.	
5.5	Will the research project involve participants that are Cardiff University staff or students or people who are likely to become students or clients of the University or the place in which you may otherwise work? *If applicable, please provide details.*
No	
SECTION 6. CONSENT PROCEDURES	
6.1	How will informed consent be obtained? *Please include who will be taking consent, how consent will be recorded, when participants will be provided with information about the research project, and how long potential participants will be given to decide whether to take part.*
The participants will be given an information sheet and will be asked to provide consent as part of the online survey.	
6.2	Will participants be offered any incentives to take part in the research project?
No	
6.3	If a questionnaire is to be used, will you give participants the option of omitting questions they do not wish to answer?
Yes	
6.4	Will participants be informed that their participation is voluntary and that they may withdraw at any time and for any reason?
Yes	
SECTION 7. POSSIBLE HARM TO PARTICIPANTS/RESEARCHERS	

7.1	Is there is a risk of the participants experiencing physical, emotional or psychological harm or distress*? If yes, please provide details of how ethical issues will be handled and how any risks will be minimised. Please consider whether the research project includes topics which could be considered as highly sensitive for participants.*
There is a remote possibility that some respondents may feel mild emotional or psychological distress, though we are not aware of such occurrence having happened in previous use of these questionnaires. In case a participant experiences any emotional or psychological distress, he /she has the option to withdraw from the survey. In the Participant Information Sheet (PIS) we will advise any participant who experiences any distress to seek advice form their general practitioner, or to contact our research team.	
7.2	Is there a risk of the Researcher(s) experiencing physical, emotional or psychological harm or distress? *If yes, please provide details of how ethical issues will be handled and how any risks will be minimised.*
No	
SECTION 8. DATA MANAGEMENT, CONFIDENTIALITY AND DATA PROTECTION	
8.1	How, and by whom, will data be collected?
Data will be collected through the Cardiff University Jisc or REDCap online survey platforms by the post graduate student investigator Rubina Shah.	
8.2	Will you be accessing or collecting Personal Data (identifiable personal information) as part of the research project? *If yes, please confirm what data will be accessed and/or collected (including details of the information participants are asked to provide on a written consent form).*
We will be collecting data about gender / age / occupational status / country / family members' relationship to the patient in our survey. This information will only be presented in an anonymised way in any publication.	
8.3	How long will you retain the Personal Data collected in connection with the research project?
5 years	
8.4	What efforts will be made to anonymise the data collected (where possible)?
All information is collected anonymously, the names of the participants are not collected and the data entry for the purpose of the analysis will be encrypted.	
8.5	Are you proposing to utilise 'public task' as the lawful basis for processing Personal Data for the purposes of the research project (as recommended in the University's GDPR Guidance for Researchers)? *If no, please explain why and what alternative lawful basis you propose to use.*
Yes	

8.6	Have you utilised/incorporated into the Participant Information Sheet the template GDPR privacy information for research participants? *If no, please explain why this has not been used.*
Yes	
8.7	For how long will the collected anonymised data be retained? Please follow the links below for the University guidance on records management and retention schedules: https://www.cardiff.ac.uk/public-information/policies-and-procedures/record-management-policy-and-retention-schedules
5 years	
8.8	Who will have access to the data?
The investigator and the research team	
8.9	Will the data be shared in any way, for example through deposit in a data repository, with third parties, or a transcription service?
No	

SECTION 9. OTHER ETHICAL CONSIDERATIONS

Please outline any other ethical considerations raised by the research project and how you intend to address these. You are obliged to bring to the attention of the SREC any ethical issues not covered in this Ethics Review Application Proforma.

The respondent might have questions about their data and how the information they provided will be used. The PIS explains that the data collection and storage shall comply with the Data Protection Act and GDPR. The respondent can also contact research team in case he /she needs more information on the project via the email provided in PIS. Furthermore, the survey has option to allow respondent to withdraw from the survey, if respondent chooses this option, all responses from the subject will be discarded.

SECTION 10. SUPPORTING DOCUMENTS

I have attached the documents, as indicated in the table below, in support of this application, as a SINGLE Word document.

Please note that the documents listed below **MUST BE** provided where relevant to the research project, alongside any other documents relevant to recruitment, consent and participation.

		Yes	**No**	**Version no.** (where applicable)
1	Research Project Protocol/Proposal	Yes		Version 3
2	Recruitment Adverts/Invitation Letters		No	
3	Participant Information Sheet	Yes		Version 3
4	Consent Form		No	Consent online (within

				the questionnaire)
5	Data Collection Tools (e.g. questionnaires)	Yes		NA
6	Other participant communications (e.g. debrief sheets)		No	
7	Protocol(s) or Standard Operating Procedure(s) of documented and ethically approved common methodology(ies) being used for the research project		No	

SECTION 11. SIGNATURES AND DECLARATIONS

General declaration

I confirm that:

a. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
b. I have the necessary skills, training and or/expertise to conduct the research project as proposed.
c. I am familiar with the University's health and safety requirements and policies and that all relevant health and safety measures have been taken into account for the research project.
d. I am familiar with, and will comply with, the University's Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and the University's Research Integrity and Governance Code of Practice.
e. The relevant equality and diversity considerations have been taken into account when designing the research project.
f. If the research project is approved, I undertake to adhere to the research project protocol, the terms of the full application as approved and any conditions set out by the Committee and any other body required to review and/or approve the research project.
g. I will notify the Committee and all other review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the Committee before implementing the amendment.

Appendix 1

STUDY PROTOCOL

version 3

Development of score interpretation bands for the Family Reported Outcome Measure (FROM-16) and mapping of the FROM-16 scores to EQ-5D utility values

Study Protocol- Development of score interpretation bands for the Family Reported Outcome Measure (FROM-16) and mapping of the FROM-16 scores to EQ-5D utility values

Investigators

Ms Rubina Shah, PhD postgraduate student, Cardiff University School of Medicine, Cardiff
Prof Andrew Y Finlay, Professor of Dermatology, Cardiff University School of Medicine Cardiff.
Prof Sam Salek, Professor of Pharmacoepidemiology, University of Hertfordshire
Dr John Ingram, Clinical Reader, Cardiff University School of Medicine Cardiff.

Background

If a person has a disease, the quality of life of their partner and family members may be greatly impacted. Although family members caring for or living with a patient may experience equal (1) or sometimes even more impact on their life quality than the patient themselves (2, 3), the wider family burden of disease has been largely unrecognised or ignored.

The study by Golics et al. (4) involving 26 medical specialities demonstrated that family members of patients suffering from a wide range of different diseases are impacted in similar ways across the areas of psychological, emotional, personal and social wellbeing. This key finding led to the development of the first, and so far only, generic family quality of life (QoL) measure (5), the Family Reported Outcome Measure (FROM-16).

The FROM-16 is a family quality of life questionnaire which measures the impact of any disease, across all medical specialties, on the QoL of family members or partners of patients. One of the useful features of the FROM-16 is that it is a user-friendly and relatively simple questionnaire with a two-minute completion time, making it a practical tool to be used in a clinical setting.

The FROM-16 comprises 16 items with three response options for each: Not at All (scoring 0), A Little (scoring 1) and A Lot (scoring 2). The 16 items are divided into two categories (domains): Emotional (comprising six items, maximum score of 12) and Personal and Social Life (comprising ten items, maximum score of 20). The lowest possible score of the FROM-16 is 0, and the highest is 32. The higher the total score, the greater the negative impact on the family member's QoL.

Although a higher score of FROM-16 indicates a greater impact on family members' QoL, for this questionnaire to be useful in a clinical or research setting, there is a need for the scores to have some practical meaning. According to Roger et al. (6)(2012), the utility of QoL questionnaires can be maximised if a clinical meaning is assigned to the questionnaire scores. This is important as in the absence of such interpretation, scores are just arbitrary numbers, leaving clinicians to guess the magnitude of effect or importance of score change in response to treatment. The ability to interpret questionnaire scores is essential if the questionnaire is to be of value in clinical decision making or monitoring clinical change, as well as for cost-effectiveness analysis (6).

In relation to another questionnaire, the Dermatology Life Quality Index (DLQI), our team developed descriptive score bands (7). This banding resulted in the DLQI becoming clinically useful to dermatologists and has facilitated integration of the DLQI into national guidelines in over 45 countries (8).

Descriptive score banding therefore gives vital meanings to absolute scores. The cut-off points that would result from the development of score bands for FROM-16 would make it easier for clinicians to identify at-risk and high-risk family members and direct them to the appropriate support services. Score bands would transform FROM-16 from being primarily a research tool to being of practical benefit to clinicians worldwide across all medical specialties.

Although the development of ways to calculate carer and/or family member utility values is encouraged by NICE, the gap in the availability of utility measures is a significant limitation to the inclusion of disease impact on carers and family members in economic evaluations (9). Our proposed mapping study aims to allow conversion of FROM-16 scores to European Quality of Life 5-Dimension (EQ-5D) utility scores which could then be used to calculate QALYs. This will help health technology assessment (HTA) agencies and other decision-makers to compare the cost-effectiveness of health interventions across multiple disease areas, also taking into account the impact on family QoL.

RESEARCH QUESTIONS

- Can score descriptor bands be developed for the FROM-16 questionnaire to enable easy interpretation of FROM-16 scores in clinical practice?
- Can methodology be created to map FROM-16 scores to utility values?

AIMS

- To develop score descriptor bands for the FROM-16 using an anchor-based technique.
- To develop a methodology to convert FROM-16 scores to EQ-5D based utility values for economic appraisal of interventions.

METHODS

This will be an online cross-sectional observational study involving patients who are members or registered with UK patient groups, forums and charities, and the partners and family members of these patients. Ethics approval will be sought from the Cardiff University School of Medicine Research Ethics committee, which conforms to the principles embodied in the Declaration of Helsinki. The study patients and their designated family member will be provided with information about the study in a Participant Information Sheet (PIS), and electronic informed consent will be sought from the participants. **The patient's role will be limited to the decision as to which person (partner or family member) will be asked to take part, to provide consent for his/her partner or family member to be invited to participate in the study, and to give basic information about themselves.** The designated partner or family member will then have the choice, after reading the PIS, to participate or not in the study and give their own consent.

Survey structure

The survey will be carried out using either the Jisc or REDCap survey platforms both of which are GDPR compliant. The survey will have two sections. Section one is to be completed by the patient. The patients will be asked to provide some basic information (including gender, age, ethnicity, disease diagnosed, disease duration and country of residence) and to provide consent for their partner/family member to participate in the study.

Section two is to be completed by the partner or family member chosen by the patient. The family member is asked to read the PIS before being asked to consent to take part in the study. The family member is asked at the start of the questionnaire to provide information about age, gender, ethnicity, country, and relationship to the patient. This will be followed by answering the FROM-16 and EQ-5D questionnaires and a "global question".

The questionnaires are in the English language. If any participant requests the survey and questionnaires in Welsh, we will endeavour to provide a translation.

.

Inclusion / Exclusion criteria

Inclusion criteria

- Patients with all health condition
- Partners and family members of these patients
- Family members aged 18 years or older
- Have the mental capacity to give electronic informed "written" consent and complete the questionnaires using an electronic device.

Exclusion criteria

- Patient or family members under age 18 years
- Unable to give electronic written informed consent or operate an electronic device to answer the survey

Distributing the survey

We will seek the help of various local and national patient groups, forums, charities and associations to distribute the questionnaires to their members. The criteria for the selection of these groups will be based on the 26 disease specialities that were included in the original creation of FROM-16 questionnaire. Patient groups will be matched to these 26 specialities to create the final list of patient groups and organisation, which will then be contacted to participate in the survey. Patient support Groups that we plan to approach will include patient organisations registered with NHS such as the North Wales Cancer Forum, South Wales Myeloma Support Group, Diabetes UK, British Heart Foundation, Allergy UK, Alzheimer's Society, Arthritis Care, Asthma UK, Primary Immunodeficiencies UK (PIDs), the Psoriasis Association, the National Eczema Society, Metabolic Support UK, Huntington's disease Association, The Stroke Association, The Brain Tumour Charity, Sickle Cell Society, Research Autism, Rethink UK, Pain Concern, Pancreatic Cancer UK, Parkinson's UK, Polycystic Kidney Disease Charity, Prostate Cancer UK, Ovacome, Pain Concern, Parkinsons UK, Allergy UK, Alzheimer's Society, Arthritis Care, Asthma UK, Bowel Cancer UK, Breast Cancer Now, Breast Cancer UK, Children's Cancer & Leukaemia Group, Childrens Heart Federation, Childrens Liver Disease Foundation, Coping with Cancer NE, Epilepsy Action, Kidney Cancer UK, Leukaemia Care and the Patients Association UK.

Participants will complete the survey online and the response data will be automatically saved on the "questionnaire platform software", for analysis.

Study Objective 1

Development of score interpretation bands using the Anchor based technique

The study aims at developing descriptor bands for FROM-16 scores using the anchor-based technique (7). The anchor-based approach will be used as it is the most appropriate for short and relatively simple questionnaires, such as FROM -16.

The consented family members /partners will complete the FROM-16 and state, on a single scale, a description of the extent of their QoL impairment by answering a global question (GQ).

"Over the last week, how much has your family member's or partner's health condition affected **your** life?"

The five possible response categories will be

0	1	2	3	4
No effect on my life	Small effect on my life	Moderate effect on my life	Very large effect on my life	Extremely large effect on my life

The relative/partner will be asked to tick one of these five responses.

While the GQ records the family member's overall assessment of the extent of their QoL impairment due to their family member/partner's disease, FROM -16 measures this impact in a structured way using a multidimensional construct. The responses to the GQ will be mapped against the FROM-16 scores, which will allow calculation of the score bands.

The technique involves relating overall scores of FROM-16 to GQ scores. Each score of the FROM-16 from 0-32, will be tabulated against the corresponding GQ score. The mode, mean and median of the GQ scores for each FROM-16 score will be calculated, and these will be then used as the basis of mapping the FROM-16 scores into a set of discrete bands. A separate set of bands will be developed if there are significant differences between gender and age groups mapping.

Study objective 2

Creation of a methodology to map FROM-16 scores to utility values

The study aims at developing a methodology to convert FROM-16 scores to EQ-5D based utility values for economic appraisal of interventions.

The methodology will be based on the recommendations given by Longworth L et al (10, 11) and by Ali, FA et al (12).

The current thinking, however, with regard to the most suitable methodology is set out below. It is recognised that this methodology could change in light of the recommendations detailed in Longworth et al. (11)

The methodology for this will follow the method used to convert DLQI scores into utility values (12). It will be a cross-sectional observational online study and will include 3000 family members completing both the FROM-16 and the EQ-5D questionnaires at the same time. The patient's family member will also be asked to provide some basic demographic information such as their age, ethnicity and gender. In addition, they will be asked to record relevant medical history and current condition(s), if any.

FROM-16 and the EQ-5D are separate generic measures that may be used to gather health-related quality of life (HRQoL) information from respondents. HRQoL data can be used to derive 'Quality-Adjusted Life Years' (QALYs), which can then be used for the economic evaluation of the intervention. While FROM-16 measures HRQoL of family members of the patient, the EQ-5D can be used to measure HRQoL of patients as well as that of their family members.

The EQ-5D-3L asks respondents to describe their health using five domains (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety). In each domain, respondents indicate whether they have 1) no problems, 2) some problems, or 3) extreme problems on the day of EQ-5D-3L completion. The study will use the UK tariff to produce values between −0.594 and 1, where 1 represents "full health," 0 represents death, and negative values represent health states valued as worse than death (13).

The FROM-16 consists of 16 items and covers two domains (Emotional and Personal & Social Life) (5). The questionnaire asks respondents how they are currently being affected by their family members' condition. Each item is scored from 0 to 2, and items are summed to produce FROM-16 scores between 0 and 32, where a lower score indicates better HRQoL.

This study aims to create a mapping model using “ordinal logistic regression" (OLR) to predict EQ-5D health utility estimates from the FROM-16 scores. This mapping study will involve the following steps:

Conceptual correlations

This will involve an assessment of conceptual overlap between the EQ-5D-3L and FROM-16. The FROM-16 and EQ-5D scores will be entered in Excel, and the correlation between the two will be studied using Spearman rank correlation coefficients.

The ordinal regression modelling algorithm

Using all data, a series of ordinal logistic regressions will be fitted for each of the five EQ-5D dimensions against the sixteen individual items of the FROM-16, and also age and sex, using SPSS version 25. All sixteen FROM-16 items will be included for each domain model to capture all the correlations induced by each FROM-16 item. Regressions will be run with age and sex alone, FROM-16 items alone, as well as age and sex combined with FROM-16 items to evaluate the contribution of age and sex, and collectively the sixteen FROM-16 items. Model comparisons will be undertaken by comparing twice the absolute difference in the maximised log-likelihoods with the Chi-square distribution with degrees of freedom equal to the difference in the number of model terms being evaluated. Additional variables such as age and sex will be used in the analysis as such factors could have a great impact on QoL (14).

Model Validation

Split-half cross-validation will be employed (15) whereby the dataset will be randomly split five times (based on statistician advice, to avoid bias) into separate estimation and validation sets using the random number generator in SPSS version 25. The estimation set will be used to derive the mapping models, whilst the out-of-sample validation set will be used for validating the fitted models. This process will be repeated with each of the five estimations/validation sets after which the sets will be reversed, resulting in a total of 10 complete models. The average predicted health utility estimate for each validation set will be then compared with the observed health utility estimate of the same set.

ANALYSIS

Once the survey is closed, the responses will be viewed, and data will be retrieved by the researcher from the “Analyse” section of the survey dashboard. The data will be transferred and saved as Excel files. The statistical analysis of the data will be carried out using SPSS version 25.

The analysis will involve descriptors such as mean and median of GQ score for each FROM-16 scores (0-32) and calculation of the kappa (κ) coefficient for each combination of cut-offs of FROM-16 values. Other statistics (e.g. Item-total correlations, paired and unpaired t-test and their non-parametric equivalents, such as Wilcoxon signed-rank test, Mann-Whitney U test and Spearman rank correlation). Gender differences in the responses will be compared with the Mann Whitney U test. Correlation between FROM-16 and GQ will be examined using the Spearman rank correlation coefficient.

For the study about the mapping of the FROM-16 scores to EQ-5D utility values, statistical analysis will include ordinal regression and chi square analysis.

Dissemination of results of study

The data will be submitted for presentation at national and international meetings and for publication to appropriate scientific journals.

Funding

There is no external funding for this study. Minor expenses will be covered by the funding assigned to Rubina Shah's PhD within the Dermatology Quality of Life account in the Division of Infection and Immunity.

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Participant Information Sheet- Patient

Study Title: Validation of Family Reported Outcome Measure (FROM-16)

If you are unwell, this also affects the lives of other people in your family. We are trying to find out how well a new questionnaire (FROM-16) helps us to measure this .

Invitation

We'd like to invite you to take part in a Cardiff University study. Thank you for taking the time to read this leaflet and considering whether to take part in this study. Please read the following information carefully before deciding whether to take part. If you have any questions, please contact the study team: contact details are at the end of this leaflet.

About the Study

A person's health condition can have a major impact not only on the quality of life (QoL) of that person but also on their family members, affecting their physical, social and psychological wellbeing. This impact of the disease on the QoL of other family members or partner is mostly ignored but is a huge unmet need. We have created a questionnaire, the 'Family Reported Outcome Measure' (FROM-16), to assess this impact. This questionnaire needs further testing before it can be used by clinicians to help them understand these problems and to try to give the right kind of support to family members and partners.

This study aims to gather information about the impact of having someone in the family with a disease on the quality of life of family members or partner of the patient. The information from this research will allow us to let clinicians know what different scores of family member's quality of life mean and to prove that the questionnaire can be used as part of finding out how well new treatments work from a family member's/partner's perspective.

