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Development of a preference-based outcome measure for use in economic evaluations of palliative care services

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Development of a preference-based outcome measure for use in economic evaluations of palliative care services

A thesis submitted to King's College London for the Degree of Doctor of Philosophy

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Author's declaration

I declare that this thesis is my original work and that the contents and views expressed are mine. I have conducted all the work reported in this thesis, with support from supervisors and others declared the Acknowledgements section.

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Development of a preference-based outcome measure for use in economic evaluations of palliative care services

Mendwas Dzingina – BuildCARE PhD Training Fellow

Abstract

Background

Numerous instruments measure outcomes in palliative care. However, these instruments are not preference-based and so are unable to yield quality-adjusted life years (QALYs). Conversely, the generic preference-based measures (PBM) are neither appropriate nor sensitive enough to measure changes in palliative care outcomes.

Aim

The objective of this thesis was to propose a new palliative-care health state classification system, called POS-E, and to estimate its preference weights so that it can be used in QALY calculations.

Methods and results

Design: Secondary data analysis followed by a cross sectional survey informed by the Health Technology Assessment guide for developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome).

This thesis consists of two main stages. The first stage explored the feasibility of deriving QALYs "**indirectly**" by mapping a commonly used palliative care instrument – the Palliative Care Outcome Scale (POS) – onto a generic PBM (EQ-5D; 3-level) using regression techniques. Data from three studies which included both POS and EQ-5D (N = 783) were combined and then randomly split into estimation and validation data sets. The overlap between both measures was assessed using principal component analysis (PCA) and correlation matrix analysis. Subsequently, we attempted to map the POS to the EQ-5D using three regression models. The mean absolute error (MAE), adjusted R^2, and predicted/observed plots were used to assess the quality of mappings. The results showed low correlations between both instruments and that the POS is associated with only two

EQ-5D dimensions (pain; and anxiety/depression). No POS items loaded onto the mobility; self-care; and usual-activities dimensions of the EQ-5D. The mapping models performed poorly at predicting utilities from POS data (MAE > 0.3 and R^2 <0.10). This suggests that the EQ-5D did not capture some important aspects of the POS, and therefore mapping is unlikely to provide an appropriate basis for indirectly estimating utilities for conducting economic evaluations in palliative care studies.

The second stage explored the feasibility of **directly** deriving palliative-care-specific QALYs using the POS. The methods used here were based on the Health Technology Assessment (HTA) guidance document on "developing and testing methods for deriving preference based measures of health from condition-specific measures (and other patient-based measures of outcome)", Brazier et al, 2012. This stage was further divided into three phases consisting of the following:

1) Revising the palliative outcome scale (POS) into a simplified health state classification amenable to valuation using items selected using Rasch and factor analyses. This involved combining data from six studies of patients receiving palliative care (N = 1011) and splitting this into two random halves – development and validation data. Analysis was undertaken on the development data and results were validated by repeating the analysis on the validation dataset. Following this, a classification system made of seven items with 1–2 levels each was derived. The POS-E describes a total 1,458 discrete health state. From this, Rasch analysis identified 14 plausible health states that were appropriate for valuation;

2) A valuation survey of palliative-care patients and healthy volunteers using a modified time-trade-off technique (TTO) to derive preference weights for the 14 health states derived from phase (1) above, and a comparison of the difference between patient values and values from healthy volunteers using simple t-tests. 102 participants (52 palliative care patients and 50 healthy volunteers) were surveyed across five sites in England. Each respondent valued eight health states and the analysis was based on a total of 408 valuations. Patient values and healthy volunteer values were very similar, with some areas of divergence. Mean TTO values ranged from 0.21 to 1 for patients, and 0.22 to 0.99 for healthy volunteers, for the worst and best health states respectively.

All TTO values corresponded logically with the order of severity of the health state classification, thereby supporting the internal validity of the health state classification system.

3) Estimating the utility weights for the full set of health states using regression techniques. This involved using regression analysis to estimate utility values for all health states using the Rasch logit score for dimensions that are correlated (i.e. have unidimensional properties).

This involved using regression models to estimate the relationship between the utility values obtained from the valuation survey, and their corresponding Rasch logit score. Subsequently, this mathematical relationship was used to estimate the utility values of all other POS-E health states (which were excluded from the valuation survey) based on their respective Rasch logit scores. Having tested several models, the model chosen for estimating the mean preference values of all other POS-E health state was the one which included linear, quadratic, cubic, and quartic terms, as it had the least predictive error and best explained the variation in the preference values obtained from the valuation survey (as indicated by low RMSE and high R-squared values), and its coefficients were all statistically significant.

Conclusion

In conclusion, the output of this thesis is a palliative care specific preference-based measure (POS-E) that can be used to calculate QALYs for cost-utility analysis of palliative care interventions. This thesis has addressed most of the theoretical and methodological concerns of cost-utility analysis in palliative care. It demonstrated that it is feasible to obtain meaningful preference values from patients with advanced chronic illness, and also that patient values are similar to similar to those of healthy people. It also showed that the QALY is still a useful vehicle for quantifying joint mortality and morbidity impacts of palliative care at individual and population level. Given the widespread use of the POS in assessing palliative care outcomes in the UK and internationally, the POS-E is expected to facilitate broader economic evaluations of palliative care interventions using current and forthcoming POS data sets.

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Related publications, and presentations

Publications incorporated into thesis

1. **Dzingina MD**, Higginson IJ. Public Health and Palliative Care in 2015. Clinics in Geriatric Medicine. 2015(0):253–63. doi:http://dx.doi.org/10.1016/j.cger.2015.01.002. [**Chapter 2**]

2. **Dzingina MD**, McCrone P, Higginson IJ. Does the EQ-5D capture the concerns measured by the Palliative care Outcome Scale? Mapping the Palliative care Outcome Scale onto the EQ-5D using statistical methods. Palliative medicine. 2017; 0(0). doi:10.1177/0269216317705608. [**Chapter 5**]

3. **Dzingina M**, Higginson IJ, McCrone P, Murtagh FEM. Development of a Patient-Reported Palliative Care-Specific Health Classification System: The POS-E. The Patient - Patient-Centered Outcomes Research. 2017:1-13. doi: 10.1007/s40271-017-0224-1. [**Chapter 6**]

4. **Dzingina M**, Murtagh FEM, Higginson IJ, McCrone P. Preference weights for a palliative care health classification system: valuation study of POS-E. Value in health (in press). Manuscript submitted to Health Economics journal [**Chapter 7**]

5. **Dzingina MD**, Reilly CC, Bausewein C, Jolley CJ, Moxham J, McCrone P et al. Variations in the cost of formal and informal health care for patients with advanced chronic disease and refractory breathlessness: A cross-sectional secondary analysis. Palliative medicine. 2017; 31(4):369-77.:doi:10.1177/0269216317690994. [**Chapter 10**]

Other publications

- Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, **Dzingina M**, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. The Lancet Respiratory Medicine. 2014; 2(12):979-87.