We hope that eventually, this information will encourage improved patient and family care and that clinicians will be better able to choose treatments that are in the best interests of the patient and his/her family members.

Why have I been invited to take part in this study?

As you have a medical condition, this means you can take part in the study. This study is about measuring the impact of your health condition on your family member using a new questionnaire (FROM-16). Your participation in the study is needed to provide consent for your chosen family member to participate in the study. There will be about 3000 other patients like you and their family members taking part in the study

Do I have to take part in this study?

Participating in this study is voluntary. You may choose not to participate in the study or withdraw at any time.

What does the study involve?

The survey has two sections. You will be asked to complete Section 1 of the survey, which includes providing consent for your family members or partner to participate in the survey and completing basic details about yourself.

Your family member/partner will be asked to complete Section 2, which includes the family member's or your partner's consent to participate in the survey and completing some basic details such as your age, gender and their relationship to the patient. The family member will also complete two short questionnaires, namely FROM-16 and EQ-5D, about how their life has been affected by your medical condition and answer a global question about about their QoL.

How long will it take?

It will take you a few minutes to read the study information and complete the patient consent form.

It will take your relative 5-7 minutes to complete the family consent form and the questionnaires.

What are the benefits of taking part?

We cannot promise the study will help you personally, but the information we get from the study may help to improve the treatment of people like yourself and support their families.

What are the possible risks of taking part?

There is no risk of physical, emotional or psychological harm or distress anticipated.

Will my taking part in this research project be kept confidential?
All information collected from (or about) you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data?' (below).

What will happen to my Personal Data?
You will not be required to provide any personal data (e.g. name, address).
Cardiff University is the Data Controller and is committed to respecting and protecting your data in accordance with your expectations and Data Protection legislation. Further information about Data Protection may be found at https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection.

As the survey data are collected your response will automatically be given a unique number so no-one will know it was you responding. If you decide not to take part, no record of your responses will be kept.

What happens to the data at the end of the research project?
At the end of the project, the data files will be kept for five years in accordance with the University requirements. No identifiable data will be shared with anyone other than the research team.

What will happen to the results of the research project?
The findings will be presented at local, national and international scientific conferences. The results will be made available to the patient support groups contributing to this study. The findings will also be published in an academic scientific journal.

What if there is a problem?

If any problem arises, please contact Ms Rubina Shah via email ShahR45@cardiff.ac.uk.

If you wish to make a complaint relating to this research project, you should contact Prof Andrew Y Finlay (Chief Investigator).

Who is organising and funding this research project?
The research is sponsored and funded by Cardiff University. This research project is not funded by a commercial organisation.

Who has reviewed this research project?
This research project has been reviewed and given a favourable opinion by the School of Medicine Research Ethics Committee, Cardiff University.

Further information and contact details

Participant Information Sheet – Family member

Study Title: Validation of Family Reported Outcome Measure (FROM-16)

If someone in a family is unwell, this also affects you as a family member living with and caring for your unwell relative. We are trying to find out how well a new questionnaire (FROM-16) helps us to measure this

Invitation

We would like to invite you to take part in a Cardiff University study. Thank you for taking the time to read this leaflet and considering whether to take part in this study. Please read the following information carefully before deciding whether to take part. If you have any questions, please contact the study team: contact details are at the end of this leaflet.

About the Study

A person's health condition can have a major impact not only on the quality of life (QoL) of that person but also on their family members, affecting their physical, social and psychological wellbeing. This impact of the disease on the QoL of other family members or partner is mostly ignored but is a huge unmet need. We have created a questionnaire, the 'Family Reported Outcome Measure' (FROM-16), to assess this impact. This questionnaire needs further testing before it can be used by clinicians to help them understand these problems and to try to give the right kind of support to family members and partners.

This study aims to gather information about the impact of having someone in the family with a disease on the quality of life of family members or partner of the patient. Information from the FROM-16 questionnaire will be used to investigate the effectiveness and robustness of the FROM-16 questionnaire in assessing the impact of

the disease on a family member or partner. The information from this research will allow us to let clinicians know what different scores mean of family member's quality of life and to prove that the questionnaire can be used as part of finding out how well new treatments work from a family member's/partner's perspective.

We hope that eventually, this information will encourage improved patient and family care and that clinicians will be better able to choose treatments that are in the best interests of the patient and his/her family members.

Why have I been invited to take part in this study?

As your relative has a medical condition, this means you can participate in the study and help us understand how your relative's heath conditions impacts your quality of life using a new questionnaire (FROM-16). There will also be about 3000 other family members of people with medical conditions taking part in the study

Do I have to take part in this study?

Participating in this study is voluntary. You may choose not to participate in the study or withdraw at any time.

What does the study involve?

The survey has two sections. Section 1 of the survey, which is to be completed by the patient, involves providing consent for you to participate in the survey and completing some basic information about themselves.

You will be asked to complete Section 2 of the survey which includes giving your consent to participate in the survey and completing some basic details about yourself such as your age, gender and relationship to the patient. You will be asked to complete two short questionnaires, namely FROM-16 and EQ-5D, about how your life has been affected by your relative's medical condition and to answer a global question about your QoL.

How long will it take?

It will take on average 5-7 minutes to complete the questionnaires.

What are the benefits of taking part?

We cannot promise the study will help you personally, but the information we get from the study may help to improve the treatment of people such as your relative and support family members such as you.

What are the possible risks of taking part?

There is no risk of physical, emotional or psychological harm or distress anticipated.

Will my taking part in this research project be kept confidential?
All information collected from (or about) you during the research project will be kept confidential, and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data?' (below).

What will happen to my Personal Data?
You will not be required to provide any personal data (e.g. name, address).
Cardiff University is the Data Controller and is committed to respecting and protecting your data in accordance with your expectations and Data Protection legislation. Further information about Data Protection may be found at https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection.

As the survey data are collected, your response will automatically be given a unique number, so no-one will know it was you responding. If you decide not to take part, no record of your responses will be kept.

What happens to the data at the end of the research project?
At the end of the project, the data files will be kept for five years in accordance with the University requirements. No identifiable data will be shared with anyone other than the research team.

What will happen to the results of the research project?
The findings will be presented at local, national and international scientific conferences. The results will be made available to the patient support groups contributing to this study. The findings will also be published in an academic scientific journal.

What if there is a problem?

If any problem arises, please contact Ms Rubina Shah via email

If you wish to make a complaint relating to this research project, you should contact Prof Andrew Y Finlay (Chief Investigator).

Who is organising and funding this research project?
The research is sponsored and funded by Cardiff University. This research project is not funded by a commercial organisation.

Who has reviewed this research project?
This research project has been reviewed and given a favourable opinion by the School of Medicine Research Ethics Committee, Cardiff University.

Further information and contact details
Should you have any questions relating to this research project, you may contact :
Ms Rubina Shah: [redacted]
Prof Andrew Y Finlay: [redacted]
Prof Sam Salek: [redacted]

Thank you for taking the time to read this leaflet

Appendix 3: Survey structure

Validation of the Family Reported Outcome Measure (FROM-16) to assess the impact of a person's health condition on their partner and family members (version 1, 28th Dec 2020)

A person's health condition has a huge impact on the quality of life of the person but sometimes also on their partner and family members. This impact has up to now been largely ignored. Researchers at Cardiff University have created a questionnaire, the Family Reported Outcome Measure (FROM-16) to assess this impact. This questionnaire needs further testing before it can be used and **this can only be achieved with the help of people such as yourself.**

We hope that eventually, this information will:

- encourage improved patient and family care
- help clinicians choose treatments that are better for the needs of the patient and his/her family members.

Please help us by completing this short questionnaire. The first part is to be completed by the patient. The second part is to be completed by that person's partner or family member. It is important that both sections are completed. All answers you provide will be kept anonymous.

A big **thank you** from our research team at Cardiff University

SECTION 1-TO BE COMPLETED BY THE PATIENT

I. Consent to take part

Once you have read the participant information sheet -patient (PIS) (Link to PIS inserted here) please confirm that you are happy for your chosen family member to complete this survey by answering 'yes' to below questions.

1. I have read and understood the Participant Information Sheet

Yes ☐

No ☐

2. I understand that taking part is voluntary and that I can withdraw at any time.

Yes ☐

No ☐

3. **I give my consent for my family member to take part in this survey**

Yes ☐

No ☐

II.Questions about yourself

1. **I am 18 years of age or over**

Yes ☐

No ☐

2. **Please choose your place of residence in the UK**

England ☐

Northern Ireland ☐

Scotland ☐

Wales ☐

3. What is your gender?

Male ☐

Female ☐

Prefer not to say ☐

4. What is your age (in years)?

5. How are you normally occupied?

In paid work..... ☐

Unemployed ..... ☐

Home maker..... ☐

Part-time Job..... ☐

In unpaid work..... ☐

Education / training ..... ☐

Retired..... ☐

Rather not say..... ☐

6. What health condition do you have?

.....

SECTION 2- TO BE COMPLETED BY FAMILY MEMBER / PARTNER

Consent to take part

Once you have read the participant information sheet-family member (PIS) (Link to PIS inserted here) please confirm that you are happy to complete this survey by answering 'yes' to below questions.

1. I have read and understood the Participant Information Sheet

Yes ☐

No ☐

2. I understand that taking part is voluntary and that I can withdraw at any time.

Yes ☐

No ☐

3. I give my consent to take part in this survey

Yes ☐

No ☐

4. What is your gender?

Male ☐

Female ☐

Prefer not to say ☐

5. What is yourage (in years)?

☐

6. How are you normally occupied?

Education / training ..... ☐

Home maker ..... ☐

In paid work..... ☐

In unpaid work..... ☐

Part-time job..... ☐

Rather not say..... ☐

Retired..... ☐

Unemployed..... ☐

7. Is your relative with the health condition your:

Brother/Sister..... ☐

Parent..... ☐

Son/Daughter..... ☐

Spouse/Partner..... ☐

Other(Please specify)..... ☐

FAMILY REPORTED OUTCOME MEASURE (FROM-16) QUESTIONNAIRE

The following questions are about how **your** life is being affected by your family member's condition **at the moment**.
Please mark one box for each of the 16 questions.

Part 1: Emotional

Because of my family member's condition...	Not at all	A little	A lot
1. I feel worried	☐	☐	☐
2. I feel angry	☐	☐	☐
3. I feel sad	☐	☐	☐
4. I feel frustrated	☐	☐	☐
5. It is difficult to find someone to talk to about my thoughts	☐	☐	☐
6. Caring for my family member is difficult	☐	☐	☐

Part 2: Personal and Social Life...

	Not at all	A little	A lot
7. It is hard to find time for myself	☐	☐	☐
8. My every day travel is affected	☐	☐	☐
9. My eating habits are affected	☐	☐	☐
10. My family activities are affected	☐	☐	☐
11. I experience problems with going on holiday	☐	☐	☐
12. My sex life is affected	☐	☐	☐
13. My work or study is affected	☐	☐	☐
14. My relationships with other family members are affected	☐	☐	☐
15. My family expenses are increased	☐	☐	☐
16. My sleep is affected	☐	☐	☐

GLOBAL QUESTION (GQ)

Over the last week, how much has your family member's or partner's health condition affected **your** life?

Please tick one of the following:

0	1	2	3	4
No effect on my life	Small effect on my life	Moderate effect on my life	Very large effect on my life	Extremely large effect on my life

EQ-5D™QUESTIONNAIRE

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

MOBILITY

I have no problems in walking about..... ☐
I have some problems in walking about..... ☐
I am confined to bed..... ☐

SELF-CARE

I have no problems washing or dressing myself..... ☐
I have some problems washing or dressing myself ..... ☐
I am unable to wash or dress myself..... ☐

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

I have no problems doing my usual activities..... ☐
I have some problems doing my usual activities..... ☐
I am unable to do my usual activities..... ☐

PAIN / DISCOMFORT

I have no pain or discomfort..... ☐
I have moderate pain or discomfort..... ☐
I have extreme pain or discomfort..... ☐

ANXIETY / DEPRESSION

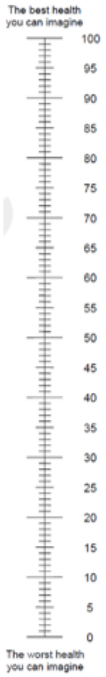
I am not anxious or depressed..... ☐
I am moderately anxious or depressed..... ☐
I am severely anxious or depressed..... ☐

We would like to know how good or bad your health is TODAY

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.



Please enter a number in the box below to indicate how your health is TODAY.

YOUR HEALTH TODAY

Have you read and answered all the questions? Yes

The survey is now complete

Thank you very much for your help

Appendix V: SMREC approval-score interpretation studies

School of Medicine
Yr Ysgol Meddygaeth

Cardiff University
Main Building
Heath Park
Cardiff CF14 4XN
Wales, UK
Prifysgol Caerdydd
Prif Adeilad
Parc y Mynydd Bychan
Caerdydd CF14 4XN
Cymru, Y Deyrnas Unedig

Monday 22nd March 2021

Rubina Shah
Division of Infection & Immunity
School of Medicine
Cardiff University

Dear Rubina

Research project title: Development of score interpretation bands for the Family Reported Outcome Measure (FROM-16) and mapping of the FROM-16 scores to EQ-5D utility values
SREC reference: 21/19

The School of Medicine Research Ethics Committee ('Committee') reviewed the above application electronically on Thursday 18th February 2021. A revised application was considered by the Committee at a meeting on Wednesday 17th March 2021.

Ethical Opinion
The Committee gave a favourable ethical opinion of the above application on the basis described in the application form, protocol and supporting documentation, **subject to the conditions** specified below.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the research project.

1. Under the section "What does the study involve?" In all the Participant Information Sheets, please rephrase "answer a global question about the severity of their QoL impairment as "answer a global question about their QoL" (otherwise it still seems to imply that taking care of someone is a purely negative experience).
2. Please ensure that any personal phone numbers are removed from all study documents.

Whilst the Committee does not propose to conduct a further review of your application/revised research project documents following implementation of the conditions above, you should notify the Committee once all conditions have been met and provide copies of any revised documentation with updated version numbers before the research commences.

Additional approvals
This letter provides an ethical opinion only. You must not start your research project until all appropriate approvals are in place.

Amendments
Any substantial amendments to documents previously reviewed by the Committee must be submitted to the Committee via email to Claire Evans (EvansCR9@cardiff.ac.uk) for consideration and cannot be implemented until the Committee has confirmed it is satisfied with the proposed amendments.

You are permitted to implement non-substantial amendments to the documents previously reviewed by the Committee but you must provide a copy of any updated documents to the Committee via email to Claire Evans (EvansCR9@cardiff.ac.uk) for its records.

Monitoring requirements
The Committee must be informed of any unexpected ethical issues or unexpected adverse events that arise during the research project. In addition to this, the Committee request an end of project report sent to the Committee via email to Claire Evans [redacted] This must be sent along with confirmation that your research project has ended and sent within the three months of the research project completion.

Appendix V: SMREC approval- FROM-16 scores interpretation studies

Documents reviewed by Committee
The documents reviewed by the Committee were:

Document	Version	Date
Application	V1.3	21/01/2021
Study Protocol	V3	-
Participant Information Sheet (Patient)	-	-
Participant Information Sheet (family member)	-	-
Survey Structure	V1	28/12/2020
Ethics Response	-	04/03/2021
Application Form	-	04/03/2021
Study Protocol	V3	-
Participant Information Sheet (Patient)	-	-
Participant Information Sheet (family member)	-	-
Survey Structure	V1	28/12/2020
Participant Invitation email template	-	-

Complaints/Appeals

If you are dissatisfied with the decision made by the Committee, please contact the Chair of the Committee via the Committee Secretary (EvansCR9@cardiff.ac.uk) in the first instance to discuss your complaint. If this discussion does not resolve the issue, you are entitled to refer the matter to the Head of School for further consideration. The Head of School may refer the matter to the University Research Integrity and Ethics Committee (URIEC), where this is appropriate. Please be advised that URIEC will not normally interfere with a decision of the Committee and is concerned only with the general principles of natural justice, reasonableness and fairness of the decision.

Please use the Committee reference number on all future correspondence.

The Committee reminds you that it is your responsibility to conduct your research project to the highest ethical standards and to keep all ethical issues arising from your research project under regular review.

You are expected to comply with Cardiff University's policies, procedures and guidance at all times, including, but not limited to, its Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and our Research Integrity and Governance Code of Practice.

Yours sincerely,

[redacted]

Chair, School of Medicine Research Ethics Committee

Dear Rubina,

Research project title: Development of score interpretation bands for the Family Reported Outcome Measure (FROM-16) and mapping of the FROM-16 scores to EQ-5D utility values
SREC reference: 21/19

Thank you for sending the attached response, updated invitation email, and updated application in response to our letter to you dated Monday 22nd March 2021 confirming a favourable ethical opinion for this study with conditions. I can confirm that the conditions as outlined in our letter have been met and no further action is required from the Committee. Please keep a copy of this email with the letter from March 22nd for your records.

Thanks,

[redacted]

Research Manager,
Research Support

Rheolwr Ymchwil,
Cefnogi Ymchwil

Appendix VI: License agreement Euroqol-FROM-16 validation studies

License agreement EQ-5D-3L Laptop/Desktop

Agreement Number: 159218

EQ-5D

BETWEEN THE FOLLOWING PARTIES:

1. **STICHTING EUROQOL RESEARCH FOUNDATION, also trading as EUROQOL RESEARCH FOUNDATION**, a foundation incorporated under the laws of The Netherlands, having its registered office in Rotterdam, and its principal place of business in (3068 AV) Rotterdam at the Marten Meesweg 107, The Netherlands; (hereinafter "**Licensor**")

2. **Rubina Shah**, a Cardiff University PhD student governed by public law incorporated under the laws of United Kingdom, having its registered office in Cardiff and its principal place of business is in (CF14 4XN) Cardiff, at the 3rd Floor Glamorgan House Heath Park, United Kingdom; (hereinafter "**Licensee**"),

   Both parties, together or separately, hereinafter also referred to as "**Party**" or "**Parties**".

WHEREAS:

A. Licensor has developed a questionnaire known as the EQ-5D questionnaire ("**EQ-5D**") which is designed to assess patients' quality of life. The EQ-5D contains a descriptive system (5 questions) as well as a visual-analogue-scale ("**VAS**") together these constitute the full version ("**Full Version**"). The EQ-5D questionnaire is available in 3 level ("**EQ-5D-3L**"), 5 level ("**EQ-5D-5L**") and Y version ("**EQ-5D-Y**") format, in various Languages and an offline and a web version. An overview of the available versions can be found at **www.euroqol.org**;

B. Licensor is the proprietor of all Intellectual Property Rights, including but not limited to copyright and neighboring rights, patent rights and rights relating to know how, database rights, trade mark and trade name rights, and design rights, in, or in connection with EQ-5D (any version) and the name EQ-5D (any version);

C. Licensor grants Licensee a non-exclusive and non-transferable License ("**License**") to use the Full Version of the EQ-5D-3L on laptops/desktops ("**EQ-5D-3L Laptop/Desktop**") for solely the designated purposes and Licensor has agreed to grant Licensee its permission to use the EQ-5D-3L Laptop/Desktop, under the conditions set out in this Agreement and the Appendices thereto.

Appendix VI: License agreement Euroqol-FROM-16 validation studies

NOW IT IS HEREBY AGREED AS FOLLOWS:

Article 1 – Definitions

1. In this Agreement the following capitalized terms shall have the following meaning:

   a) **Agreement** means this License agreement including the recital and the Appendices referred to;
   b) **Appendix** is an appendix to this Agreement;
   c) **Effective Date** means the date on which this License enters into effect, which is the date of **24th of Feb 2021**;
   d) **Language** is a localized translation of the EQ-5D-3L Laptop/Desktop to be used within a Territory;
   e) **Liability** is the obligation of a Party arising from an unforeseen adverse event or damage to the other Party, the settlement of which would result in the transfer or use of assets, provision of services or other yielding of economic benefits;
   f) **Intellectual Property Rights** means copyrights, neighbouring rights, patents, design rights, trademarks, service marks, database rights, know-how, trade or business names, rights in confidential information and all other intellectual property rights and rights of a similar nature, whether registered or unregistered and wherever in the world such rights arise. Licensor's Intellectual Property Rights include the aforementioned rights regarding or in connection with EQ-5D (any version) and the name EQ-5D (any version);
   g) **Study** is a well-defined experiment aimed at addressing a particular research question, but not primarily aimed at the collection of a large amount of data, as described in the Study Protocol;
   h) **Term** means the term of this Agreement as set out in article 8 of this Agreement;
   i) **Territory** is the geographic region in which the EQ-5D-3L Laptop/Desktop is to be applied and is described in Appendix 1 to this Agreement.
   j) **Vendor** is a third-party arranging hardware and reproductions of EQ-5D versions on behalf of Licensee.

2. Headings have been inserted for convenience of reference only and do not affect the interpretation of any of the provisions of this Agreement.
3. A reference in this Agreement to an article or schedule is to the relevant article of or schedule to this Agreement.

Article 2 - License

1. Licensor hereby grants to Licensee from the Effective Date and for the Term of this Agreement a non-exclusive and non-transferable License to use the EQ-5D-3L Laptop/Desktop for solely the designated purposes as described in this Agreement.
2. The License granted under this Agreement is provided to Licensee free of charge.
3. The License is limited to the Languages set out in Appendix 1, unless written permission is provided by Licensor for the use of the Language in another country.
4. The License applies under the condition that that Licensee:

Appendix VI: License agreement Euroqol-FROM-16 validation studies

(i) only uses Language(s) supplied or approved by Licensor;
(ii) uses the Language(s) solely in the Territory referred to in Appendix 1;
(iii) always uses the Full Version of the EQ-5D-3L Laptop/Desktop .

5. Unless agreed otherwise, Licensee is explicitly not entitled to translate, modify, distribute for commercial purposes, abridge, convert, alter, amend, communicate to the public, the EQ-5D-3L Laptop/Desktop , including but not limited to any minor or significant change in wording or organization of the EQ-5D-3L Laptop/Desktop .
6. Licensee shall not sub-license, assign, transfer, pledge or otherwise encumber its rights and/or obligations under this Agreement, without prior written approval of Licensor.
7. Parties agree that, except as required by law, they will not use the name, trade name, trademark, or other identifier of the other party for any advertising, promotion, press, media or other public purpose except upon advance written notice of approval. The EQ-5D (any version) used by Licensee shall incorporate the following wording: '*© EuroQol Research Foundation. EQ-5D™ is a trademark of the EuroQol Research Foundation.*
8. Licensor will keep secret and confidential all information supplied by Licensee.

Article 3 – Intellectual Property Rights

1. All Intellectual Property Rights, in, or in connection with the EQ-5D-3L Laptop/Desktop , flowchart, legend, dictionary and manual, are vested and shall remain vested in Licensor.
2. Licensee is not allowed to modify, alter, amend the EQ-5D-3L Laptop/Desktop or develop any (new) translation of the EQ-5D-3L Laptop/Desktop version, without permission of Licensor.
3. All Intellectual Property Rights deriving from any modification, alteration, amendment or any (new) translation of the EQ-5D-3L Laptop/Desktop , flowchart, legend, dictionary or manual by Licensee pursuant to this Agreement will vest in Licensor. Upon the signing of this Agreement, Licensee automatically transfers and assigns in advance irrevocably all Intellectual Property Rights in, or in connection with any modification, alteration, amendment or any (new) translation of the EQ-5D-3L Laptop/Desktop , flowchart, legend, dictionary or manual, which transfer Licensor hereby accepts. Licensee warrants that the Intellectual Property Rights shall be assigned and transferred to Licensor without any encumbrance pursuant to article 3.3. In addition, any moral rights shall to the best of Licensee's knowledge be waived at the termination of this Agreement.
4. Upon the first request of Licensor and in as far as is necessary, Licensee shall provide all co-operation and assistance to ensure that the Intellectual Property Rights as set out in the above article 3.3 are transferred and assigned to Licensor, including, but not limited to the immediate execution or procurement of all such documents necessary to assign and transfer the aforementioned Intellectual Property Rights in and to the EQ-5D-3L Laptop/Desktop to Licensor.
5. The Intellectual Property Rights in the software or hardware developed by Licensee or Vendor for making available the EQ-5D-3L Laptop/Desktop for the designated purposes are and shall remain vested in Licensee or, in as far as is relevant, in Vendor.

Appendix VI: License agreement Euroqol-FROM-16 validation studies

Article 4 - Process

1. Licensee is required to register or verify the registration of the Study in which the EQ-5D-3L Laptop/Desktop will be used at the website of Licensor by using the online registration form.
2. Licensee requires the prior written consent from Licensor for use of the EQ-5D-3L Laptop/Desktop version by any Vendor, which Licensee engages in connection with the use of the EQ-5D-3L Laptop/Desktop version. Licensor agrees to use its best efforts to respond to all such requests within five (5) business days.
3. Licensee has permission to use the EQ-5D-3L Laptop/Desktop for solely the designated purposes in accordance with this Agreement and the instructions of Licensor.
4. Licensor shall provide the latest source text (i.e. in English) plus translations of the source text (if applicable) to Licensee in MS Excel format. Licensee shall reproduce the EQ-5D-3L Laptop/Desktop in the layout prescribed by Licensor. Licensee shall collaborate with Licensor regarding elements of the EQ-5D-3L Laptop/Desktop and/or translations of the text that might be difficult to reproduce.
5. Before making the EQ-5D-3L Laptop/Desktop version available for the purpose of the Study Licensee shall provide screenshots of the reproduced EQ-5D-3L Laptop/Desktop version plus translations to Licensor for approval. Licensor agrees to use its best efforts to review the provided screenshots within ten (10) business days, unless otherwise agreed by parties. The layout/screenshots of the reproduced EQ-5D-3L Laptop/Desktop are shown in Appendix 2 of this Agreement.
6. For the avoidance of doubts, Licensor will be the final arbiter of whether or not a reproduced EQ-5D-3L Laptop/Desktop version is compliant. Licensee shall not make the EQ-5D-3L Laptop/Desktop version available to Study Participants without Licensor's prior written approval.

Article 5 - Notifications

1. All requests for approval, notifications etc. by Licensee shall be sent to:
   Gerben Bakker, User Support Officer, Marten Meesweg 107, 3068 AV Rotterdam, The Netherlands [redacted]
2. All notifications etc. by Licensor shall be sent to:
   [redacted]

Article 6 – Study Data

1. Licensee is the proprietor with regard to all personal and other data which is collected in connection with the use of the EQ-5D. Parties agree that Licensee will be solely responsible with regard to the compliance with all applicable laws and regulations in respect of the protection of personal data.

2. Licensee shall indemnify and hold Licensor harmless against any and all claims, liabilities, costs and expenses, which may arise out of any applicable law or regulation in respect of the protection of personal data.

Article 7 - Liability, indemnification and penalty payment

1. Licensor's total Liability relating to or in connection with this Agreement shall be limited to compensation of Licensee's direct loss that is attributable to Licensor. Licensor shall not be liable for any other damages or losses, including but not limited to any indirect, consequential or special damages or losses. In no event shall Licensor's total Liability, whether arising from contract, tort or any other kind of Liability, exceed an amount of EUR 600 (six hundred Euros) for the term of this Agreement.
2. For the avoidance of any doubt, Licensor is not liable towards Licensee for any damage resulting from the misuse of the EQ-5D-3L Laptop/Desktop or any other EQ-5D product or version.
3. The limitations and exclusions of Liability mentioned in this article 7 shall not apply in the event and to the extent that the damage is the result of the intent or gross negligence of Licensor or its executive staff.
4. Licensee shall indemnify Licensor and hold Licensor harmless against any and all damages, claims, liabilities, costs and expenses, which may arise out of or are related to the (mis)use and/or reproduction of the content of the EQ-5D-3L Laptop/Desktop provided by Licensor to Licensee, except in case of gross negligence or wilful misconduct by Licensor.
5. In the event that Licensee fails to comply with any of the terms as set forth in this Agreement, Licensee shall pay Licensor – after written notification – for each event a penalty payment of EUR 10,000 (say: ten thousand Euros) without prejudice to Licensor's right to i) seek compensation for the actual amount of the losses incurred in excess of the amount of the penalty and/or ii) terminate the License granted in article 2 of this Agreement and/or the Agreement in its entirety with immediate effect, all without Licensee being entitled to any compensation or damages.
6. If, at any time during the term of this Agreement, Licensee learns of any infringement by a third party of any Intellectual Property Rights in connection with the EQ-5D-3L Laptop/Desktop , Licensee shall promptly notify Licensor. Licensor shall at their discretion decide to institute or not institute proceedings against the infringing party.

Article 8 – Term and termination

1. This Agreement commences on the Effective Date and, except in case of earlier termination as described in article 8.2, shall continue to be in force until the end of the Study.
2. Either Party may terminate this Agreement immediately by giving written notice to the other Party, in the event that:

   (i) the other Party commits any material breach of its obligations under this Agreement and, after having been notified to remedy the breach, fails to do so within fifteen (15) days following receipt of notice of such breach;

(ii) the other Party is adjudicated bankrupt or insolvent, has been granted a suspension of payment, administration, supervision or makes a general assignment for the benefit of its creditors;
(iii) compulsorily or voluntarily enters into liquidation, except for the purposes of a bona fide reconstruction or amalgamation and with the prior written approval of Licensor; or
(iv) the other Party is dissolved.

3. In addition to the above, Licensor may also terminate this Agreement in the event that Licensee directly or indirectly comes under the control of a third party or enters into a legal merger with such third party.
4. Licensee is required to notify Licensor in writing about any restructuring, merger or acquisition of the Licensee within thirty (30) days from the day of formal announcement. Any resulting change in control of ownership of Licensee provides Licensor the possibility to revise the terms of this Agreement.
5. In the event that this Agreement is terminated as described in article 8.2, the License granted ceases immediately and Licensee is not entitled to use the EQ-5D-3L Laptop/Desktop , in any form, any longer.
6. Termination shall not affect any article of this Agreement that by its nature and intent remains valid after termination. Terms and conditions included in this Agreement whose nature require them to be applicable even after termination of this Agreement will continue to exist after such termination, including but not limited to the following articles of this Agreement: 3, 7, 9, 10.

Article 9 - Dispute resolutions and governing law

1. Any dispute arising out of or in connection with this Agreement, including any question regarding its existence, validity or termination, shall be referred to and finally resolved by arbitration conducted in accordance with the International Chamber of Commerce Rules for Arbitration ("**ICC Rules**") for the time being in force, which rules are deemed to be incorporated by reference.
2. The number of arbiters shall be one (1) and shall be appointed by the Court of Arbitration. In principle, the arbiter shall not have the nationality of either of the parties. The place of arbitration shall be Rotterdam. The arbitral procedure shall be conducted in the English Language. The arbitral court shall decide in accordance with the rules of law.
3. Notwithstanding the foregoing, nothing shall affect either Party's right to seek an immediate remedy of an injunction, specific performance or similar court order to enforce the defaulting Party's obligations.
4. This Agreement shall be governed by and construed in accordance with the laws of the Netherlands.

Article 10 – Miscellaneous

1. If any provision of this Agreement is declared to be void, invalid or unlawful by any court or tribunal of competent jurisdiction, such provision shall be deemed severed from the remainder of this Agreement and the balance shall remain in full force and effect. Parties shall use all reasonable endeavors to replace the invalid or unenforceable provision by

a valid provision, the effect of which is as close as possible to the intended effect of the invalid or unenforceable provision.

2. No delay or indulgence by either Party in enforcing any of the terms and conditions of this Agreement or the granting of time by either Party to the other shall prejudice, affect or restrict the rights and powers of the said Party nor shall any waiver by either Party of any breach of this Agreement operate as a waiver of or in relation to any subsequent or any continuing breach of it.
3. Any failure to exercise or any delay in exercising a right or remedy provided by the Agreement or at law will not constitute a waiver of the right or remedy or a waiver of any other rights or remedies. A waiver of a breach of any of the terms and conditions of the Agreement or of a default under the Agreement will not constitute a waiver of any other breach or default and will not affect the other terms and conditions of the Agreement.
4. Licensee shall strictly adhere to all applicable laws and regulations. This amongst other things means that Licensee acknowledge that under the Agreement it is only allowed to process any personal data in as far as such processing takes place in accordance with all rules, regulations and principles for the protection of personal data that are applicable.
5. This Agreement may only be amended by a document in writing signed by duly authorized officers of both Parties hereto.

AGREED AND SIGNED

For and on behalf of	For and on behalf of
EuroQol Research Foundation:	**Rubina Shah:**

[redacted]

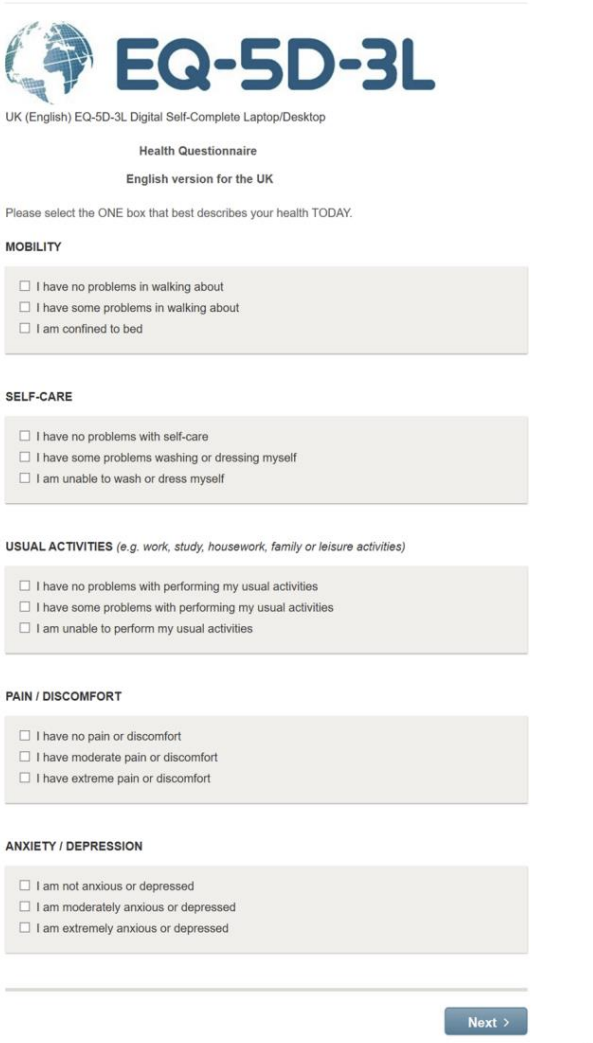
Appendix VI: License agreement Euroqol-FROM-16 validation studies

License agreement EQ-5D-3L Laptop/Desktop

Agreement Number: 159218

EQ-5D

APPENDIX 2 – Screenshot



EuroQol Research Foundation
Marten Meesweg 107
3068 AV Rotterdam, The Netherlands
Non-commercial Web v1.7

T +31 88 440 01 90
E userinformationservice@euroqol.org
www.euroqol.org

Appendix VI: License agreement Euroqol-FROM-16 validation studies

License agreement EQ-5D-3L Laptop/Desktop

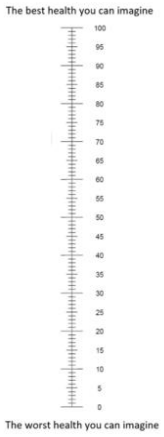
Agreement Number: 159218

EQ-5D

We would like to know how good or bad your health is TODAY.

You will see a scale numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.



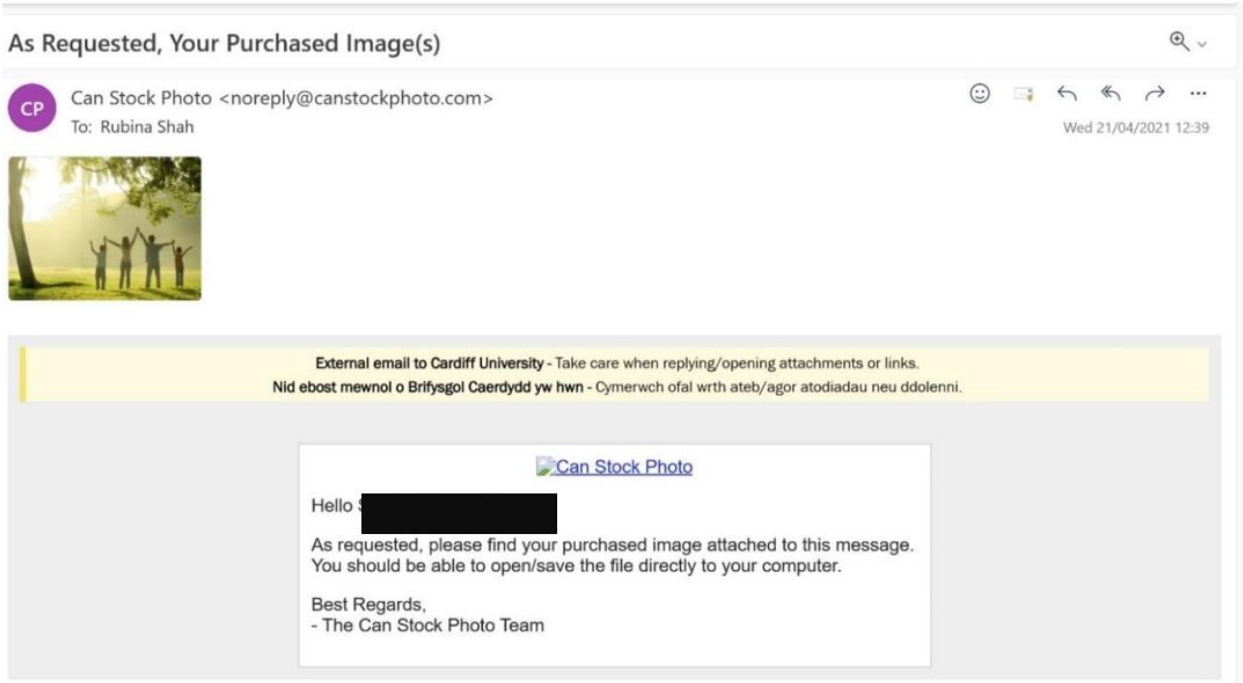
Please enter a number in the box below to indicate how your health is TODAY.