Presentations and published abstracts

1. **Dzingina MD**, Mccrone P, Higginson, I.J. (2016). Does the EQ-5D Capture the Concerns Measured by the POS? Palliative Medicine, DOI: 10.1177/0269216316646056: P58
   9th World Research Congress of the European Association for Palliative Care – Dublin, Ireland: June 2016. [Oral]

2. **Dzingina MD**, Higginson, I.J, McCrone P, Murtagh F. (2015) Development of a Preference-based Outcome Measure for Use in Economic Evaluations of Palliative Care Services. European Journal of Palliative Care. ISBN 978-0-9542022-3-1: P1-069
   14th World Research Congress of the European Association for Palliative Care. Copenhagen, Denmark: May 2015. [Poster]

3. Guo P., **Dzingina M**., Firth A.M., Davies J.M., Flach C., Douiri A., O'Brien S.M., Pinto C., Pask S., Higginson I.J., Eagar K., Murtagh F. (2017). What Casemix Criteria Best Predict Costs of Palliative Care Provision in the UK? A Casemix Development Study across Palliative Care Settings. European Journal of Palliative Care. FC16. 15th World Congress of the European Association for Palliative Care – Madrid, Spain: May 2017 [Oral]

4. Ellis-Smith C, Evans CJ, Bone AE, Henson LA, **Dzingina MD**, Kane PM, Higginson IJ, Daveson BA, on behalf of BuildCARE. (2016) Measures to Assess Commonly Experienced Symptoms for People with Dementia in Long-term Care Settings: A Systematic Review. Palliative Medicine, DOI: 10.1177/0269216316646056: P59

9th World Research Congress of the European Association for Palliative Care – Dublin, Ireland: June 2016. [Oral]

5. Dzingina MD, Higginson, I.J, McCrone P, Murtagh F. (2018). A New Preference-based Measure for Economic Evaluation of Palliative Care Interventions: POS-E. 10th World Research Congress of the EAPC – Bern, Switzerland May 2018. [Accepted for an oral presentation]

Invited Presentations

1. QALY expert meeting (EAPC 2017): Using the QALY in palliative and end-of-life care. Madrid, 2017
2. Workshop on the economics of end of life care, University of Birmingham, Birmingham. September 2015
3. Outcome measures in palliative care: estimating a preference-based measure of health-related quality of life (HRQoL) for the POS – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 2). Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 10th February 2017
4. Outcome measures in palliative care: estimating a preference-based measure of health-related quality of life (HRQoL) for the POS – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 2). Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 12th February 2016
5. Outcome measures in palliative care: estimating a preference-based measure of health-related quality of life (HRQoL) for the POS – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 2). Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 6th February 2015
6. Developing a preference-based outcome measure for use in economic evaluations of palliative care services – **Mendwas Dzingina**. Workshop on health economics in palliative care. National Guideline Centre, Care Quality Improvement Department, Royal College of Physicians London. 14th December 2015.

7. Improving Outcome measurement: using POS with those with English as a second language – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 1); Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 10th February 2014
8. Improving Outcome measurement: translation and cultural validation – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 2); Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 11th February 2014
9. Development of a preference-based outcome measure for use in economic evaluations of palliative care services – **Mendwas Dzingina**. London University-based Health Economics PhD Students' Showcase. King's College London. 22nd October 2014.
10. Improving Outcome measurement: using POS with those with English as a second language – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 1); Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 18th February 2013
11. Improving Outcome measurement: translation and cultural validation – **Mendwas Dzingina**. Palliative care Outcome Scale (POS) workshops to advance clinical care and research (Day 2); Cicely Saunders Institute of Palliative care and Rehabilitation; King's College London. 19th February 2013

List of abbreviations

AQLQ	Asthma Quality of Life Questionnaire
ADDQoL	Audit of Diabetes-Dependent Quality-of-Life
ANOVA	Analysis of Variance
BWDCE	Best-Worst Discrete Choice Experiment
BWS	Best-Worst Scaling
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CLAD	Censored Least Absolute Deviation
COPD	Chronic Obstructive Pulmonary Disease
CSM	Condition-Specific Measure
CUA	Cost Utility Analysis
DCE	Discrete Choice Experiment
DIF	Differential Item Functioning
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
EQ-5D	EuroQol 5-Dimension
GHQ	General Health Questionnaire
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HRQoL	Health-Related Quality of Life

HTA	Health Technology Assessment
HUI	Health Utilities Index
ICECAP-SCM	ICECAP-Supportive Care Measure
ICER	Incremental Cost Effectiveness Ratio
IPOS	Integrated Palliative care Outcome Scale
IRT	Item Response Theory
KHQ	King's Health Questionnaire
MAUT	Multi-Attribute Utility Theory
ME	Magnitude Estimation
MID	Minimal Important Difference
MVH	Measurement and Valuation of Health
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OAB-q	Overactive Bladder Questionnaire
OLS	Ordinary Least Squares
PalY	Palliative care Yardstick
PBM	Preference-Based Measure
PCA	Principal Components Analysis
POS	Palliative care Outcome Scale
POS-E	Palliative Care Outcome Scale – Economic evaluation
PPI	Patient Public Involvement

PROM	Patient-Reported Outcome Measure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSI	Person Separation Index
PTO	Person Trade Off
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RMSE	Root Mean Squared Error
SF-36	Short Form (36) Health Survey
SF-6D	Short Form 6-Dimension
SG	Standard Gamble
TTO	Time Trade-Off
UK	United Kingdom
VAS	Visual Analogue Scale
VIP	Valuation Index Palliative
WHO	World Health Organization