YOUR HEALTH TODAY =

EuroQol Research Foundation
Marten Meesweg 107
3068 AV Rotterdam, The Netherlands
Non-commercial Web v1.7

T +31 88 440 01 90
E userinformationservice@euroqol.org
www.euroqol.org

Appendix VII: Receipt of image purchased from the Can Stock



This IMAGE was used for study promotion

Appendix VIII: List of Patient Support Groups approached

	UK patient support group approached	Participated
1.	**Action for Pulmonary Fibrosis**	Yes
2.	**Against breast cancer**	Yes
3.	Age UK	No
4.	Allergy UK-follow	No
5.	**Alopecia UK**	Yes
6.	Alzheimer's Society	No
7.	Alzheimer's Research UK	No
8.	Anxiety UK	No
9.	**Arthritis Action UK**	Yes
10.	Rethink UK	No
11.	BHF	No
12.	Bowel Cancer UK	No
13.	**Breast Cancer Now**	Yes
14.	Breast cancer support group Scotland	No
15.	British Liver Trust	No
16.	Cancer Focus NI	No
17.	Cancer Research UK	No
18.	**Carer Wales**	Yes
19.	**Cerebral Palsy CP (SCOPE)**	Yes
20.	Changing Faces (CF)	No
21.	**CHSS (Chest, Heart and Stroke Scotland)**	Yes
22.	Coeliac UK	No
23.	Colostomy UK	No
24.	**Crohn's & Colitis UK**	Yes
25.	Cystic Fibrosis	No
26.	Dementia UK	No
27.	**Diabetes UK**	Yes
28.	**Diabetes UK Sheffield**	Yes
29.	**Epilepsy Action**	Yes
30.	**Epilepsy Society**	Yes
31.	**Fibromyalgia and chronic pain support group UK**	Yes
32.	**Fight for Sight**	Yes
33.	Follicular Lymphoma	No
34.	**Genetic Alliance UK**	Yes
35.	**Glaucoma UK**	Yes
36.	Heart research UK	No
37.	hello@suffolkfamilycarers.org	No
38.	**Huntington's disease Association**	Yes
39.	**IBS patient support group**	Yes
40.	**JDRF.org.uk**	Yes

Appendix VIII: List of Patient support groups approached

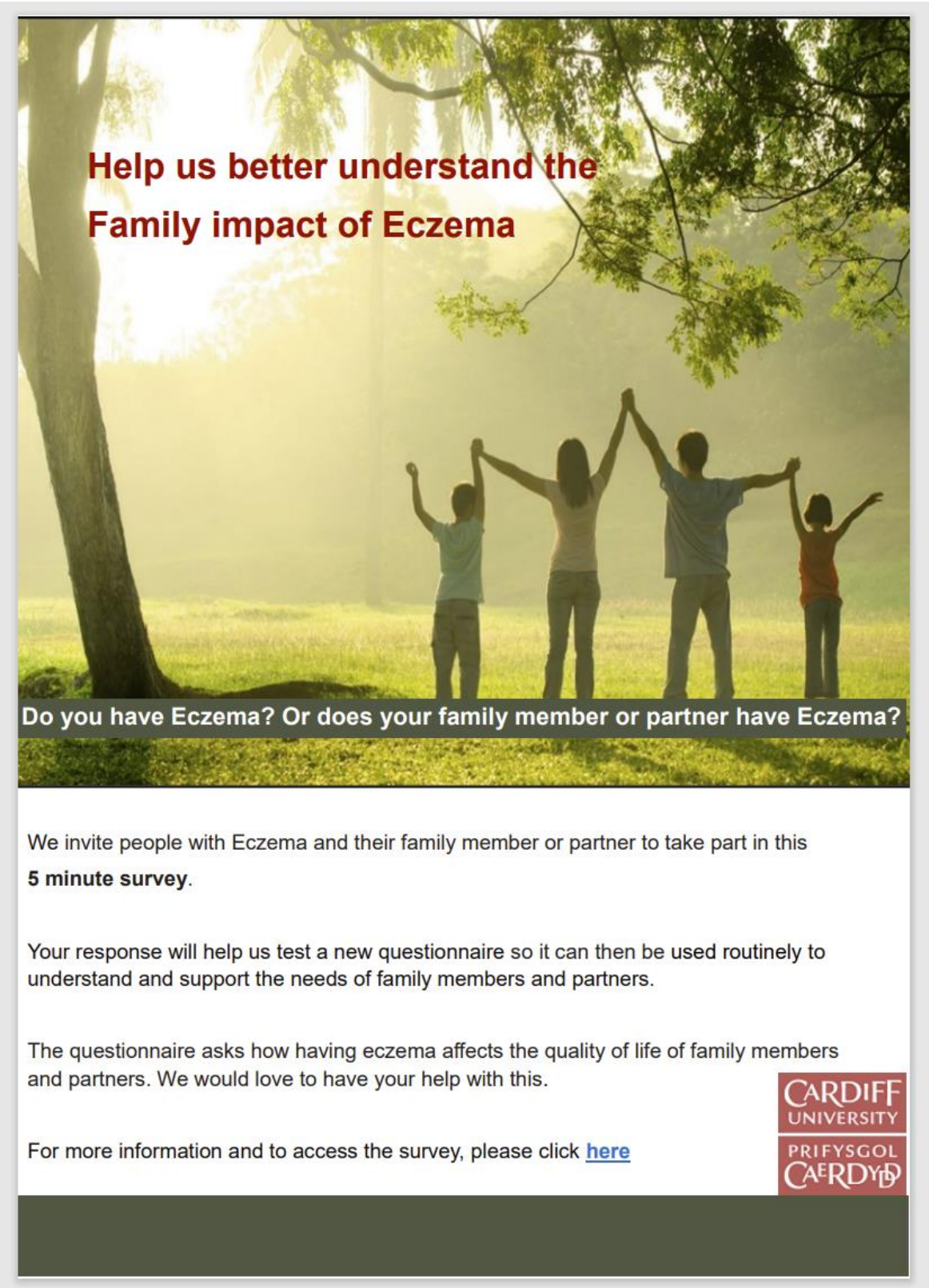
41.	**Kidney Patient Involvement Network**	Yes
42.	**Kidney Wales**	Yes
43.	Leukaemia UK	No
44.	Living with Osteopenia & Osteoporosis	No
45.	**Lymphoma Action**	Yes
46.	Lymphoma Association –	No
47.	Macular Society	No
48.	**Metabolic Support UK**	Yes
49.	**Myelodysplastic Syndromes (MDS)**	Yes
50.	**ME Research UK**	Yes
51.	**Melanoma Action and Support Scotland**	Yes
52.	Melanoma Scotland-	No
53.	Melanoma UK	No
54.	**Meningitis Now**	Yes
55.	Mental health UK	No
56.	**Migraine Trust**	Yes
57.	**Motor Neurone Disease Association**	Yes
58.	**MS registry**	Yes
59.	**MS Trust**	Yes
60.	**Myeloma UK**	Yes
61.	National AIDS Trust	No
62.	**National Eczema Society**	Yes
63.	NICHS -Northern Ireland Chest Heart and Stroke	No
64.	Northern Ireland Kidney Patients' Association – NIKPA	No
65.	Osteoporosis Support (UK ONLY)	No
66.	Osteoporosis UK	No
67.	Blood cancer UK	No
68.	**Ovacome-ovarian cancer charity**	Yes
69.	**Pain Concern**	Yes
70.	**Pancreatic Cancer UK**	Yes
71.	**Parents of children with Type 1 Diabetes**	Yes
72.	**Parkinson's UK**	Yes
73.	**Pernicious Anaemia Society**	Yes
74.	**Polycystic Kidney Disease Charity**	Yes
75.	**Progressive Supranuclear Palsy Association**	Yes
76.	Prostates Scotland	No
77.	Nottingham Support Group for carers of children with eczema	No
78.	**Prostate Cancer UK**	Yes
79.	**Psoriasis and Psoriatic Arthritis (PAPAA)**	Yes
80.	**Psoriasis Association**	Yes
81.	**Pulmonary Hypertension Association UK**	Yes
82.	Research Autism	No

Appendix VIII: List of Patient support groups approached

83.	Restless Legs Syndrome RLS	No
84.	**Retina UK**	Yes
85.	**Royal National Institute for the Deaf**	Yes
86.	Royal Osteoporosis Society-	No
87.	Sarcoma UK	No
88.	Shift MS	No
89.	Sickle Cell Society	No
90.	**Functional Neurological Disorder- FND Hope UK**	Yes
91.	South Thames Sickle Cell & Thalassaemia Network	No
92.	**Spinal Muscular Atrophy UK**	Yes
93.	Stroke UK	No
94.	**The Asthma UK and British Lung Foundation Partnership**	Yes
95.	**The Brain Tumour Charity**	Yes
96.	**The encephalitis society**	Yes
97.	**The National Rheumatoid Arthritis Society**	Yes
98.	**The Patients Association**	Yes
99.	Leukaemia Care	No
100.	**UK Parents of Kids with IBD (Ulcerative Colitis and Crohn's)**	Yes
101.	Bladder health UK	No
102.	**Urostomy Association**	Yes
103.	York Haematology Support Group	No
104.	Womb Cancer Support UK	No
105.	**Verity PCOS UK.**	Yes
106.	versusarthritis.org	No

	Research support platform	Participated
1.	**HealthWise Wales**	Yes
2.	**Autism research centre, Cambridge database**	Yes
3.	**Join Dementia UK**	Yes

Appendix IX: Example of poster used in study promotion



Appendix X: A lay summary for family members/partners

What does the Family Reported Outcome Measure (**FROM-16**) score mean?

Study Summary Report for Family Members/Partners

Impact of a Relative's Disease on Family Members/Partners

Date: July 2023

[redacted]

What does the Family Reported Outcome Measure (**FROM-16**) score mean?

Background

The lives of family members are often affected by a person's health condition, but this important impact is often ignored. Our research team at Cardiff University has created a simple questionnaire, the **'Family Reported Outcome Measure' (FROM-16)**, to measure this impact. FROM-16 comprises 16 items with a total score range of 0 – 32 (lower scores mean better Quality of Life (QoL)). To make FROM-16 suitable for routine practice and help clinicians understand what different FROM-16 scores mean, **we conducted a study to put scores into meaningful score bands.**

Methods

In 2021 we asked family members (aged 18 years and older) of patients registered with 58 patient support groups, including patient research support groups such as "HealthWise Wales", "Join Dementia" and "Autism Research Centre", to complete an online questionnaire. Family members were asked to complete a FROM-16 questionnaire and another standard questionnaire called the Euroqol Five Dimension (EQ-5D-3L). The family members also answered a question about the overall impact of their relative's health condition on their QoL with a 5-point response (**No effect** on QoL, **small effect**, **moderate effect**, **very large effect** and **extremely large effect** on QoL). We used this information and family members' FROM-16 responses to create **five score bands for FROM-16.**

Results

A total of 4,413 family members of people with more than **200 health conditions** completed the questionnaire. This meant that we included family members with a wide range of impacts from no effect to extremely large effect on their QoL, which was important to create the bands. **Figure 1** shows the proposed FROM -16 banding. **This study has been published in BMJ Open and can be**

accessed at https://bmjopen.bmj.com/content/bmjopen/13/3/e066168.full.pdf. A copy is also attached.

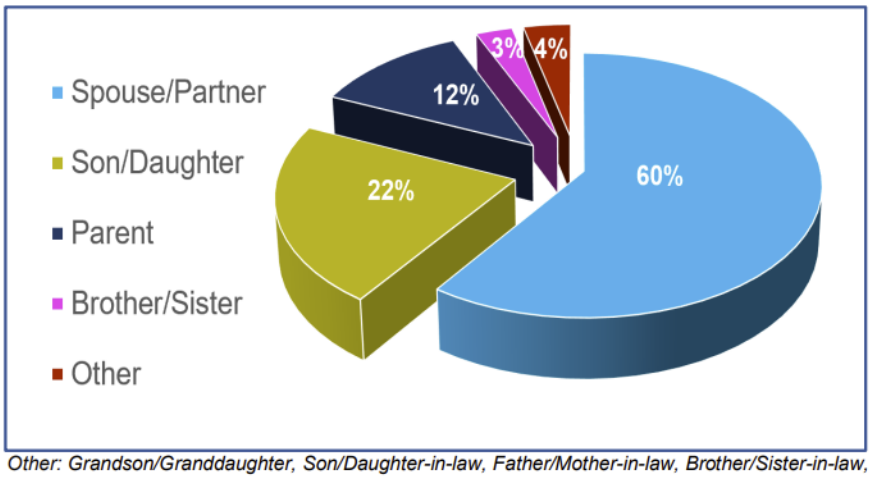
Figure 1 Proposed FROM -16 score banding: Impact on the QoL of the family member/partner

FROM-16 Banding	0-1	2-8	9-16	17-25	26-32
	No effect	Small effect	Moderate effect	Very large effect	Extremely large effect

This means that healthcare professionals such as Doctors, Nurses or Pharmacists can now identify family members/partners who are most affected and provide them with the right kind of support.

65% of the family members were females. 60% of the family members were spouses/partners, followed by sons/daughters, parents and brothers/sisters of the person with the health condition (see Figure 2).

Figure 2 Family member's relationship to the patient



Other: Grandson/Granddaughter, Son/Daughter-in-law, Father/Mother-in-law, Brother/Sister-in-law, Uncle/Aunt, Nephew/Niece, Step-parent, Step-Son/daughter, friend

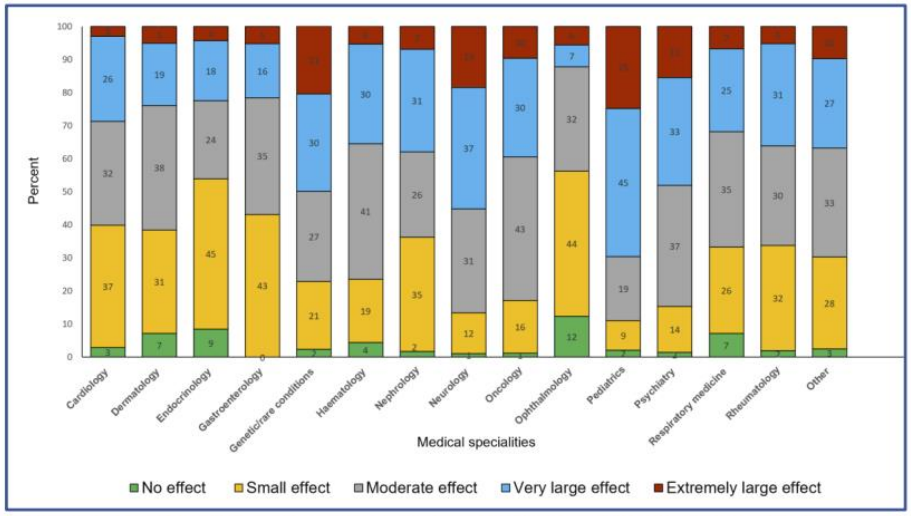
This means FROM-16 can now be used to understand the wider impact of a relative's disease.

The average FROM-16 score for family members was 15.2 **(range 0-32). However 42% of family members had a FROM-16 score of 17 or over, meaning a "Very**

2

large effect on their quality of life". We compared the FROM-16 scores of family members of patients across different disease areas. Although the impact on family members can be seen across all areas in **Figure 3** below**, parents/family members of children** were most impacted, with **70%** experiencing **very large and extremely large effects**, followed **by family members of people with neurological 56%, genetic 51%** and **mental health conditions 48%** (See **Figure 3**). The **'Other'** category included **13 disease areas**; of these the family members of people with **critical illness**, **stroke, movement disorders** and **urological conditions** were most affected.

Figure 3 QoL impact on family members of patients across different disease areas



Other: Audiology, Chronic Pain, Critical Care, Gynaecology, Hepatology, Immunology, Infectious diseases, Movement disorder, Multiple health conditions, Orthopaedics, Otolaryngology, Stroke, Urology and Wound Healing.

These results show that there is a great need to measure this impact in routine care to identify and provide support to family members.

As well as the "banding" work, results from this study were also used to create a way **to use FROM-16 to find out how well new treatments work. When this is published you will be able to find out about this on the FROM-16 website**: https://www.cardiff.ac.uk/medicine/family-reported-outcome-measure.

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Appendix XI: Euroqol Five Dimension-three level (EQ-5D-3L)

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

MOBILITY *(walking about)*

I have no problems walking about ❑
I have some problems walking about ❑
I have a lot of problems walking about ❑

LOOKING AFTER MYSELF

I have no problems washing or dressing myself ❑
I have some problems washing or dressing myself ❑
I have a lot of problems washing or dressing myself ❑

DOING USUAL ACTIVITIES *(for example, going to school, hobbies, sports, playing, doing things with family or friends)*

I have no problems doing my usual activities ❑
I have some problems doing my usual activities ❑
I have a lot of problems doing my usual activities ❑

HAVING PAIN OR DISCOMFORT

I have no pain or discomfort ❑
I have some pain or discomfort ❑
I have a lot of pain or discomfort ❑

FEELING WORRIED, SAD OR UNHAPPY

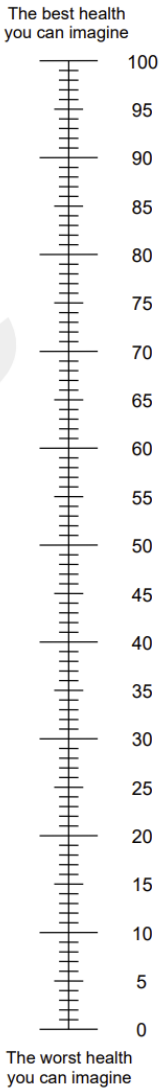
I am not worried, sad or unhappy ❑
I am a bit worried, sad or unhappy ❑
I am very worried, sad or unhappy ❑

Appendix XI: Euroqol Five Dimension-three level (EQ-5D-3L)

UK version

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line that shows how your health is TODAY.
- Now, write the number you marked on the line in the box below.

YOUR HEALTH TODAY =



Appendix XII: SPSS syntax for computing EQ-5D-3L utility values

Computing EQ-5D index values with SPSS using the MVH-A1 TTO value set

The variables for the 5 dimensions of the EQ-5D descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions in the EQ-5D health profile (i.e. 1, 2, or 3). The variable 'UK_TTO' contains the values of the EQ-5D index on the basis of the MVH TTO set of weights.

You can copy and paste the syntax below directly into an SPSS syntax window.

```
*********************************************************************
*          SPSS syntax code for the computation of                  *
*          index values with the UK MVH-A1 TTO value set*
*********************************************************************

compute UK_TTO = 1.0.

if (mobility eq 2) UK_TTO = UK_TTO - 0.069.
If (mobility eq 3) UK_TTO = UK_TTO - 0.314.

if (selfcare eq 2) UK_TTO = UK_TTO - 0.104.
if (selfcare eq 3) UK_TTO = UK_TTO - 0.214.

if (activity eq 2) UK_TTO = UK_TTO - 0.036.
if (activity eq 3) UK_TTO = UK_TTO - 0.094.

if (pain eq 2) UK_TTO = UK_TTO - 0.123.
if (pain eq 3) UK_TTO = UK_TTO - 0.386.

if (anxiety eq 2) UK_TTO = UK_TTO - 0.071.
if (anxiety eq 3) UK_TTO = UK_TTO - 0.236.

if (mobility ne 1 or activity ne 1 or selfcare ne 1 or pain ne 1 or anxiety ne 1)
 UK_TTO = UK_TTO - 0.081.

if (mobility eq 3 or selfcare eq 3 or activity eq 3 or anxiety eq 3 or pain eq 3)
 UK_TTO = UK_TTO - 0.269.

if (missing(mobility) or missing(activity) or missing(selfcare) or missing(pain) or
missing(anxiety))
 UK_TTO = 9.

missing values UK_TTO (9).

execute.
```

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Appendix XIII: R software syntax for 1000 Monte Carlo simulations

For a smaller sample, MCS should be repeated 1000 times. Although the study sample was large, R software was used to run 1000 simulations, and results were compared to single MCS s and expected value results. Below syntax code was used in R software to run 1000 MCS.

```
library(eq5d)   #required library. Package needs to be installed first.

#read in the prob's as csv. No spaces between cols and no col names needed.
mydata = read.csv("C:/Users/wppwjw/OneDrive - Cardiff University/Work/Rhibina/Mapping.csv")

dat = as.data.frame(mydata)
nr = nrow(dat)  #how many rows? 4228 this time

#Initialise results data frame
ra <- data.frame(matrix(ncol = 1001, nrow = nr))
ra[] = 0

set.seed(0)    #makes it repeatable. Resets the random number

 for(i in 1:nr)  {   #loop over each row nr
  for(j in 2:1001){    #1000 simulations for each row
   ra_un = runif(5,0,1)    #generates 5 new random numbers each simulation
   for (k in 1:5){   #loop over the 5 categories
    c = (k-1)*3 + 1   # finds the right categories in the data. c = 1,4,7,10,13
    mul = 10^(k-1)    # constructs the 5 digits in a number. mul = 1,10,100,1000,10000

    if(ra_un[k] <= dat[i,c]){
     ra[i,j] = 1*mul + ra[i,j]
    }
    else if(ra_un[k] <= dat[i,c] + dat[i,(c+1)]){
     ra[i,j] = 2*mul + ra[i,j]
    }
    else    {
     ra[i,j] = 3*mul + ra[i,j]
    }
   }
   ra[i,j] = eq5d(scores=ra[i,j], country="UK", version="3L", type="TTO")
  }
  ra[i,1] = mean(as.numeric(ra[i,2:1001]))
 print(paste(i," ",ra[i,1]))
}

ra_t = ra  #backup ra in case following goes wrong

cc <- vector()
cc = c("Average",paste0("Loop",1:1000))  #creates the column names
colnames(ra_t) = cc

write.csv(ra_t,"C:/Users/wppwjw/OneDrive - Cardiff University/Work/Rhibina/Output 26May.csv")
```

PAGE 1 of EXCEL Sheet -Mapping Algorithm: for conversion of FROM-16 scores to EQ-5D-3L utility values

Appendix XIV: FROM-16 Mapping Algorithm

The mapping of the FROM-16 scores to utility values for use in economic appraisal should be based on aggregated group scores. The example provided is for illustrative purposes only.