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1. Introduction

At the 67th World Health Assembly (23rd MAY 2014), the World Health Organisation (WHO) passed the first ever resolution on palliative care recommending National health systems to provide palliative care in conjunction with potentially curative treatment, and not just as an "*optional extra"*.[4] The resolution also urges member states to develop and implement policies which support the integration of cost-effective and equitable palliative care services throughout the continuum of care, across all levels.[5]

Palliative care is currently being incorporated into mainstream health service provision in the UK. In order to provide resources required to meet the needs of dying patients, health policy makers require information on the 'value for money' of palliative care treatments and interventions. Economic evaluation using cost-utility analysis (CUA) is the recommended means for generating such information.[6] There is a dearth of full economic evaluations, especially CUAs, in palliative care.[7, 8]

CUA compares interventions in terms of their cost per quality adjusted life year (QALY) gained. QALYs combine life expectancy (in years) and quality of life (expressed in the form of "health state values") into a single metric, based on peoples' preferences. The quality of life (QOL) portion is estimated by assigning a numerical value to each health state experienced by a patient on a scale from one for full health, to zero for states regarded equivalent to being dead (and negative values for states worse than being dead).[9]

A common way of estimating health-state values is to use a 'generic' preference-based measure (PBM), such as the EuroQOL five dimensions questionnaire (EQ-5D).[10] All PBMs have a preference-based algorithm for assigning values to each health state. In other words, a PBM could be regarded as a quality-of-life tool whose item-levels have been assigned 'preference weights' which reflect the desirability (or importance) of each item level relative to the others. These preference weights are usually obtained by asking members of the general public preference elicitation questions, such as 'time-trade-off' (TTO) or 'standard gamble' (SG).[2] Generic PBMs were developed on the basis that they could be used in all patients, irrespective of their medical condition because they concentrate on core aspects of health-related quality of life (HRQoL). This claim has been supported in many interventions and disease groups, for example, Marra et al.

(2005) demonstrated the discriminative ability of four generic measures across severity levels for patients with rheumatoid arthritis.[11]

However, medical conditions, generic PBMs have been found to be inappropriate or insensitive to "small but important changes". In the discipline of palliative care, there are concerns that generic PBMs are heavily focused on physical function (e.g. 4 of the 5 dimensions of the EQ-5D measure physical aspects of HRQoL), and so do not incorporate many aspects of HRQoL important to palliative-care patients.[12, 13] This has led to proposals for the development of a palliative-care-specific PBM that would be appropriate for palliative-care patients with a variety of conditions.[12, 14] Presently, no such measure exists. The Palliative Care Outcome Scale (POS) has been suggested as suitable for this purpose.[12]

This thesis addresses the above problem by developing a preference-based measure for use in economic evaluations of palliative care.

1.2 Structure of thesis

The remainder of this thesis is divided into eight chapters. Chapter 2 provides the background and context, and reviews the literature underpinning this thesis. It examines the extent to which economic evaluations have been used in palliative care studies and explores the theoretical literature for arguments for and against using QALYs in palliative care. The literature search was conducted in December 2013. It reports the methods used to elicit preferences for estimating QALYs and for conducting cost-utility analysis, and it explores the appropriateness of such methods in palliative care. It also provides the rationale and theoretical underpinnings of the thesis. Chapter 3 describes the aims and objectives. Chapter 4 provides an overview of the methods used in the thesis and the relevant methodological considerations. Chapter 5 describes the methods and results of the first of three empirical studies conducted: a secondary analysis of data merged from several studies. Factor analysis and statistical mapping were used to explore the relevance of the standard EQ-5D measure against a validated palliative care instrument – the palliative care outcome scale (POS). The findings here demonstrated the need for the research conducted in the subsequent chapters.

Chapter 6 describes the methods and results for the second of three empirical studies conducted – a secondary analysis of POS data merged from several studies. Factor analysis and Rasch analysis of POS data were conducted to create a palliative care specific health classification system (POS-E) for the POS; and select a sub-sample of health states suitable for valuation. The findings here informed the development of the study in the next chapter.

Chapter 7 describes the methods and results for the third and final empirical study – a cross-sectional valuation study of 50 healthy volunteers and 52 patients with advanced serious illness. As well as seeking to address the main research question in this thesis, this study also sought to examine whether patient preferences differed from those of healthy volunteers.

Chapter 8 concludes by bringing together and discussing the findings of the whole thesis. It summarises the main contributions and limitations of the research, highlights implications of the findings, and identifies areas for further research.

2. Background

2.1. Palliative care

The World Health Organisation (WHO) defines palliative care as '*the active holistic care of patients with advanced progressive disease, aimed at achieving the best possible QoL for patients and families, through the management of pain and other symptoms, as well as provision of spiritual, psychological and social support; which may be initiated early in the course of treatment along with other curative treatments'*.[15]

According to WHO estimates, globally, about 20 million people (of which 6% are children and 67% are >60 years old) need palliative care annually.[16] This number doubles if those that could benefit from palliative care earlier in their illness are included.[4, 16]

Cancer patients account for a third of people in need of palliative care. The rest include people suffering from a variety of chronic progressive diseases such as cardiovascular diseases, HIV/AIDS, drug-resistant tuberculosis, chronic obstructive pulmonary disease, renal failure etc.[4] The common causes of death among adults in need of palliative care are cardiovascular disease (38.5%), cancer (34%), chronic respiratory diseases (10.3%) and HIV/AIDS (5.7%).[16]

In the UK, the model of palliative care provision is based on complexity of need. Patients (and family) with low to moderate complexity are provided 'general-palliative-care' by their usual professional care providers, as part of routine clinical practice. Those with moderate to high complexity of need are provided 'specialist-palliative-care', by a specialist-palliative-care team, either through the NHS or the voluntary sector.[17] An essential part of palliative care is end-of-life care, which refers to the care provided to a patient whose illness has reached a state of progressive decline – usually within the last days, weeks or months of life. Nonetheless, the need for end-of-life care may be considered in the earlier stages of several incurable non-cancer illnesses.[17]

In the UK, palliative care is provided to patients and their families through both the NHS and/ or the charitable sector. The majority of healthcare professionals have had training in – and deliver –

generalist palliative care, with specialist teams providing additional support and care for more complex patients and their families. An important part of palliative care is end-of-life care, which is provided during a person's last days to weeks of life. However, aspects of end-of-life care, may be considered in the earlier stages of many illnesses.[17]

The principles that underpin palliative care are based on the integration of symptom-control, psychosocial care and disease management, and so require true interdisciplinary collaboration. The goals of palliative care include improving patient and family QOL[18], satisfaction, and patients' perceptions of 'purpose' and 'meaning of life'.[19] Additionally, there is evidence to suggest that palliative care reduces emergency department attendances and hospital admissions towards the end of life and so provides benefits to the health care system and wider society.[4]

Palliative care is now regarded as a major public health issue for several reasons including:

1. Recognition by global health policy makers including the W.H.O. in its 67th world health assembly described above;
2. The aging world population and the shift in the main causes of morbidity and mortality from communicable to chronic non-communicable diseases;
3. Evidence of unmet palliative care need globally;
4. Inequities in access to appropriate care including among older people, people with dementia, gay and bisexual people, people living in deprived areas, and drug addicts.

The article that follows presents current and future trends of global causes of morbidity and mortality and presents arguments to support the notion that palliative care is a public health concern, and so it would be useful to not only demonstrate its effectiveness but also its cost-effectiveness.

2.1.1 Public health and palliative care

Public Health and Palliative Care in 2015

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KEYWORDS

• Public health • Palliative care • Cost-effectiveness • End-of-life
• Quality adjusted life year

KEY POINTS

- Palliative care is a public health concern, because the problems faced by patients and their families represent a substantial burden of illness and cost to society, which is likely to increase markedly in the future as the world's population continues to age.
- There is evidence to support palliative care services, but not yet enough information on the cost-effectiveness of many specific palliative care treatments/interventions.
- The lack of economic evaluations deprives decision makers of information required to best meet the needs of patients with progressive disease and at the end of life.
- It would be useful to empirically assess the appropriateness of generic measures of health-related quality of life (such as the EQ-5D) and the quality-adjusted life year framework in palliative care.

WHY IS PALLIATIVE CARE A MAJOR PUBLIC HEALTH CHALLENGE?

Palliative Care: Traditional Roots

The World Health Organization (WHO) defines palliative care as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual."[1,2]

The principles that underpin palliative care are based on the integration of symptom control, psychosocial care, and disease management, and so require true interdisciplinary collaboration. The goals of palliative care include improving patient and family quality of life,[3,4] satisfaction, and patients' perceptions of purpose and meaning of life.[5] Additionally, there is evidence to suggest that palliative care reduces emergency department attendances and hospital admissions toward the end of life and so provides benefits to the health care system and wider society.[6–8]

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Palliative care was initially developed in the British hospice movement in the 1960s. Guided by the pioneering work of Cicely Saunders, the concept evolved to include multidimensional needs of patients with a comprehensive approach practiced by a multidisciplinary team focusing initially, on end-of-life cancer patients attended to in hospices.

An early reference to palliative care being identified as a public health topic was published by Eric Wilkes[9] in the 1980s, following the recognition that most deaths were related to chronic conditions other than cancer, and that these occurred in hospitals and at home without any palliative care specialist intervention. On the basis of this reality, he proposed developing palliative care in all settings.

Global Health Policy

At the 67th World Health Assembly (May 23, 2014), the WHO passed the first ever resolution on palliative care recommending national health systems to provide palliative care in conjunction with potentially curative treatment, and not just as an optional extra.[6] The resolution also urges member states to develop and implement policies that support the integration of cost-effective and equitable palliative care services in the continuum of care, across all levels.[1]

Earlier resolutions regarding palliative care mainly focused on cancer patients and the end of life.[10] However, the WHO mandate on palliative care has evolved and currently extends to include patients with chronic noncancer conditions, in the early phase of their disease, as highlighted in the first ever palliative care resolution. It is evident that this evolution of the WHO mandate reflects the evolution of the concept of palliative care as a whole, which consists of

- Extending care beyond cancer and into more general chronic conditions
- Promoting early palliative interventions in the clinical evolution of the disease
- Applying palliative care measures in all settings of the health care system
- Identifying complexity versus prognosis as criteria for specialist interventions

In other words, the focus of palliative care has shifted from the concept of terminal illness to advanced chronic illness with a limited prognosis, and from a specialty (oncology) approach, to a national health care system approach.[10,11]

Aging Population and Shift in Causes of Morbidity and Mortality

According to the United Nations (UN), the life expectancy of the world's population has increased from 48 years from 1950 to 1955 to 68 years from 2005 to 2010.[12] This increase in life expectancy has been attributed to a decrease in mortality rates and a decline in fertility.[12] All regions of the world have experienced an increase in life expectancy, and this is predicted to increase in the future.[4,13,14] Currently, the pattern varies, with higher numbers of people dying in late old age in developed countries compared with lower and middle income countries. For example, Evans and colleagues[15] found that centenarian (a person aged 100 years or over) deaths increased by 56% between 2001 and 2010 in England.

The exact number of centenarians living worldwide is uncertain but is thought to be around 317,000 and is projected to rise to about 18 million by the end of this century.[15] In 2011, it was estimated that the 22% of the world's population was aged 60 years or older, and this proportion is expected to reach 32% in 2050 and 33% in 2100.[12] The number of persons aged 80 or over (oldest-old) is projected to increase almost eightfold in 2050.[4,12]

Over the last 6 decades, there has also been a shift in causes of morbidity and mortality. This shift can be attributed to 2 concepts of population transition: the

demographic and epidemiologic theories of transition.[12,16] Demographic transition, characterized by a shift from high fertility and mortality rates to low fertility and mortality rates, leads to population aging (**Fig. 1**), which ultimately contributes to the change in patterns of causes of death witnessed in the last 6 decades.[16] This change in the predominant causes of death—away from a pattern dominated by communicable diseases toward one in which noncommunicable diseases (NCDs) account for the overwhelming majority of deaths—is referred to as epidemiologic transition.[12,16] Estimates from the UN show that in 2008, NCDs (eg, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, or lung cancer) accounted for 80% of deaths in developed countries, excluding Eastern Europe.[12]

In addition to this shift, there is greater comorbidity, with older people in the more advanced stages of illness often suffering several diseases, compounded with functional, sensory, or cognitive impairment.[4,17,18] Indeed the sickest 5% in health care, which includes mostly people with multiple comorbidities, may drive as much as half of health care spending,[19] thus suggesting that their needs should be addressed especially.