Step 1: Enter the respondent's age, sex, and the responses to the 16 items of FROM-16, as shown below in the Excel sheet

1	Conversion of FROM-16 Item Score to EQ-5D utility values Using Multinomial Logistic Regression (Enter Age, Sex & FROM-16 scores below per subject)																		
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
2	**Subject ID**	**Age (years)**	**Sex M= 0, F=1**	**Worry**	**Angry**	**Sad**	**Frustrated**	**Talking about thoughts**	**Difficulty caring**	**Time for self**	**Travel**	**Eating habits**	**Family activities**	**Holiday**	**Sex life**	**Work or study**	**Family relationships**	**Family expenses**	**Sleep**
3																			
4	1	73	0	1	0	0	1	1	2	0	0	1	0	0	0	0	0	0	1
5	2	37	0	1	1	1	2	2	1	1	1	1	2	2	1	0	2	2	2
6	3	51	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	4	63	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
8																			
9																			
10																			
11																			
12																			
13																			
14																			
15																			

Formula explained -Mapping Algorithm using Multinomial logistic regression

Step 2: Estimate probability each domain by substituting the values of constant, regression coefficients and values of the independent variables from Table 3.16 in the Chapter 3 in the two equations below:

$$\log\left(\frac{\Pi_2}{\Pi_1}\right) = \alpha_{mobility\ (Some\ problem)} + (\beta_{age} * Age) + (\beta_{sex} * Sex) + (\beta_{worry} * Worry) + (\beta_{angry} * Angry) + (\beta_{sad} * Sad) + (\beta_{frustrated} * Frustrated) + (\beta_{thoughts} * Talking\ about\ thoughts) + (\beta_{caring} * Difficulty\ caring) + (\beta_{time\ for\ self} * Time\ for\ self) + (\beta_{travel} * Tarvel) + (\beta_{eating\ habits} * Eating\ habits) + (\beta_{family\ activities} * Family\ activities) + (\beta_{holiday} * Holiday) + (\beta_{sex\ life} * Sex\ life) + (\beta_{work} * Work/study) + (\beta_{family\ realtionship} * Family\ realtionship) + (\beta_{family\ expenses} * Family\ expenses) + (\beta_{sleep} * Sleep)$$

$$\log\left(\frac{\Pi_3}{\Pi_1}\right) = \alpha_{mobility(Extrem\ problem)} + (\beta_{age} * Age) + (\beta_{sex} * Sex) + (\beta_{worry} * Worry) + (\beta_{angry} * Angry) + (\beta_{sad} * Sad) + (\beta_{frustrated} * Frustrated) + (\beta_{thoughts} * Talking\ about\ thoughts) + (\beta_{caring} * Difficulty\ caring) + (\beta_{time\ for\ self} * Time\ for\ self) + (\beta_{travel} * Tarvel) + (\beta_{eating\ habits} * Eating\ habits) + (\beta_{family\ activities} * Family\ activities) + (\beta_{holiday} * Holiday) + (\beta_{sex\ life} * Sex\ life) + (\beta_{work} * Work/study) + (\beta_{family\ realtionship} * Family\ realtionship) + (\beta_{family\ expenses} * Family\ expenses) + (\beta_{sleep} * Sleep)$$

α = the constant of the equation

β = the coefficient of the predictor or independent variables(here age, gender and 16 items of FROM-16), β is the effect of the independent variable on the log-odds of being in category 2(some problem) and category 3 (Extreme problem) instead of category 1(no problem) in above equations.

Similarly, calculate probability values for other domains: selfcare, usual activities, pain/discomfort and anxiety/depression as shown on the next page (page 2 of Excel sheet)

PAGE 2 of EXCEL Sheet -Mapping Algorithm using Multinomial logistic regression

1	Estimated probability of each score per EQ-5D domain per subject (copy formula* down each column up to the last subject)																								
2	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS
3	MOBILITY					Selfcare					Usual activities					Pain/Discomfort					Anxiety/Depression				
4	log(n2/n1)	log(n3/n1)	P1	P2	P3	log(n2/n1)	log(n3/n1)	P1	P2	P3	log(n2/n1)	log(n3/n1)	P1	P2	P3	log(n2/n1)	log(n3/n1)	P1	P2	P3	log(n2/n1)	log(n3/n1)	P1	P2	P3
5	-0.449	-5.984	0.609	0.389	0.002	-1.8200	-5.8340	0.858	0.139	0.003	-0.5460	-3.5690	0.622	0.360	0.018	0.0500	-1.3480	0.433	0.455	0.112	-0.8190	-3.1780	0.675	0.297	0.028
6	-0.66	-2.809	0.634	0.328	0.038	-0.9470	-3.8370	0.709	0.275	0.015	0.1230	-1.5590	0.427	0.483	0.090	0.3470	-0.2240	0.311	0.440	0.249	1.7550	0.8860	0.109	0.628	0.263
7	-1.887	-7.072	0.868	0.131	0.001	-3.0460	-6.4970	0.953	0.045	0.001	-1.7770	-4.8850	0.850	0.144	0.006	-0.8540	-3.5700	0.688	0.293	0.019	-2.0970	-5.6440	0.888	0.109	0.003
9	-1.519	-6.56	0.819	0.179	0.001	-2.7620	-6.4040	0.939	0.059	0.002	-1.5900	-4.3870	0.822	0.168	0.010	-0.5940	-3.1960	0.628	0.347	0.026	-1.3660	-4.6500	0.791	0.202	0.008
10																									

Using FROM -16 values from Table 1, Estimated probabilities can be calculated using probability equations derived from Multinomial logistic regression as below (Example of first row)

Eq-5D-3L dimensions	Formula* →		P1	P2	P3
Mobility	U=log(n2/n1)	-3.468+(B4*0.031)+(C4*-0.05)+(D4*0.276)+(E4*0.094)+(F4*-0.303)+(G4*-0.071)+(H4*0.199) +(I4*0.002)+(J4*-0.066)+ (K4*0.152)+ (L4*0.221)+(M4*0.083)+(N4*-0.004)+(O4*0.095)+(P4*-0.241)+(Q4*-0.072)+(R4*0.333)+(S4*0.127) = **-0.449**	1/(1+EXP(U4) +EXP(V4)) **= 0.609**	EXP(U4)/(1+EXP(U4) +EXP(V4)) **= 0.389**	=EXP(V4)/(1+EXP(U4) +EXP(V4)) **= 0.002**
	V=log(n3/n1)	-7.48+(B4*0.008)+(C4*-0.059)+(D4*-0.14)+(E4*0.288)+(F4*0.346)+(G4*- 0.078) +(H4*0.458)+(I4*0.341) +(J4*0.204) +(K4*0.018) +(L4*0.15)+(M4*0.211)+(N4*0.249)+(O4*-0.06)+(P4*-0.152)+(Q4*0.455)+(R4*0.479)+(S4*-0.16)= **-5.984**			
Selfcare	Z=log(n2/n1)	-3.25+(B4*0.004)+(C4*-0.297)+(D4*0.387)+(E4*0.009)+(F4*-0.136)+(G4*-0.024)+(H4*0.132) + (I4*0.064) +(J4*-0.159)+ (K4*0.187)+(L4*0.292)+(M4*0.031)+(N4*-0.08)+(O4*0.119)+(P4*-0.262)+(Q4*0.068) +(R4*0.346)+(S4*0.223) = **-1.8200**	1/(1+ EXP(Z4) +EXP(AA4)) **= 0.858**	=EXP(Z4)/(1+EXP (Z4)+EXP(AA4)) **= 0.139**	=EXP(AA4)/(1+EXP(Z4) +EXP(AA4)) **= 0.003**
	AA=log(n3/n1)	-6.497+(B4*0)+(C4*0.153)+(D4*-0.227)+(E4*0.221)+(F4*0.624)+(G4*-0.525)+(H4*0.172)+ (I4*0.68)+(J4*0.124)+ (K4*0.183)+(L4*0.141)+(M4*0.149)+(N4*0.275) +(O4*0)+(P4*0.227)+(Q4*0.081)+(R4*0.563) +(S4*-0.258) = **-5.8340**			
Usual activities	AE=log(n2/n1)	-2.746+(B4*0.019)+(C4*-0.089)+(D4*0.17)+(E4*0.042)+(F4*-0.211)+(G4*-0.042)+(H4*0.203) +(I4*0.09)+(J4*-0.038)+(K4*0.161)+(L4*0.107)+(M4*0.19)+(N4*0.027)+(O4*0.109)+(P4*0.037)+(Q4*-0.005)+(R4*0.3)+(S4*0.195) = **-0.5460**	1/(1+EXP(AE4) +EXP(AF4)) **= 0.622**	EXP(AE4)/(1+EXP (AE4)+EXP(AF4)) **= 0.360**	=EXP(AF4)/(1+EXP (AE4)+EXP(AF4)) **= 0.018**
	AF=log(n3/n1)	-5.344+(B4*0.009)+(C4*-0.205)+(D4*0.255)+(E4*0.137)+(F4*0.264)+(G4*-0.266)+(H4*0.192)+(I4*0.301)+(J4*0.228) +(K4*0.313)+(L4*0.202) +(M4*0.194)+(N4*0.083) +(O4*0.202) +(P4*0.032)+(Q4*0.044)+(R4*0.395)+(S4*0.133) =**-3.5690**			
Pain/Discomfort	AJ=log(n2/n1)	-2.18+(B4*0.026)+(C4*-0.008)+(D4*0.17)+(E4*0.081)+(F4*-0.328)+(G4*0.025)+(H4*0.134)+(I4*-0.121)+(J4*0.022) +(K4*0.093) +(L4*0.094)+(M4*0.092)+(N4*0.002)+(O4*0.116)+(P4*-0.133)+(Q4*0.076) +(R4*0.239)+(S4*0.151) = **0.0500**	1/(1+EXP(AJ4) +EXP(AK4)) **=0.433**	=EXP(AJ4)/(1+EXP (AJ4)+EXP(AK4)) **=0.455**	=EXP(AK4)/(1+EXP (AJ4)+EXP(AK4)) **=0.112**
	AK=log(n3/n1)	-4.437+(B4*0.017)+(C4*-0.247)+(D4*0.383)+(E4*0.129)+(F4*-0.352)+(G4*0.01)+(H4*0.323) +(I4*0.085)+(J4*-0.267) +(K4*0.305)+(L4*0.364)+(M4*0.035)+(N4*-0.027)+(O4*0.131)+(P4*-0.329)+(Q4*-0.063)+(R4*0.527)+(S4*0.598) = **-1.3480**			
Anxiety/Depression	AO=log(n2/n1)	-1.434+(B4*-0.013)+(C4*0.269)+(D4*0.522)+(E4*0.269)+(F4*0.117)+(G4*-0.021)+(H4*0.403)+(I4*0.029) +(J4*0.244) +(K4*0.102)+(L4*0.198)+(M4*0.1)+(N4*0.047)+(O4*0.069)+(P4*0.031)+(Q4*0.21)+(R4*-0.083)+(S4*0.404) = **-0.8190**	1/(1+EXP(AO4) +EXP(AP4)) **= 0.675**	EXP(AO4)/(1+EXP (AO4)+EXP(AP4)) **= 0.297**	EXP(AP4)/(1+EXP (AO4)+EXP(AP4)) **= 0.028**
	AP=log(n3/n1)	-4.012+(B4*-0.032)+(C4*-0.037)+(D4*0.715)+(E4*0.395)+(F4*0.353)+(G4*-0.085)+(H4*0.777)+(I4*0.223)+(J4*0.356) +(K4*0.154)+(L4*0.613)+(M4*0.059)+(N4*-0.214)+(O4*0.073)+(P4*-0.028)+(Q4*0.277)+(R4*0.082)+(S4*0.704) = **-3.1780**			

PAGE 3 of EXCEL Sheet -Mapping Algorithm using Multinomial logistic regression

Step 3: Generate random numbers between 0 and 1 using the formula*=RAND()
Step 4: Predict the EQ-5D-3L domain response score using the formula in below **text box** (linked to predicted domain probabilities on page 2 of Excel sheet)
Step 5: Utility value can now be calculated using UK TTO tariff.

	AU	AV	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG
1	Random Number Generator* for each domain (copy formula* down each column up to the last subject)						Predicted score for each EQ-5D domain (copy formula down each column up to the last subject)						
2	Mobility Random	Selfcare Random	Usual activities Random	Pain/Discomfort Random	Anxiety/Depression Random	Monte Carlo Simulation	Mobility Score	Selfcare Score	Usual Activities Score	Pain/ Discomfort Score	Anxiety/ Depression Score	Conversion of EQ-5D-3L domain score to Utility value	Utility value #
3													
4	0.4327	0.3375	0.4336	0.6160	0.7480		1	1	1	2	2		0.725
5	0.0500	0.6179	0.6628	0.5896	0.9098		1	1	2	2	3		0.255
6	0.8473	0.8269	0.1669	0.3770	0.8189		1	1	1	1	1		1.000
7	0.9918	0.8300	0.5017	0.6157	0.5256		2	1	1	1	1		0.850

The predicted domain scores may be converted to utility scores using the relevant TTO value sets specific to your country. These value sets as well as the syntax for SPSS (incase of large datasets) may be obtained from http://www.euroqol.org

#The utility value is calculated here using the UK MVH tariff equation developed by Dolan et al. 1996.

***=RAND() formula will generate random numbers between 0 and 1;**

Formula for EQ-5D-3L Domain score (linked to predicted domain probabilities on page 2)

Mobility score = IF(AU4=<W4,1,0)+IF(AND(AU4>W4,AU4=<(W4+X4)),2,0)+IF(AU4>(1-Y4),3,0)
Selfcare = IF(AV4=<AB4,1,0)+IF(AND(AV4>AB4,AV4=<(AB4+AC4)),2,0)+IF(AV4>(1-AD4),3,0)
Usual activities = IF(AW4=<AG4,1,0)+IF(AND(AW4>AG4,AW4=<(AG4+AH4)),2,0)+IF(AW4>(1-AI4),3,0)
Pain/Discomfort = IF(AX4=<AL4,1,0)+IF(AND(AX4=AL4,AX4=<(AL4+AM4)),2,0)+IF(AX4>(1-AN4),3,0)
Anxiety/Depression = =IF(AY4=<AQ4,1,0)+IF(AND(AY4>AQ4,AY4=<(AQ4+AR4)),2,0)+IF(AY4>(1-AS4),3,0)

Appendix XV: Amendments to IRAS protocol- Responsiveness/MCID

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Validation of Family Reported Outcome Measure (FROM-16)
IRAS project ID* (or REC reference if no IRAS project ID is available):	281134 (20/EE/0242)
Sponsor amendment reference number*:	SPON1817-20 NSA01
Sponsor amendment date* (enter as DD/MM/YY):	11 April 2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	As a consequence of COVID having impacted our research programme, we need to make the following minor amendments in the recruitment procedure of studies 1 and 3 of the IRAS protocol. These studies are longitudinal, and a criterion for patient/relatives to be recruited is that the patient should be starting a new therapy, where a change in quality of life (QoL) is reasonably expected within three months. The data for both studies will be collected at the same time. The clinician will identify and approach patients and their family members to gain their permission to participate in the study. The procedure outlined in the initial and approved study protocol required patients and family members to complete questionnaires during their clinic visit, and follow-up questionaries were to be emailed or posted to participants, based on the patient's and their family member's preference. We now propose that once patients have given their consent to their clinician to be contacted by the researcher with further information, they will not complete the questionnaire in the clinic. Instead, they will complete the questionnaire at their home, restricting face to face contact with participants. They will either answer a postal questionnaire or an online questionnaire using a GDPR compliant platform, Redcap (Research Electronic Data Capture), or Jisc Surveys operated via https://admin.onlinesurveys.ac.uk. The online version of the questionnaire will be anonymous: all participants will be provided with a code which they will have to enter to access the online questionnaires. In view of the time limitation of my PhD (completion date January 2023), and the continuing impact of the pandemic on face to face (F2F) clinic interactions with patients, it will not be possible for me to collect data for studies 1 and 3 by directly meeting with patients. Allowing participants to complete the questionnaires anonymously online or by completing the questionnaire by post will help me achieve the study outcomes within the given time frame of my PhD while reducing the previously planned contact with participants. This proposed amendment in the study procedure will not have any impact on the scientific value of the study. Furthermore, the continuing pressures on NHS staff now provide significant obstacles to staff being able to divert any time or energy to supporting research projects such as ours. Therefore, we would also like to change the target sample size for studies 1 and 3 of the IRAS protocol from 375 (based on 95% power and 20% target difference) to more realistic sample size of 70 (based on 80% power and 0.5 effect size). A sample size of 50-99 is considered adequate for such studies (Mokkink et al. 2019).