Current prevention and treatment efforts targeted at risk factors may delay or prevent the onset of NCD morbidity and mortality. Nevertheless, NCD morbidity and mortality are expected to increase as the world's population ages. This is primarily because the increase in NCD morbidity and mortality attributable to population aging is expected to greatly exceed the expected decline in NCD mortality attributable to preventative measures targeted at risk factors. In other words, although prevention strategies can reduce the burden of NCDs, the net burden is likely to be higher in the future because of population aging (**Table 1**).

Another issue related to population aging is the decrease in the proportion of younger people, and ratio of working-age to older people, as populations undergo epidemiologic transition.[20] This means fewer people, particularly women who have customarily been relied on to care for people at the end of life, will be able to find time to provide care for older people at the end of life. Moreover, because health systems vary in the degree to which they can provide resources to support home or institutional care for people at the end of life, some families will find the financial cost and burden of caring for older family members at the end of life unmanageable.[20]

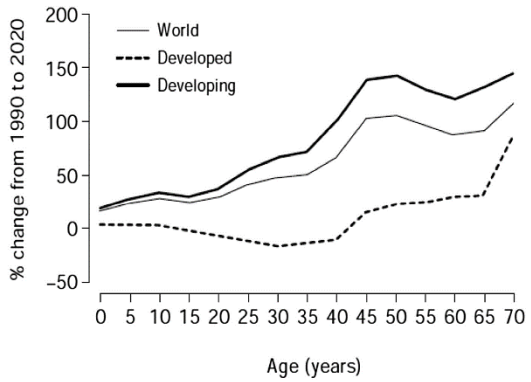


Fig. 1. Projected change in global population by age from 1990 to 2020. (*From* Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease study. Lancet 1997;24:1503; with permission.)

Table 1
Leading projected causes of mortality for 2030 compared with 2015 causes

Disease	Predicted 2030 Ranking	Predicted 2015 Ranking
Ischemic heart disease	1	1
Stroke	2	2
Chronic obstructive pulmonary disease	3	4
Lower respiratory infections	4	3
Diabetes mellitus	5	8
Trachea, bronchus, lung cancers	6	7
Road injury	7	9
HIV/AIDS	8	6
Diarrheal diseases	9	5
Hypertensive heart disease	10	10

From WHO. Global health estimates summary tables: projection of deaths by cause, age and sex (xls:global summary projections). Available at: http://www.who.int/healthinfo/global_burden_disease/projections/en/. Accessed July 01, 2013; with permission.

Evidence of Unmet Palliative Care Need

According to WHO estimates, globally, about 20 million people (of whom 6% are children, and 67% are >60 years old) need palliative care annually.[2,21] This number doubles if those who could benefit from palliative care earlier in their illness are included.[2,6,21]

Cancer patients account for a third of people in need of palliative care. The rest include people suffering from a variety of chronic progressive diseases such as cardiovascular diseases, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), drug-resistant tuberculosis, chronic obstructive pulmonary disease, or renal failure.[6,21] The common causes of death among adults in need of palliative care are cardiovascular disease (38.5%), cancer (34%), chronic respiratory diseases (10.3%), and HIV/AIDS (5.7%).[2,21] It is conceivable that palliative care need will continue to increase as the world's population ages, so it is crucial to continue to measure palliative care need, using robust methods, to enable appropriate planning of services. Murtagh and colleagues[21] have recently developed a method for estimating palliative care need based on death registration data, incorporating both underlying and contributory causes of death. This method was found to be more appropriate for estimating palliative care need at a population level when compared with other pre-existing methods.[11,22,23]

INEQUITIES IN CARE

Poverty and Economic Deprivation

Evidence suggests that people in the lowest socioeconomic class tend to die younger, with poorer quality of life than those in higher socioeconomic classes.[24–26] Also, there are more hospital deaths in areas of high socioeconomic deprivation, despite preferences to the contrary.[25–27] Furthermore, because it tends to be more difficult to raise charitable funds for home and hospice care in deprived areas, the level of palliative care provision may be inversely proportional to the level of need—the inverse care law.[28] In addition to the complex range of factors that contribute toward the inverse care law, knowledge and awareness of palliative care and related services also appear to be important here. Koffman and colleagues[29] surveyed 252 cancer

patients at 2 hospitals in London and found that the least materially deprived patients were significantly more likely to: recognize and describe the term palliative care (odds ratio [OR] = 8.4; P = .002) and understand the role of Macmillan nurses (OR = 6.68; P<.0001) when compared with their most deprived peers.

Older People

In many countries, older patients and their caregivers do not have equal access to palliative care when compared with younger patients.[30] This may partly be accounted for by the fact that most patients receiving palliative care are cancer patients, who on average, are younger; age, however, appears to be an independent factor both in place of death and access to specialist care. A systematic review by Burt and Raine[31] on the effect of age on referral to specialist palliative care reported that "older people were less likely to be referred to, or to use, specialist palliative care." Although this direct age discrimination is important, the main concern is perhaps that of indirect discrimination through failure to provide adequate palliative care to older people in the hospital. A European population-based survey by Gomes and colleagues[32] found that between 51% and 84% of people across 7 countries said they would prefer to die at home if they had advanced cancer. Despite this, 34% to 63% of deaths occurred in the hospital, and older people were found to be more likely to die in the hospital when compared with their younger counterparts.[33] Furthermore, a UK national end-of-life care survey of 473 bereaved informal care givers found that 75.6% of patients younger than 85 years were reported to have had an official record of preference for place of death, but this was only true for 39% of the oldest old (people aged 85 years and over).[34] The study also found that being over the age of 85 was associated with a 64% reduction in the odds of dying at home (OR = 0.36).[34]

Dementia

In recent years, dementia has become a major health challenge worldwide, and it accounts for increasing health resource use, particularly in higher income countries.[35] In 2005, the global prevalence of dementia was estimated to be 23.4 million, with an incidence of 4.6 cases annually (a new case every second).[36] The prevalence of dementia is expected to reach 81.1 million people by 2040, most of whom will live in lower income countries (60% in 2001, rising to 71% by 2040).[36] Research suggests that symptoms of dementia are similar to those of cancer; however, patients with dementia experience these symptoms for longer periods than those with cancer.[37] "Patients with dementia often receive poor end-of-life care, with inadequate pain control and without access to the palliative care services that patients with cancer are offered."[38]

Other Groups

Other disadvantaged groups include

- Black and minority ethnic groups
- People with learning disabilities
- Lesbian, gay, bisexual, and transgender groups
- Prisoners
- Refugees and asylum seekers
- Drug misusers
- Homeless people

PUBLIC HEALTH: OLD VERSUS NEW APPROACHES

Public health is concerned with the health of people at a population level.[39] It focuses on reducing morbidity and mortality and improving the health of communities, towns, cities, and nations. Because public health focuses on major causes of morbidity and mortality, it must evolve as the causes of morbidity and mortality change, as highlighted in the previous section. For example, while public health approaches in the 18th and 19th centuries focused on sanitary and environmental reforms,[40] and antibacterial therapies to curb transmission of communicable diseases (eg, cholera, tuberculosis, and malaria), which were the main causes of morbidity, the epidemiologic transition to NCDs in the 20th century necessitated the development of new public health approaches to addressing the problems posed by these killers of the new age.[16,41]

As a result, the new public health emerged with one of its main themes being that interventions be conducted with people rather than on people.[41] In essence, the main difference between the new and old public health is that the professional dominance of those from the outside—assuming that that they knew what was best for the community—was challenged.[41] For example, in the era of the old public health, health professionals adopted an institutionalized view toward hospice and end-of-life care (viewing death and dying as polluting experiences requiring containment, in hospice).[42] However, the ideas of the new public health and community empowerment promote moving away from the focus on containment of pollution and poverty to highlighting social and collective responsibility.[41]

The current public health approach to palliative care includes these ideas, and is an integral part of the wider global health promotion campaign. New initiatives are being developed that aim not only to promote the involvement of community members in care, but also in research. An example of such initiatives is the Patient, Family and Public Involvement (PPI)[43] in Palliative Care Research initiative, which is currently being developed at the Cicely Saunders Institute in London. The aims of the PPI initiative are primarily to: improve the quality, impact, and clinical relevance of palliative care research, and to demystify preconceptions and raise awareness of palliative care and palliative care research.[43]

EFFECTIVENESS AND COST-EFFECTIVENESS OF PALLIATIVE CARE

The effectiveness of palliative care can be considered at 2 levels. There is the general issue of the effectiveness of expert palliative care services and approaches, and there is also the effectiveness of individual new interventions, services, or approaches, including those that train those less experienced in palliative care.

There is now evidence to support expert (or specialist) palliative care multiprofessional teams. These appear to improve symptom control, reduce depression and psychological distress, in some instances improve patient quality of life, and in some studies improve survival.[7,8,44–48] They also can reduce care giver burden.[49] However, it should be stressed that these studies were carried out on services staffed usually by experts trained in palliative care. Therefore it is important that as palliative care services develop more widely outcomes are assessed on a routine basis, to ensure that the palliative care services continue to achieve high-quality outcomes for patients and families. Otherwise there may be a temptation for funders and commissioners of services to cut corners.[50,51]

There is, however, less evidence that specific training programs or pathways adapted from hospices and palliative care services and provided to generalists can improve care. The Liverpool care pathway failed to provide evidence of significant patient or

care giver benefits in a cluster randomized controlled trial.[52] Many other training systems are in development but are not yet well evaluated. Equally, new techniques and treatments often need evaluation.

It is important for palliative care interventions to be routinely subjected to economic evaluation for at least 2 reasons. First, economic evaluation can enable comparisons between palliative care services to determine the most efficient use of currently allocated resources. "Services that can be shown to be relatively ineffective and costly can be replaced by those that achieve more for less."[53]

Second, and most importantly, palliative care will always compete with other health care services for the same funds. It is the responsibility of health policy makers to consider value for money when deciding what services to fund. Arguing for special consideration based on an intrinsic value of a service is rarely sufficient. Failure to demonstrate the cost-effectiveness of interventions can result in weak arguments in the competition for scarce resources.[53] Moreover, the WHO resolution on palliative care urges member states to develop and implement policies that support the integration of cost-effective and equitable palliative care services in the continuum of care, across all levels.[1] Therefore, to enable health policy makers to provide the resources required to meet the needs of dying patients, it is necessary for the palliative care community to provide information on the value for money of palliative care. Economic evaluation using cost-utility analysis, which compares interventions in terms of their cost per quality-adjusted life years (QALYs) gained, is a common means of providing such information.[54,55]

However, economic evaluations, particularly cost utility analyses of palliative care, are relatively rare, partly because of the difficulties of estimating costs and outcomes. For example, a 2014 review of the cost-effectiveness of palliative care found that: the majority of studies focused only on costs (cost analysis); only 1 study reported cost-effectiveness analysis, and none of the studies reported cost utility analysis.[56] The authors concluded that in most cases, palliative care was significantly cheaper than comparators.[56] "Economic evaluation of palliative interventions poses some challenges, both for palliative medicine and for economics."[53]

A major challenge around measuring cost in palliative care is that it is difficult to attribute true costs (and outcomes) to 1 particular service or intervention, because, within a single episode of illness, palliative care patients are usually cared for by various providers in different settings, simultaneously.[57] Also, because palliative care patients have complex needs and demands, it is necessary to adjust for need and complexity (case mix) when comparing costs between providers. It is reassuring that in several countries, palliative care funding models that account for case mix are being developed, such as: the Australian National Sub-acute and Non-acute Patient (AN-SNAP) system[58,59] and the current development work on a palliative-care currency in the United Kingdom.[60]

Although issues exist around measuring cost, the measurement of outcomes is arguably more challenging in the context of economic evaluations, particularly cost-utility analysis, of palliative care. This may partly be because some of the goals of palliative care, such as improving the quality of the experience of death, may be incompatible with how the QALY is estimated (ie, centered around maximizing healthy years or QALYs). There has been a lot of debate on the appropriateness of the QALY as an outcome measure in cost utility analyses of palliative care services.[53,61–65] A major criticism of the QALY framework is that standard tools, such as the EQ-5D[66,67] and SF-6D,[67] which have preference weights that enable the estimation of QALYs, are generic in nature, and so, do not capture specific domains that are important to palliative care.[62,64] Several validated palliative care-specific outcome

measures exist, such as the Palliative Care Outcome Scale (POS),[68] and the McGill Quality of Life Questionnaire (MQOL),[69] which capture important palliative care domains. However, unlike the EQ-5D, these palliative care-specific outcome measures do not incorporate preference weights, and so cannot be used to estimate QALYs for cost utility analysis.