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	No	**Yes**	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	

Appendix XV: Amendments to IRAS protocol- Responsiveness/MCID

Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes	**No**
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes	**No**
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes	**No**
Did the study involve children OR does the amendment introduce this?:	Yes	**No**
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**	No
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes	**No**

	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	No	**Yes**	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	No	**Yes**	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	No	**Yes**	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	**Yes**		No	

Section 2: Summary of change(s)

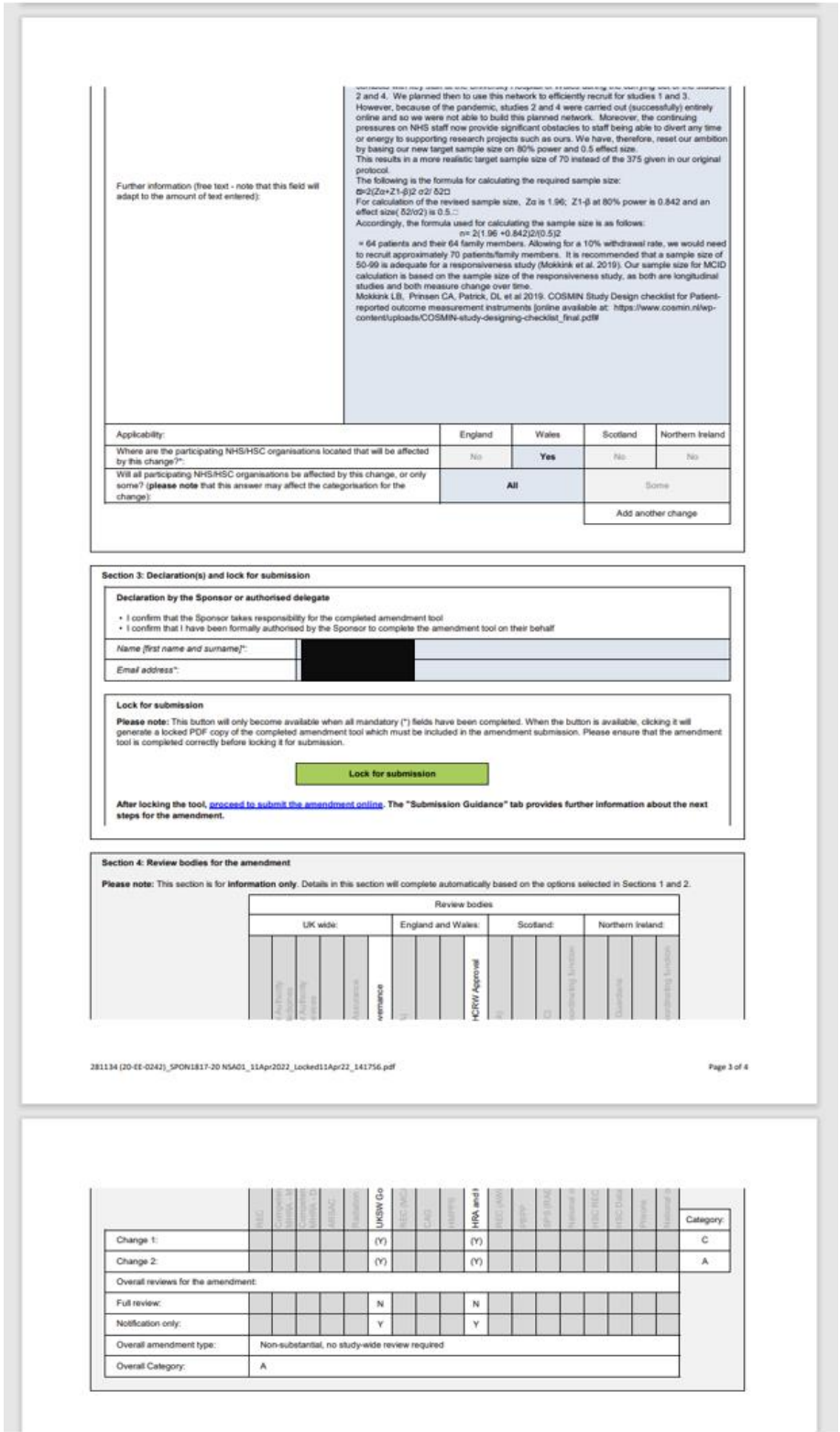
Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1	
Area of change (select)*:	Participant Procedures
Specific change (select - only available when area of change is selected first)*:	Participant procedures - minor change that can be implemented within existing resource at participating organisations - Please specify in the free text below
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	The procedure outlined in the initial and the approved study protocol required patients and family members to complete questionnaires during their clinic visit, and follow-up questionaries were to be emailed or posted to participants, based on the patient's and their family member's preference. We now propose that once patients have given their consent to their clinician to be contacted by the researcher with further information, they will not complete the questionnaire in the clinic. Instead, they will complete the questionnaire at their home, restricting face to face contact with participants. So this change will not require any further resources other than that which already existed for example: support of the clinician to identify and approach patients and their family members to gain their permission to participate in the study. This change will only reduce face to face contact directly with the patient and family member and also make procedure more efficeint.

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	No	**Yes**	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Remove all changes below	

Change 2	
Area of change (select)*:	Study Design
Specific change (select - only available when area of change is selected first)*:	Participant numbers - Minor change to sample size
	Change to sample size for Studies 1 and 3 We would also like to change the target sample size for studies 1 and 3 of the IRAS protocol. Our previous sample size of 375 was based on 95% power and 20% target difference. Our expectations of being able to recruit this number of participants was based on the assumption that during 2020 and 2021 we would create and develop a wide range of close personal contacts with key staff at the University Hospital of Wales during the carrying out of the studies

Appendix XV: Amendments to IRAS protocol- Responsiveness/MCID



Further information (free text - note that this field will adapt to the amount of text entered):

2 and 4. We planned then to use this network to efficiently recruit for studies 1 and 3. However, because of the pandemic, studies 2 and 4 were carried out (successfully) entirely online and so we were not able to build this planned network. Moreover, the continuing pressures on NHS staff now provide significant obstacles to staff being able to divert any time or energy to supporting research projects such as ours. We have, therefore, reset our ambition by basing our new target sample size on 80% power and 0.5 effect size.
This results in a more realistic target sample size of 70 instead of the 375 given in our original protocol.
The following is the formula for calculating the required sample size:
ϖ=2(Zα+Z1-β)2 σ2/ δ2□
For calculation of the revised sample size, Zα is 1.96; Z1-β at 80% power is 0.842 and an effect size(δ2/σ2) is 0.5.□
Accordingly, the formula used for calculating the sample size is as follows:
n= 2(1.96 +0.842)2/(0.5)2
= 64 patients and their 64 family members. Allowing for a 10% withdrawal rate, we would need to recruit approximately 70 patients/family members. It is recommended that a sample size of 50-99 is adequate for a responsiveness study (Mokkink et al. 2019). Our sample size for MCID calculation is based on the sample size of the responsiveness study, as both are longitudinal studies and both measure change over time.
Mokkink LB, Prinsen CA, Patrick, DL et al 2019. COSMIN Study Design checklist for Patient-reported outcome measurement instruments [online available at: https://www.cosmin.nl/wp-content/uploads/COSMIN-study-designing-checklist_final.pdf#

Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	No	**Yes**	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:	[redacted]
Email address:	

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:					England and Wales:				Scotland:				Northern Ireland:				
									HCRW Approval									

281134 (20-EE-0242)_SPON1817-20 NSA01_11Apr2022_Locked11Apr22_141756.pdf Page 3 of 4

	UKSW Gov	HRA and HCRW	Category:
Change 1:	(Y)	(Y)	C
Change 2:	(Y)	(Y)	A
Overall reviews for the amendment:			
Full review:	N	N	
Notification only:	Y	Y	
Overall amendment type:	Non-substantial, no study-wide review required		
Overall Category:	A		

Appendix XV: Amendments to IRAS protocol- Responsiveness/MCID

Amendment Tool

v1.6 06 December 2021

For office use

QC: No

Section 1: Project information

Short project title*:	Validation of Family Reported Outcome Measure (FROM-16)
IRAS project ID* (or REC reference if no IRAS project ID is available):	281134 (20/EE/0242)
Sponsor amendment reference number*:	SPON1817-20_NSA02
Sponsor amendment date* (enter as DD/MM/YY):	05/06/2022
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	We have moved the Global severity question (GSQ) from study 3 of IRAS (the MCID study) to study 1 of IRAS (the Sensitivity to Change). The reason is that the GSQ question relates to the severity of a patient's disease and can only be best answered by the patient. This question is now no longer relevant to the MCID study, which must be based on family member only data. Furthermore adding this question to study one will allow us to assess FROM-16's sensitivity to patients' disease severity in addition to change in patients' QoL over time, thus adding to the strength of the study.

Project type (select):	**Specific study**			
	Research tissue bank			
	Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	**Yes**		No	
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	**NHS/HSC REC**			
	Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	Yes		**No**	
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England	Wales	Scotland	Northern Ireland
	Yes	No	No	No
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	Yes		**No**	
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	Yes		**No**	
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	Yes		**No**	
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	Yes		**No**	
Did the study involve adults lacking capacity OR does the amendment introduce this?:	Yes		**No**	
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	Yes		**No**	
Did the study involve prisoners or young offenders who are in custody or supervised by the probation service OR does the amendment introduce this?:	Yes		**No**	
Did the study involve children OR does the amendment introduce this?:	Yes		**No**	
Did the study involve NHS/HSC organisations prior to this amendment?:	**Yes**		No	
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	Yes		**No**	
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	No	**Yes**	No	No
Which nations had participating NHS/HSC organisations prior to this amendment?	No	**Yes**	No	No
Which nations will have participating NHS/HSC organisations after this amendment?	No	**Yes**	No	No
Was this a "single site, self sponsored" study in England or Wales prior to this amendment?	**Yes**		No	

Section 2: Summary of change(s)

Appendix XV: Amendments to IRAS protocol- Responsiveness/MCID

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the Amendment Tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, click the "Add another change" box.

Change 1				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below			
Further information In particular, please describe why this change can be implemented within the existing resource in place at the participating organisations (free text - note that this field will adapt to the amount of text entered)*	This is a minor change which involves the patient instead of a family member completing the GSQ at the same time when he / she completes EQ-5D questionairre at two points in time. Therefore, this change can be implemented within the existing resources inplace at the participating organization.			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	No	**Yes**	No	No
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	**All**		Some	
			Add another change	

Section 3: Declaration(s) and lock for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name [first name and surname]:*	[redacted]
*Email address**:	

Lock for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Lock for submission

After locking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:				
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	**UKSW Governance**	REC (MCA)	CAG	HMPPS	**HRA and HCRW Approval**	REC (AIWA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:						(Y)				(Y)									C
Overall reviews for the amendment:																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	C																		

Appendix XVI: HRA approval for the amendments- Responsiveness/MCID

From: New IRAS Dev <no-reply-iras@hra.nhs.uk>
Sent: 11 April 2022 16:25
To: Rubina Shah [redacted]
Subject: IRAS 281134. Amendment

External email to Cardiff University - Take care when replying/opening attachments or links.
Nid ebost mewnol o Brifysgol Caerdydd yw hwn - Cymerwch ofal wrth ateb/agor atodiadau neu ddolenni.

IRAS Project ID: 281134
Sponsor amendment reference: SPON1817-20 NSA01

Thank you for submitting your study amendment. In accordance with the outcome of your completed amendment tool, this amendment requires no further regulatory review. Please now share this amendment with your UK research sites, in accordance with the instructions in your completed amendment tool.

For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

For all NHS research sites in England and Wales, please now share this amendment by email directly with those sites, including both the R&D offices and research teams.

IRAS 281134. Amendment Download Save to OneDrive

IRAS 281134. Amendment

ND New IRAS Dev <no-reply-iras@hra.nhs.uk>
To: Rubina Shah
Mon 20/06/2022 10:36

External email to Cardiff University - Take care when replying/opening attachments or links.
Nid ebost mewnol o Brifysgol Caerdydd yw hwn - Cymerwch ofal wrth ateb/agor atodiadau neu ddolenni.

IRAS Project ID: 281134
Sponsor amendment reference: SPON1817-20_NSA02

Thank you for submitting your study amendment. In accordance with the outcome of your completed amendment tool, this amendment requires no further regulatory review. Please now share this amendment with your UK research sites, in accordance with the instructions in your completed amendment tool.

For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

For all NHS research sites in England and Wales, please now share this amendment by email directly with those sites, including both the R&D offices and research teams.

Do not reply to this email as this is an unmonitored address and replies to this email cannot be responded to or read.

Appendix XVII: Participant information Sheet- Responsiveness/MCID

Patient Information Sheet

Study Title: Validation of Family Reported Outcome Measure (FROM-16)

If someone in a family is unwell, this also affects the lives of other people in the family. We are trying to find out how well a new questionnaire (FROM-16) helps us to measure this.

Invitation

We'd like to invite you to take part in a Cardiff University study. Thank you for taking the time to read this leaflet and considering whether to take part in this study. Please read the following information carefully before deciding whether to take part. If you have any questions, please contact the study team: contact details are at the end of this leaflet.

About the Study

Chronic health conditions can have a major impact on the quality of life of patients, but also on their family members, affecting also their physical, social and psychological wellbeing. This impact of the disease on the quality of life of other family members or partner is mostly ignored but is a huge unmet need. We have created a questionnaire, the 'Family Reported Outcome Measure' (FROM-16) to measure this impact. This questionnaire needs further testing before it can be used by clinicians to help them understand these problems and to try to give the right kind of support to family members and partners.

This study aims to gather information about the impact of having someone in the family with a health condition on the quality of life of family members or partner of patient. Information from the FROM-16 questionnaire will be used to investigate the effectiveness and robustness of the FROM-16 questionnaire in assessing the impact of the disease on a family member or partner. The information from this research will allow us to let clinicians know what different scores and score changes mean and to prove that the questionnaire can be used as part of finding out how well new treatments work.

We hope that eventually this information will encourage improved patient and family care, and that clinicians will be better able to choose treatments that are in the best interests of the patient and his/her family members.

Why have I been chosen for this study?
You have been diagnosed with a medical condition, and are attending a clinic with a member of your family, or a member of your family is visiting you in hospital. This means you can take part in this study. There will be about 70 other patients like yourself taking part in the study.

Do I have to take part in this study?

Participating in this study is voluntary. Choosing not to participate in the study or withdrawing from the study at any time will have no effect on your regular medical care.

What does the study involve?

Your clinician will first contact you and your relative to seek your permission for you and your family member/partner to take part in this study. If both you and your family member/partner give permission, you can then both take part in the study.
You will be asked to complete an online or postal questionnaire (the EQ-5D-3L) about how your life is being affected by your medical condition. You will also state on a single question, a description of the severity of your health condition by answering a global severity question (GSQ).

Your family member or your partner will be asked to complete a different questionnaire (FROM-16) about the ways that their life has been affected by your medical condition.

After about 12 weeks, we will contact you both again by post or email, to ask you to complete a similar questionnaire again. The family member/ partner will also complete a Global Rating of Change Questionnaire (GRCQ) to indicate how much (if any) they have noticed their quality of life has changed.

There are no tests. There will be no change to your treatment. You will not need to take any extra or different medication.

How long will it take?

It takes on average 5 minutes to complete the questionnaire.

What are the benefits of taking part?

We cannot promise the study will help you but the information we get from the study may help to improve the treatment of people, and support the families of people with the same disease that your have.

What are the possible risks of taking part?
This study involves questionnaires so there are no risks associated with it.

What happens when the research stops?
The results of this study will be used as a part of a PhD thesis and will be published in a scientific journal. You will not be identified in any report or publication. You will be provided with a copy of this publication if you are interested.
We hope results of this finding will increase usability of FROM-16 questionnaire across all disease areas and will help family members affected by the patients disease to receive support.

What if there is a problem?
If you have any queries about the study or if any problems arise, please contact us directly. Contact numbers for the study team are given at the end of this leaflet.

Will my taking part be kept confidential?
All the information which is collected from you will be kept strictly confidential. Each person involved is given a code number for confidentiality. Only the investigators will have access to your details that link with the code number. The results of the study will not reveal your name or address or other identifiable information.

Who has reviewed the project?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been approved by an NHS Research Ethics Committee **HRA and Health and Care Research Wales (HCRW), REC reference: 20/EE/0242.**

Who is funding the project?

The project is being funded by Cardiff University.

What should I do if I have any complaints about the conduct?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [telephone nbr]. If you remain unhappy and wish to complain formally, you can do this using the NHS Complaints Procedure. Details can be obtained from Cardiff and Vale University Health Board website [http://www.wales.nhs.uk/sitesplus/864/page/40894].

Who do I contact if I have further questions?

It is important that all your questions are answered prior to signing the written consent. If you have any further questions or require additional information you may contact the following investigators:

Thank you for taking the time to read this leaflet

Patient Information Sheet

Study Title: Validation of Family Reported Outcome Measure (FROM-16)

If someone in a family is unwell, this also affects the lives of other people in the family. We are trying to find out how well a new questionnaire (FROM-16) helps us to measure this.

Invitation

We'd like to invite you to take part in a Cardiff University study. Thank you for taking the time to read this leaflet and considering whether to take part in this study. Please read the following information carefully before deciding whether to take part. If you have any questions, please contact the study team: contact details are at the end of this leaflet.

About the Study

Chronic health conditions can have a major impact on the quality of life of patients, but also on their family members, affecting also their physical, social and psychological wellbeing. This impact of the disease on the quality of life of other family members or partner is mostly ignored but is a huge unmet need. We have created a questionnaire, the 'Family Reported Outcome Measure' (FROM-16) to measure this impact. This questionnaire needs further testing before it can be used by clinicians to help them understand these problems and to try to give the right kind of support to family members and partners.

This study aims to gather information about the impact of having someone in the family with a health condition on the quality of life of family members or partner of patient. Information from the FROM-16 questionnaire will be used to investigate the effectiveness and robustness of the FROM-16 questionnaire in assessing the impact of the disease on a family member or partner. The information from this research will allow us to let clinicians know what different scores and score changes mean and to prove that the questionnaire can be used as part of finding out how well new treatments work.

We hope that eventually this information will encourage improved patient and family care, and that clinicians will be better able to choose treatments that are in the best interests of the patient and his/her family members.

Why have I been chosen for this study?
You have been diagnosed with a medical condition, and are attending a clinic with a member of your family, or a member of your family is visiting you in hospital. This means you can take part in this study. There will be about 70 other patients like yourself taking part in the study.

You will be asked to complete an online questionnaire. The questionnaire will ask you to complete some basic demographic questions (such as age, sex, relationship to your relative),the FROM-16 questionnaire about the ways your life has been affected by your relative's medical condition.

Your relative will be asked to complete a different online questionnaire (the EQ-5D-3L) about how their life has been affected by their medical condition. Your relative will also state on a single question, a description of the severity of their health condition by answering a global severity question (GSQ).

After about 12 weeks, we will contact you both again by post or email, to ask you to fill in similar questionnaires again. You will also complete a Global Rating of Change Questionnaire (GRCQ) to indicate how much (if any) you have noticed your quality of life has changed.

There are no tests. There will be no change to your treatment. You will not need to take any extra or different medication.

How long will it take?

It takes on average 5 minutes to complete the questionnaire.

What are the benefits of taking part?

We cannot promise the study will help you but the information we get from the study may help to improve the treatment of people, and support the families of people with the same disease that your have.

What are the possible risks of taking part?
This study involves questionnaires so there are no risks associated with it.

What happens when the research stops?
The results of this study will be used as a part of a PhD thesis and will be published in a scientific journal. You will not be identified in any report or publication. You will be provided with a copy of this publication if you are interested.
We hope results of this finding will increase usability of FROM-16 questionnaire across all disease areas and will help family members affected by the patients disease to receives support.

What if there is a problem?

If you have any queries about the study or if any problems arise, please contact us directly. Contact numbers for the study team are given at the end of this leaflet.

Will my taking part be kept confidential?
All the information which is collected from you will be kept strictly confidential. Each person involved is given a code number for confidentiality. Only the investigators will have access to your details that link with the code number. The results of the study will not reveal your name or address or other identifiable information.

Who has reviewed the project?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been approved by an NHS Research Ethics Committee **HRA and Health and Care Research Wales (HCRW), REC reference: 20/EE/0242.**

Who is funding the project?

The project is being funded by Cardiff University.

What should I do if I have any complaints about the conduct?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [telephone nbr]. If you remain unhappy and wish to complain formally, you can do this using the NHS Complaints Procedure. Details can be obtained from Cardiff and Vale University Health Board website [http://www.wales.nhs.uk/sitesplus/864/page/40894].

Who do I contact if I have further questions?