SUMMARY

Palliative care is a public health concern, because the problems faced by patients and their families represent a substantial burden of illness and cost to the society that is likely to increase markedly in the future as the world's population continues to age. There are also inequities in access to palliative care, continued unmet need. There is evidence to support palliative care services, but not yet enough information on the cost-effectiveness of many specific palliative care treatments/interventions. The lack of economic evaluations deprives decision makers of information required to best meet the needs of patients with progressive disease and at the end of life. These issues highlight the need for research in health economics and palliative care. It would be useful to empirically assess the appropriateness of generic measures of health-related quality of life (such as the EQ-5D) and the QALY framework in palliative care.

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2.2. Outcome measurement in cost-utility analysis

The Quality Adjusted Life Year (QALY) has become the gold standard measure of outcome in cost-utility analysis, which combines survival and quality of life (QoL) in a single metric.[20] The Washington Panel of Cost-Effectiveness [21]recommended its use in economic evaluations in 1996 and it is currently recommended in the methodological guidance for technology appraisal issued by the National Institute for Health and Clinical Excellence in England.[22] Although there are arguments against the use of QALYs in evaluating healthcare technologies and interventions[23], it is widely used in practice and there is consensus that its use in resource allocation decision making is appropriate.

Preference-based measures of health (PBMH) have become a common means of generating health state values for computing quality-adjusted life years (QALYs). The status of PBMH was considerably enhanced by the recommendations of the US Public Health Service Panel on Cost-Effectiveness in Health and Medicine.[24]

Most Preference-based measures of health, such as the EQ-5D, SF-6D, and the Health Utilities Index 3, have a generic health state descriptive system.[25-27] There has been an important debate in the literature about the role of generic and condition-specific measures.[28-30] Developers of generic measures, such as the EQ-5D and SF-36, claim they are to be suitable for all patients, irrespective of their medical condition.[31, 32] This is achieved by concentrating on core aspects of health-related quality of life (HRQoL). However, for certain medical conditions – including palliative care – generic measures do not cover all relevant dimensions, or are insensitive to "*small but important changes*."[29, 33] The EQ-5D, for example, has been shown to cover less than 50% of the dimensions of health listed in a survey of laypeople in England.[34] A condition-specific measure (CSM), on the other hand, focuses on those aspects of health affected by a single condition.

However, the vast majority of the available CSMs have been developed in order to describe and measure, rather than value, HRQoL – i.e., they are non-preference-based measures (non-PBMs). Therefore, CSMs cannot be used to derive utility values for the estimation of QALYs in CUAs.

Nevertheless, there are two main approaches to addressing this issue: the first involves "mapping" from CSMs directly onto generic PBMs[35]; the second approach is to develop a preference-based CSM either de novo (for example[36, 37]; Stevens et al., 2005[38]) or from an existing CSM (for example Brazier et al., 2005, 2008 & 2010;[39-41] Rowen et al., 2011;[42] Sundaram et al.,[43] 2010; Yang et al., 2009 & 2011[44, 45]).

Methods of estimating utility values are discussed in detail in what follows.

2.2.1 Estimating utility values

Estimating preferences for health states involves three stages consisting of identifying and describing the health states in a disease area, population or condition; deriving preference weights for a selection of the health state identified using valuation methods; and finally deriving preference weights for the rest of the health states by applying regression techniques to the preference weights obtained from the valuation study.

Describing health states

Health states are usually described using either a generic or a condition-specific outcome measure. A health state is constructed by selecting one response category from each item of the measure, and combining all item responses. Outcome measures that are used for the describing health states comprise 'health state classifications'. In a health-state classification, each item normally represents a separate dimension.

Health states can also be described by vignettes; which are usually narrative descriptions developed based on interviews with patients and clinical experts, capturing various domains of HRQoL, such as pain and symptoms, degree of physical and social functioning, treatment and side effects.[2] Vignettes are in essence condition - and treatment-specific. Finally, sometimes health states are not described, but instead patients are asked to value their own health.

The disadvantages of vignettes include their failure to describe the full range of health states that are usually observed in a patient population, as each vignette describes only one state. Therefore, although vignettes can provide detailed descriptions of specific health states, they often lack the

sensitivity to capture small, but important, changes in HRQoL. Furthermore, vignettes may be difficult to link to outcomes reported in clinical trials. Finally, the psychometric properties of vignettes are more difficult to empirically assess compared with standardised measures.[2]

Valuing health states

Valuation refers to the process of attaching preference weights to the health states represented by a measure. Preferences may be elicited from patients, carers, health professionals, or members of the general public. Until recently, there were three main preference elicitation methods: the Visual Analogue Scale (VAS); the Standard Gamble technique (SG); and the Time Trade-Off technique (TTO). These valuation methods involve manipulating probabilities or lengths of life, thereby generating cardinal responses. More recently, there is increasing interest in employing valuation methods that generate ordinal information such as ranking, Discrete Choice Experiments (DCEs) and Best Worst Scaling (BSW).[2, 46, 47] A detailed description the various valuation methods is provided in what follows.