It is important that all your questions are answered prior to signing the written consent. If you have any further questions or require additional information you may contact the following investigators:

Thank you for taking the time to read this leaflet.

Appendix XVIII: SMREC ethics application-COVID-19 study

SCHOOL OF MEDICINE

APPLICATION FOR ETHICAL REVIEW

For Office Use Only	
SREC Reference: [x]	Meeting/Review Date: [x]

SECTION 1. GENERAL INFORMATION	
Application Type:	☐ Staff √☐ PGR student ☐ PGT/Masters Student ☐ Undergraduate
Research Project Title:	Impact of COVID-19 on quality of life of the patient and family members
Short Title (where applicable):	
For Staff Projects	
Name of Chief/Principal Investigator:	
Contact details:	
Other members of research team:	
For Student Projects	
Name of Student:	Rubina Shah
Contact details:	[redacted]
Course name:	PhD
Other members of research team:	

SECTION 2. SCREENING QUESTIONS			
		Yes	**No**
2.1	Is the research project categorised as 'Research' (as defined in the Cardiff University Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data)? *If **no** (i.e. the research project is a Service Evaluation or Audit), the Committee is not required to conduct a review of the proposal. Please see definitions below:* 'Research' means any project which attempts to derive generalisable new knowledge or apply existing knowledge, including studies that aim to generate hypotheses, as well as studies that aim to test them. 'Service Evaluation' is an activity which seeks to assess how well an existing service is performing. The activity is designed and conducted with the sole purpose of defining or judging a current service. 'Audit' is an activity which usually involves a quality improvement cycle that measures performance against	Yes	

	usually involves a quality improvement cycle that measures performance against predetermined standards and recommends specific actions to improve performance. *If your project is classed as a service evaluation or audit, it will not require ethical review by the School of Medicine Research Ethics Committee. If you are unsure as to whether your project is a service evaluation, then please send a copy of the project proposal to the Committee Secretary, [redacted] for review by the Chair.*		
2.2	Does the research project involve human participants, human material or human data (as defined in the Cardiff University Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data)? *If **no**, you are not required to submit the research proposal to this Committee. **Please do not continue with this application.***	Yes	
2.3	Does the research project require review by an external ethics committee (refer to Appendix 1 of the Cardiff University Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data)? Please note that this includes all research projects involving participants who lack the capacity to consent. *If **yes**, the research project should be submitted to the relevant external ethics committee for review and does not fall within the remit of this Committee. Please contact the Research Governance Team for further advice. **Please do not continue with this application.***		No
2.4	Has the research project been ethically reviewed by another university or research institution (for example, where the Chief/Principal Investigator for the research project is based at another institution)? *If **yes,** please provide evidence of the review conducted (such as an outcome letter or communication) and the ethical review policy of the relevant institution or committee. **Please do not continue with this application.***		No
2.5	Does the research project only involve the use of information that is publicly and lawfully available e.g. census data, population statistics published by government departments and personal letters/diaries in public libraries. Note: research projects involving the use of Human Data obtained from social media (or similar internet forums) do not fall within this category. *If **yes**, you are not required to submit the research proposal to this Committee. **Please do not continue with this application.***		No
2.6	Does the research project fall within the scope of the UK Policy Framework for Health and Social Care Research? This Framework		No

	broadly applies to research taking place within, or involving, the health and social care systems. If you intend to recruit research participants or obtain patient data through the NHS, then you will require NHS LREC approval. Your application will fall outside of the School's remit to review so please do not continue with this application. *If **yes**, you will need to apply to the Research Governance Team for Sponsorship using the Advanced Project Information Proforma (APIP) (available on the Cardiff University intranet). The Research Governance Team will advise you on the approvals that are required for the research project after it has conducted a review of the APIP and supporting documentation.* ***Please do not continue with this application until you have sought advice from the Research Governance Team.***		
2.7	Does the research project involve the collection or use of Human Tissue (including, but not limited to, blood, saliva and bodily waste fluids)? *If **yes**, the research project should be submitted to the Human Tissue Act Compliance Team (HTACT) prior to submission to an ethics committee.* ***Please do not continue with this application until you have sought advice from HTACT.***		No
2.8	Does the research project fall within the scope of the University's Security-sensitive Research Policy? This Policy broadly applies to research involving terrorism, extremism or radicalisation (or access to materials of such a nature). *If **yes**, you must register the research in accordance with the Policy and comply with the IT and security arrangements contained in the Policy.*		No
2.9	Has the research project received scientific review? (For student research projects, review by the research project supervisor is an acceptable form of scientific review) *If **no**, please obtain appropriate scientific review before submitting the application to this Committee.*	Yes	
If the research project involves the use of animals, please contact the Cardiff University Biological Standards Office bso@cardiff.ac.uk to seek further advice.			
SECTION 3. PROJECT SUMMARY			
3.1	Summarise the research project (including the purpose and its methodology) using language that would be understood by a lay person. (500 word maximum)		
Despite the huge number of recent research publications concerning COVID-19, there is very little information on the psychological and social impact of COVID-19 on the patient and their families. To date, there is no information on the lived experience of people infected with COVID-19 and their family members, though the need for this has been identified (Holmes et al, 2020).			

The present study will explore the impact of COVID-19 on patients and family members/ partners of people with lived experience of COVID-19. The study will be based on an online survey using social media platforms. We hope this study will help healthcare workers and government agencies to better understand the support needs of patients and their partners and family members.	
3.2	Describe the research question(s).
What is the impact of COVID-19 on the quality of life of patient and their family members or partners?	
3.3	Estimated start date.
May 2020	
3.4	Estimated end date (usually the end of data collection).
August 2020	
3.5	Is the research project funded? *If **yes**, please name the funding body.*
No	
3.6	Are there any potential conflicts of interest? *If **yes**, please confirm the action you propose to take to address such conflicts.*
AYF and MSS are joint copyright owners with Cardiff University of FROM-16	

SECTION 4. FULL REVIEW CRITERIA				
		Yes		**No**
4.1	Will the research project be performed without the participants' prior consent?			No
4.2	Does the research design include an element of deception, including covert research?			No
4.3	Will the research project involve children under the age of 18 or 'at risk' (vulnerable) adults or groups? *The Cardiff University Safeguarding Children and Adults at Risk: Policy and Guidance sets out examples of 'at risk' or 'vulnerable' adults.*			No
4.4	Does the research project include topics which may be considered highly sensitive for participants?			No

	This includes sexual behaviour, illegal activities, political, religious or spiritual beliefs, race or ethnicity, experience of violence, abuse or exploitation, and mental health.			
4.5	Does the research project require access to records of a sensitive or confidential nature, including Special Category Data, for the purposes of the General Data Protection Regulation and Data Protection Act 2018?			No
4.6	Is permission of a gatekeeper required for initial or continued access to participants? *This includes participants in custody and care settings, or research in communities where access to research participants is not possible without the permission of another adult, such as another family member or a community leader.*			No
4.7	Does the research project involve intrusive or invasive procedures? *This includes the administration of substances, vigorous physical exercise, procedures involving pain or more than mild discomfort to participants (including the risk of psychological distress, discomfort or anxiety to participants).*			No
4.8	Does the research project involve visual or audio recordings where participants may be identified?			No
4.9	Does the research project involve the collection or use of human tissue?			No
4.10	Is there a risk to the safety and wellbeing of the Researchers?			No

PROCEDURE TO FOLLOW, BASED ON RESPONSES IN SECTION 4:

- If any 'Yes' box applies, the research project should follow a full ethics review.
- If all 'No' boxes apply, the research project may be considered for proportionate review.

SECTION 5. RECRUITMENT	
5.1	How will you recruit participants to the research project? *If appropriate, please include sampling criteria.*
Through an online survey using social media	
5.2	How many participants are you aiming to recruit? *If applicable, please include a breakdown of participants by type and number.*
Participants type: COVID-19 patients and family members Number: >500 participants	
5.3	What are the inclusion and exclusion criteria for participants?

Inclusion criteria

- Patients who have had COVID-19 and family members
- Adult person aged 18 years or older
- Have the mental capacity to give informed written consent and complete the questionnaire using an electronic device.

Exclusion criteria

- Family member/ partner also having COVID-19
- People not affected by COVID-19
- Patient and family members under age 18 years
- Unable to give written informed consent or operate an electronic device to answer the survey

5.4	How will the research project address recruitment of participants who are not fluent in the English/Welsh language?
The research project is currently in the English language and other languages are not available. However, we will engage in Welsh if requested. There is a validated Welsh translation of the Family Reported Outcome Measure (FROM-16) and arrangements would be made for translation of the rest of the survey if requested	
5.5	Will the research project involve participants that are Cardiff University staff or students or people who are likely to become students or clients of the University or the place in which you may otherwise work? *If applicable, please provide details.*
No	
SECTION 6. CONSENT PROCEDURES	
6.1	How will informed consent be obtained? *Please include who will be taking consent, how consent will be recorded, when participants will be provided with information about the research project, and how long potential participants will be given to decide whether to take part.*
The participants will be given an information sheet and will asked to provide consent as part of the online survey.	
6.2	Will participants be offered any incentives to take part in the research project?
No	
6.3	If a questionnaire is to be used, will you give participants the option of omitting questions they do not wish to answer?
Yes	
6.4	Will participants be informed that their participation is voluntary and that they may withdraw at any time and for any reason?
Yes	

SECTION 7. POSSIBLE HARM TO PARTICIPANTS/RESEARCHERS	
7.1	Is there is a risk of the participants experiencing physical, emotional or psychological harm or distress? *If yes, please provide details of how ethical issues will be handled and how any risks will be minimised. Please consider whether the research project includes topics which could be considered as highly sensitive for participants.*
It is possible that answering quality of life questionnaires may cause distress, for example if the questions draw attention to sensitive issues, though we are not aware of any such problems having been caused by the use of EQ-5D or FROM-16 in previous studies. Subjects who experience distress from completing the survey will be encouraged to seek advice from their doctor or from a psychologist, or to contact us directly. As this is an international survey, we are not able to provide country specific advice. Labott SM, Johnson TP, Fendrich, Feeny NC. Emotional risks to respondents in survey research: some empirical evidence. J Empir Hum Res Ethics 2013; 8(4): 53-66.	
7.2	Is there a risk of the Researcher(s) experiencing physical, emotional or psychological harm or distress? *If yes, please provide details of how ethical issues will be handled and how any risks will be minimised.*
No	
SECTION 8. DATA MANAGEMENT, CONFIDENTIALITY AND DATA PROTECTION	
8.1	How, and by whom, will data be collected?
Data will be collected through Cardiff University 'Onlinesurvey' by the investigator Rubina Shah,	
8.2	Will you be accessing or collecting Personal Data (identifiable personal information) as part of the research project? *If yes, please confirm what data will be accessed and/or collected (including details of the information participants are asked to provide on a written consent form).*
No, we are not collecting any personal data	
8.3	How long will you retain the Personal Data collected in connection with the research project?
Not applicable	
8.4	What efforts will be made to anonymise the data collected (where possible)?
All information is collected anonymously	
8.5	Are you proposing to utilise 'public task' as the lawful basis for processing Personal Data for the purposes of the research project (as recommended in the University's GDPR Guidance for Researchers)? *If no, please explain why and what alternative lawful basis you propose to use.*
Yes	
8.6	Have you utilised/incorporated into the Participant Information Sheet the template GDPR privacy information for research participants? *If no, please explain why this has not been used.*
Yes	

8.7	For how long will the collected anonymised data be retained? Please follow the links below for the University guidance on records management and retention schedules: https://www.cardiff.ac.uk/public-information/policies-and-procedures/record-management-policy-and-retention-schedules
5 year	
8.8	Who will have access to the data?
The investigator and the research team	
8.9	Will the data be shared in any way, for example through deposit in a data repository, with third parties, or a transcription service?
No	

SECTION 9. OTHER ETHICAL CONSIDERATIONS

Please outline any other ethical considerations raised by the research project and how you intend to address these. You are obliged to bring to the attention of the SREC any ethical issues not covered in this Ethics Review Application Proforma.

A participant might be concerned about how their data will be used. We have addressed this in the PIS Section 9.

A participant may be concerned that, if they choose not to complete the survey, that their responses may still be recorded. We have addressed this in the PIS Section 9 which states that if a participant decides not to take part**, or to withdraw from the survey,** no record of the responses will be kept.

As this survey is intended to be disseminated by social media, rather than being administered by research team members, there is a possibility that it may be inappropriately completed or completed by individuals who do not conform to the inclusion and exclusion criteria. Such inappropriate responses could adversely affect the results. However, the motivation required to complete the questionnaires makes the likelihood of this low. We will discuss this point as a limitation of the study when the results of this survey are published.

People who have had Covid-19 or their family members, once they come across this survey may feel an obligation to complete it, in order to help others. We have therefore specifically stated in Section 3 of the PIS:

"Do I have to take part?

Taking part in this research study is entirely voluntary and it is up to you to decide whether or not to take part"

Declaration of Interest. Prof Andrew Finlay and Prof Sam Salek are amongst the four joint copyright owners of the FROM-16.

SECTION 10. SUPPORTING DOCUMENTS

I have attached the documents, as indicated in the table below, in support of this application, as a SINGLE Word document.

Please note that the documents listed below **MUST BE** provided where relevant to the research project, alongside any other documents relevant to recruitment, consent and participation.				
		Yes	**No**	**Version no.** (where applicable)
1	Research Project Protocol/Proposal	Yes		Ver 4
2	Recruitment Adverts/Invitation Letters		No	
3	Participant Information Sheet	Yes		Ver 4
4	Consent Form		No	Consent online (within questionnaire)
5	Data Collection Tools (e.g. questionnaires)	Yes		Ver4
6	Other participant communications (e.g. debrief sheets)			
7	Protocol(s) or Standard Operating Procedure(s) of documented and ethically approved common methodology(ies) being used for the research project		No	

SECTION 11. SIGNATURES AND DECLARATIONS

General declaration

I confirm that:

a. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
b. I have the necessary skills, training and or/expertise to conduct the research project as proposed.
c. I am familiar with the University's health and safety requirements and policies and that all relevant health and safety measures have been taken into account for the research project.
d. I am familiar with, and will comply with, the University's Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and the University's Research Integrity and Governance Code of Practice.
e. The relevant equality and diversity considerations have been taken into account when designing the research project.
f. If the research project is approved, I undertake to adhere to the research project protocol, the terms of the full application as approved and any conditions set out by the Committee and any other body required to review and/or approve the research project.
g. I will notify the Committee and all other review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the Committee before implementing the amendment.

FOR STAFF PROJECTS

Signed:

Chief/Principal Investigator

Appendix 1

PROTOCOL

version 4 (28Th May 2020)

IMPACT OF COVID-19 ON QUALITY OF LIFE OF THE PATIENT AND FAMILY MEMBERS

IMPACT OF COVID-19 ON QUALITY OF LIFE OF THE PATIENT AND FAMILY MEMBERS

Investigators

Ms Rubina Shah, PhD postgraduate student, Cardiff University School of Medicine, Cardiff
Prof Andrew Y Finlay, Professor of Dermatology, Cardiff University School of Medicine Cardiff.
Prof Sam Salek, Professor of Pharmacoepidemiology, University of Hertfordshire

Background

Despite the huge number of recent research publications concerning COVID-19, there is very little information on the psychological and social impact of COVID-19 on the patient and their families. Most recent studies focus on identifying the epidemiological and clinical characteristics of infected patients (Huang, 2020; Chen 2020), the genomic characterization of the virus (Lu, 2020), and psychological impact on healthcare professionals (Cai et al, 2020; Shanafelt et al, 2020; Godlee, 2020). To date, there is little information on the lived experience of people infected with COVID-19 and their family members, though the need for this has been identified (Holmes et al, 2020).

The present study will explore the impact of COVID -19 on patients and family members/ partners of people with lived experience of COVID-19. The study will be based on an online survey using social media platforms. We hope this study will help healthcare workers and government agencies to better understand the support needs of patients and their partners and family members.

RESEARCH QUESTION

What is the impact of COVID-19 on the quality of life of the patient and their family members or partners?

METHODS

This study will be a prospective cross-sectional online survey aimed at assessing the impact of COVID-19 on quality of life of COVID-19 survivors and their family members/ partners using an anonymous online questionnaire. The survey will be carried out using the Cardiff university online platform, Cardiffonlinesurveys.ac.uk. (see appendix 3 'Survey')

Expedited Ethics approval will be sought from the Cardiff University School of Medicine Research Ethics committee, which conforms to the principles embodied in the Declaration of Helsinki. The study participants will be provided with information about the study (appendix 2) via a link in the survey. The participants will be able to give informed consent via a tick box option at the start of the survey.

The survey has two sections. Section one is to be completed by the COVID-19 survivor. The patient will be asked to provide some basic demographic details and to complete a EuroQoL (EQ-5D) questionnaire, which takes a few minutes to complete.

Section two is completed by the partner or a close family member of the patient. The family member completes some basic demographic details and a Family Reported Outcome Measure (FROM-16) questionnaire.

The demographic characteristics recorded will be age, gender, whether the patient was admitted to hospital because of COVID-19, country, and relationship of the partner/family member to the patient.

Inclusion /Exclusion criteria

Inclusion criteria

- People who have had COVID-19 and their family member or partner
- Adult aged18 years or older
- Have the mental capacity to give informed written consent and complete the questionnaire using an electronic device.

Exclusion criteria

- Family member/ partner also having COVID-19
- People not affected by COVID-19
- Patient and family member or partner under age 18 years
- Unable to give written informed consent or to operate an electronic device to answer the survey

Distributing the survey

To maximise response rate, the survey will be distributed using various social media channels such as Facebook, Twitter and Google+ launched directly from the Sharing section of the survey dashboards, by simply clicking on the relevant “share” icons. The survey will also be shared via WhatsApp and Linked-in by posting the Public URL link on these sites.

To reach out to more respondents, the survey will be published on the 'Call for Participants' platform, a simple advertising platform focused on bringing opportunities for taking part in academic research to the general public. It will be accessed through the link on the dashboard https://www.callforparticipants.com/researcher

ANALYSIS

Once the survey is closed, the responses will be viewed, and data will be retrieved by the research team by clicking the “Analyse” section of the survey dashboard. The data will be transferred and saved as Excel files. The statistical analysis of the data will be carried out using SPSS version 25.

The analysis will involve descriptive statistics and parametric statistical tests such as Item-total correlations, inter-item correlations, paired and unpaired t-test and their non- parametric equivalents, such as Wilcoxon signed-rank test, Mann-Whitney U test and Spearman rank correlation, depending on the distribution nature of the data.

Dissemination of results of study

The data will be submitted for presentation at national and international meetings and for publication to appropriate scientific journals. The summary of the results will also be disseminated by social media using the same methods as used for recruiting participants.

References

WHO (2020) WHO database: COVID-19, Global literature on coronavirus disease https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

Chen, N. (2020) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 395, 507–513.

Huang, C. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506. [CrossRef]Wuhan, China: A descriptive study. Lancet 395, 507–513.

Li, Q. (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N. Engl. J. Med

Cai H, Tu B, Ma J, et al.(2020). Psychological impact and coping strategies of frontline medical staff in Hunan between January and March during the outbreak of Coronavirus Disease 2019 (COVID-19) in Hubei, China. Med Sci Monit. 2020;26. doi:10.12659/msm.924171.

Godlee Fiona.(2020). Protect our healthcare workers BMJ; 369 :m1324 available at

https://www.bmj.com/content/369/bmj.m1324

Holmes, EA, O'Connor, RC, Perry, VH, Tracey, I, Wessely, S, Arseneault, L, Ballard, C, Christensen, H, Cohen Silver, R, Everall, I, Ford, T, John, A, Kabir, T, King, K, Madan, I, Michie, SF, Przybylski, AK, Shafran, R, Sweeney, A, Worthman, CM, Yardley, L, Cowan, K, Cope, C, Hotopf, M & Bullmore, E (2020), 'Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science', The Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(20)30168-1

WHO, (2020) World Health Organization Coronavirus disease (COVID-19) Situation Dashboard https://covid19.who.int/

Appendix 2

PARTICIPANT INFORMATION SHEET-COVID-19

version 4 (28th May 2020)

Project title: Impact of COVID-19 on quality of life of the patient and family members

We are trying to find out how COVID-19 affects the quality of life of people who have had COVID-19 and their family members.

This invitation is for anyone whose partner or family member has had from COVID-19.

Invitation

We would like to invite you to take part in a Cardiff University study. Before you decide whether or not to take part, it is important to understand why we are doing the research and what it involves. Please read this information carefully and discuss it with others, if you wish.

What is the purpose of this research project?

Being infected with COVID-19 may have a huge impact on the physical, social and psychological wellbeing of the affected person as well as on their family members, but the extent of this impact is not known. In this study people who have had Covid-19 and their partner or close family member will answer a short questionnaire online to give this information. We hope this study will help healthcare workers and government agencies understand better the support needed by patients and their families.

Why have I been invited to take part?

You have been invited because you are an adult over the age of 18, and you have a partner or relative (over the age of 18) who has had COVID-19.

Do I have to take part?

Taking part in this research study is entirely voluntary and it is up to you to decide whether or not to take part.

What will taking part involve?

First you are asked to read about the study in the participant information sheet. Next you are asked to agree to a series of short statements giving your consent to take part. Next you do the survey, which has two sections.

Section One is to be completed by the person in your family who has had COVID-19. This person is asked to give some basic information such as age and gender and to complete a simple questionnaire (EQ-5D). This takes only a few minutes.

Section Two is completed by the partner or other close family member of the affected person. The family member will also be asked to give some basic information and to fill in the simple FROM-16 questionnaire. This takes only a few minutes. All answers you provide will be kept strictly confidential.

This survey is in English and other languages are not available. However, we will engage in Welsh if requested (contact ShahR45@cardiff.ac.uk).

Will I be paid for taking part?
No. There is no payment given to those taking part.
.

What are the possible benefits of taking part?
The benefit of taking part is mainly the satisfaction of knowing that your contribution will help us understand the impact that having COVID-19 has on the Quality of Life of affected people and their family members. This information may help healthcare workers understand the support needs of patients and their family members.

What are the possible risks of taking part?
There is a small risk that answering this survey may cause distress, for example if the questions draw attention to sensitive issues. If you are affected in this way, we suggest that you stop completing the questionnaire and seek advice from your doctor or from a psychologist or contact us directly.

Will my taking part in this research project be kept confidential?
All information collected from (or about) you during the research project will be kept confidential and any personal information you provide will be managed in accordance with data protection legislation. Please see 'What will happen to my Personal Data?' (below).

What will happen to my Personal Data?
You will not be required to provide any personal data (e.g. name, address).
Cardiff University is the Data Controller and is committed to respecting and protecting your data in accordance with your expectations and Data Protection legislation. Further information about Data Protection may be found at
https://www.cardiff.ac.uk/public-information/policies-and-procedures/data-protection.
The survey platform used (Jisc Online Survey) and the handling of data in this study comply with the requirements of General Data Protection Regulation (GDPR)

As the survey data are collected your response will automatically be given a unique number so no-one will know it was you responding. If you decide not to take part, or to withdraw from the survey, no record of your responses will be kept.

What happens to the data at the end of the research project?

At the end of the project the data files will be kept for five years in accordance with the University requirements. No identifiable data will be shared with anyone other than the researc team.

What will happen to the results of the research project?
The findings will be presented at local, national and international scientific conferences. The findings will also be published in an academic scientific journal.

What if there is a problem?
If any problem arises, please contact the Ms Rubina Shah via email ShahR45@cardiff.ac.uk.

If you wish to make a complaint relating to this research project, you should contact Prof Andrew Y Finlay (Chief Investigator).

Who is organising and funding this research project?
The research is funded by Cardiff University. This research project is not funded by a commercial organisation.

Who has reviewed this research project?
This research project has been reviewed and given a favourable opinion by the School of Medicine Research Ethics Committee, Cardiff University.

Further information and contact details
Should you have any questions relating to this research project, you may contact :

Thank you for taking the time to read this leaflet

Appendix 3

Impact of COVID-19 on quality of the patient and family members/partners Survey

(COVID-19 SURVEY version 4 (28th May 2020)

Having Covid-19 can have a huge impact on people's wellbeing. We want to find out in more detail how Covid-19 affects the quality of life of the affected person and their partner or family member. This is important because this will help healthcare workers to understand and meet the needs of families. Please help us by completing this short questionnaire. The first part is to be completed by the person who has had COVID-19. The second part is to be completed by that person's partner or family member. It is important that both sections are completed. All answers you provide will be kept anonymous.

A big **thank you** from our research team at Cardiff University, United Kingdom!

Consent to take part

Once you have read the participant information sheethttps://cf-my.sharepoint.com/personal/shahr45_cardiff_ac_uk/Documents/Partcipant%20information%20sheet(PIS)_COVID-19%20ver3.docx please confirm you are happy to complete this survey by placing a mark in the 'yes' box below.

I am 18 years of age or over

Yes ☐

No ☐

Please state country you are in

☐

I have read the information sheet provided

Yes ☐

No ☐

I would like to take part in this survey

Yes ☐

No ☐

SECTION 1-TO BE COMPLETED BY THE PERSON WHO HAD COVID-19

What is your gender?

Male ☐

Female ☐

What is your age?

☐

How are you normally occupied?

In paid work..... ☐

Unemployed ..... ☐

In education or training..... ☐

In unpaid work..... ☐

Work in the home / manage the family..... ☐

Retired..... ☐

Rather not say..... ☐

Do you have any existing chronic health conditions?

Yes..... ☐

No..... ☐

Did you have to stay in a hospital because of COVID-19?

Yes..... ☐

NO..... ☐

EQ-5D™QUESTIONNAIRE

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

MOBILITY

I have no problems in walking about..... ☐

I have some problems in walking about..... ☐

I am confined to bed..... ☐

SELF-CARE

I have no problems washing or dressing myself..... ☐

I have some problems washing or dressing myself ..... ☐

I am unable to wash or dress myself..... ☐

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

I have no problems doing my usual activities..... ☐

I have some problems doing my usual activities..... ☐

I am unable to do my usual activities..... ☐

PAIN / DISCOMFORT

I have no pain or discomfort..... ☐

I have moderate pain or discomfort..... ☐

I have extreme pain or discomfort..... ☐

ANXIETY / DEPRESSION

I am not anxious or depressed..... ☐

I am moderately anxious or depressed..... ☐

I am severely anxious or depressed..... ☐

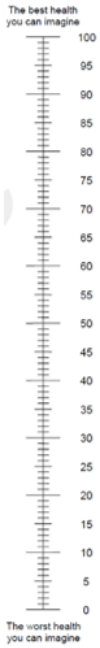
We would like to know how good or bad your health is TODAY

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an **X** on the scale to indicate how your health is TODAY. Now, please write the number you marked on the scale in the box below.



SECTION 2- TO BE COMPLETED BY FAMILY MEMBER / PARTNER

What is your gender?

Male ☐

Female ☐

What is your age?

☐

How are you normally occupied?

In paid work..... ☐

Unemployed..... ☐

In education or training..... ☐

In unpaid work..... ☐

Work in the home / manage the family..... ☐

Retired..... ☐

Rather not say..... ☐

What is your relationship to your family member who had COVID-19?

Spouse / Partner..... ☐

Parents..... ☐

Son /Daughter..... ☐

Brother /Sister..... ☐

Other (Please specify)..... ☐

Did you he/she had to stay in a hospital because of COVID-19?

Yes..... ☐

NO..... ☐

FAMILY REPORTED OUTCOME MEASURE (FROM-16) QUESTIONNAIRE

The following questions are about how **your** life is being affected by your family member's condition **at the moment**.
Please mark one box for each of the 16 questions.

Part 1: Emotional

Because of my family member's condition...	Not at all	A little	A lot
1. I feel worried	☐	☐	☐
2. I feel angry	☐	☐	☐
3. I feel sad	☐	☐	☐
4. I feel frustrated	☐	☐	☐
5. It is difficult to find someone to talk to about my thoughts	☐	☐	☐
6. Caring for my family member is difficult	☐	☐	☐

Part 2: Personal and Social Life…	**Not at all**	**A little**	**A lot**
7. It is hard to find time for myself	☐	☐	☐
8. My every day travel is affected	☐	☐	☐
9. My eating habits are affected	☐	☐	☐
10. My family activities are affected	☐	☐	☐
11. I experience problems with going on holiday	☐	☐	☐
12. My sex life is affected	☐	☐	☐
13. My work or study is affected	☐	☐	☐
14. My relationships with other family members are affected	☐	☐	☐
15. My family expenses are increased	☐	☐	☐
16. My sleep is affected	☐	☐	☐

Have you read and answered all the questions?	Yes	☐

Thank you very much for your help

" If you would like to know the results of this survey, they will be available later in 2020 on our FROM-16 website:

https://www.cardiff.ac.uk/medicine/resources/quality-of-life-questionnaires/family-reported-outcome-measure

Appendix XIX: SMREC ethics approval for COVID-19 study

School of Medicine
Yr Ysgol Meddygaeth

Cardiff University
Main Building
Heath Park
Cardiff CF14 4XN
Wales, UK
Prifysgol Caerdydd
Prif Adeilad
Parc y Mynydd Bychan
Caerdydd CF14 4XN
Cymru, Y Deyrnas Unedig

Thursday 28th May 2020

Rubina Shah
Division of Infection & Immunity
School of Medicine
Cardiff University

Dear Rubina,

Research project title: Impact of COVID-19 on quality of life of the patient and family members
SREC reference: SMREC 20/60

The School of Medicine Research Ethics Committee ('Committee') reviewed the above application electronically on Thursday 21st May 2020. A revised application was considered by the Chair on Thursday 28th May 2020.

Ethical Opinion
The Committee gave a favourable ethical opinion of the above application on the basis described in the application form, protocol and supporting documentation.

Additional approvals
This letter provides an ethical opinion only. You must not start your research project until all appropriate approvals are in place.

Amendments
Any substantial amendments to documents previously reviewed by the Committee must be submitted to the Committee via email to Claire Evans (EvansCR9@cardiff.ac.uk) for consideration and cannot be implemented until the Committee has confirmed it is satisfied with the proposed amendments.

You are permitted to implement non-substantial amendments to the documents previously reviewed by the Committee but you must provide a copy of any updated documents to the Committee via email to Claire Evans (EvansCR9@cardiff.ac.uk) for its records.

Monitoring requirements
The Committee must be informed of any unexpected ethical issues or unexpected adverse events that arise during the research project. In addition to this, the Committee request an end of project report sent to the Committee via email to Claire Evans [redacted]. This must be sent along with confirmation that your research project has ended and sent within the three months of the research project completion.

Documents reviewed by Committee
The documents reviewed by the Committee were:

Document	Version	Date
Application Form	V1 09/03/20	21/05/20
Protocol	V3 13/05/20	21/05/20
Participant Information Sheet	V3 07/05/20	21/05/20
Survey	V3 07/05/20	21/05/20
Appendix 4	V1 09/03/20	21/05/20
Appendix 5	V1 09/03/20	21/05/20
Application Form	V1 09/03/20	28/05/20
Protocol	V4 28/05/20	28/05/20
Participant Information Sheet	V4 28/05/20	28/05/20
Survey	V4 28/05/20	28/05/20
Appendix 4	V1 09/03/20	28/05/20
Appendix 5	V1 09/03/20	28/05/20
Response to Chair	28/05/20	28/05/20

Appendix XIX: SMREC ethics approval for COVID-19 study

Complaints/Appeals

If you are dissatisfied with the decision made by the Committee, please contact the Chair of the Committee via the Committee Secretary (EvansCR9@cardiff.ac.uk) in the first instance to discuss your complaint. If this discussion does not resolve the issue, you are entitled to refer the matter to the Head of School for further consideration. The Head of School may refer the matter to the University Research Integrity and Ethics Committee (URIEC), where this is appropriate. Please be advised that URIEC will not normally interfere with a decision of the Committee and is concerned only with the general principles of natural justice, reasonableness and fairness of the decision.

Please use the Committee reference number on all future correspondence.

The Committee reminds you that it is your responsibility to conduct your research project to the highest ethical standards and to keep all ethical issues arising from your research project under regular review.

You are expected to comply with Cardiff University's policies, procedures and guidance at all times, including, but not limited to, its Policy on the Ethical Conduct of Research involving Human Participants, Human Material or Human Data and our Research Integrity and Governance Code of Practice.

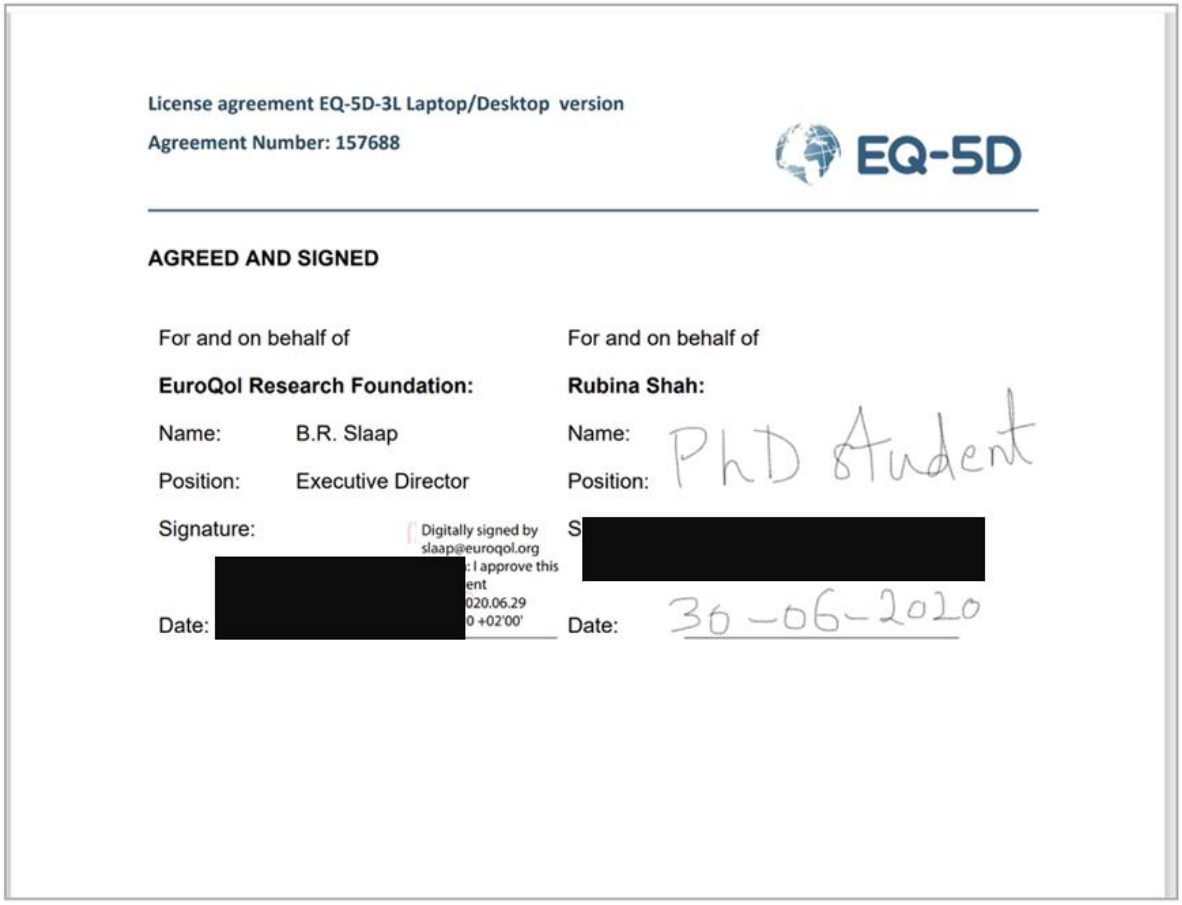
Yours sincerely,

[redacted]

Acting Chair, School of Medicine Research Ethics Committee

[redacted]

Appendix XX: Euroqol approval for EQ-5D-3L- COVID-19 study



License agreement EQ-5D-3L Laptop/Desktop version

Agreement Number: 157688

EQ-5D

AGREED AND SIGNED

For and on behalf of		For and on behalf of	
EuroQol Research Foundation:		**Rubina Shah:**	
Name:	B.R. Slaap	Name:	PhD Student
Position:	Executive Director	Position:	
Signature:	Digitally signed by slaap@euroqol.org : I approve this ent 020.06.29 0 +02'00'	S	[redacted]
Date:	[redacted]	Date:	30-06-2020

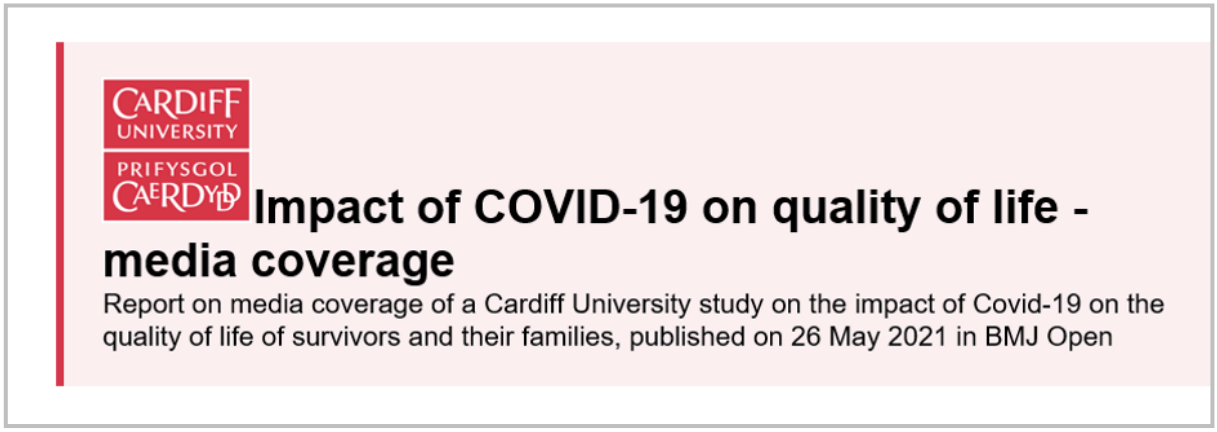
Appendix XXI: Cardiff University media report-COVID-19 study

Email excerpt

Here's the BMJ Open link and the Cardiff University news story.

The study has had extensive coverage (mainly through the Press Association):

- Nearly 200 articles in regional and national press, including:
- Daily Mail: https://www.dailymail.co.uk/wires/pa/article-9618989/Long-Covid-severely-affecting-families-suffering--study.html
- London Evening Standard: https://www.standard.co.uk/news/uk/experts-cardiff-university-of-oxford-oxford-sheffield-b937244.html
- Belfast Telegraph: https://www.belfasttelegraph.co.uk/news/uk/long-covid-severely-affecting-families-of-those-suffering-study-40470135.html
- The National (Scotland): https://www.thenational.scot/news/uk-news/19328482.long-covid-severely-affecting-families-suffering---study/
- The National (Wales): https://www.thenational.wales/news/national/19328482.long-covid-severely-affecting-families-suffering---study/
- BBC Radio Wales news bulletins



Cardiff University media report COVID-19 study (Shah et al. 2021)