Cardinal methods

Visual Analogue Scale (VAS)

The VAS is a simple line with defined anchor states, such as 'full health' on the one side of the line and 'death' or 'worst possible health state' on the other. Respondents are asked to place their preference for specific health states along the line. The scale has interval properties, so that the distances between the placements of health states correspond to the respondents' relative differences in preference between the states.[48, 49] Anchoring the scale between 'best imaginable state' and 'worst imaginable state' allows valuation of the 'death' state and elicitation of preferences for states considered worse than death.[27] It has been argued that using clear and unambiguous endpoints on the scale ensures comparability of judgements between respondents.[2] A graphic illustration of VAS is shown in Figure 1 below.

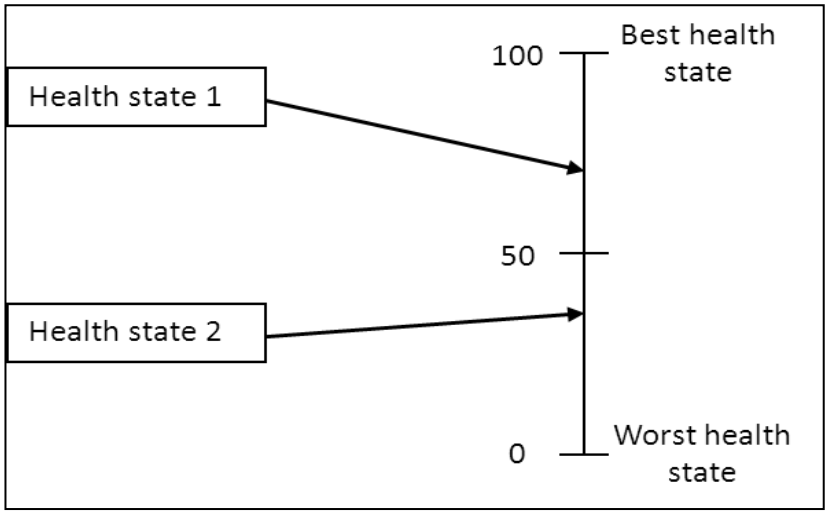


Figure 1: Illustration of a Visual Analogue Scale (VAS): Adapted from Brazier et al 2008[1]

Standard Gamble (SG)

The SG technique asks respondents to consider the level of risk that they are willing to take with their life in a certain health state in order to return to full health. It is based on the axioms of the von Neumann-Morgenstern utility theory, according to which when rational individuals are faced with a choice between options they will choose the option that maximises their expected value of utility.[50] SG gives the respondent a choice between a certain intermediate outcome and the uncertainty of a gamble between two possible situations, one of which is better than the certain outcome and the other is worse. For chronic health states considered better than death, alternative 1 involves a gamble between life in full health for *t* years (probability p) or immediate death (probability 1 – p); alternative 2 is the certain outcome of life in the health state for *t* years. The probability p is varied until the respondent is indifferent between the gamble and the certain outcome. At this point, the probability p expresses the utility value attached on the health state. For chronic health states considered worse than death, alternative 1 involves a gamble between life in full health for t years (probability p) or life in the health state in question for *t* years (probability 1 – p); alternative 2 involves the certain outcome of immediate death. The probability p is varied until the respondent is indifferent between the gamble and the certain outcome. The utility value of a health state deemed worse than death is then given by the formula –p/(1-p).[2, 48]

A diagram of the SG task for a chronic health state is illustrated in Figure 2.

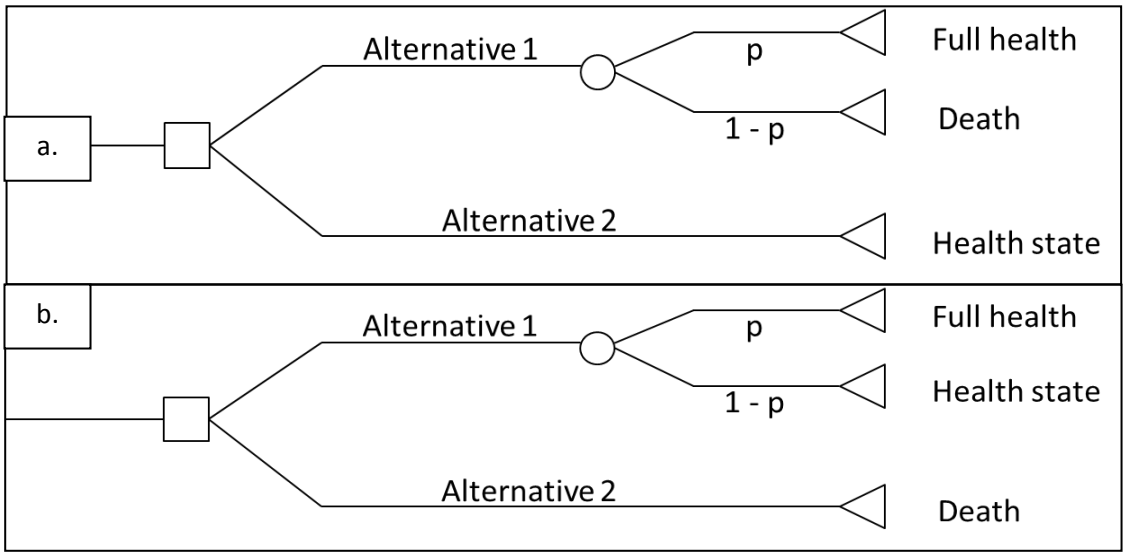


Figure 2: Schematic diagram of standard gamble for a chronic health state a) preferred to death and b) considered worse than death (Adapted from Brazier et al 2008)[1]

Time Trade-Off (TTO)

The TTO technique was suggested by Torrance and colleagues (1972) as an alternative to SG that is simpler to use but provides similar results.[51] Unlike SG, TTO elicits decisions under certainty. The TTO task asks respondents to trade HRQoL for life-years. More specifically, for a specified health state (h_i) that is worse than full health but better than death respondents are asked to choose either to live for a period of t years in this state, or to shorten their lifespan to x years in full health, where $x < t$. The number of x years in full health is varied, until the point where the respondent is indifferent or switches preferences between the two alternatives. The utility value given to the state h_i is then x/t.[2]

For health states considered worse than death, the TTO task can be modified. For example, in the Measurement and Valuation of Health study (MVH)[52] that was used at the valuation of EQ-5D[3], respondents were first asked whether they preferred to live in a specified health state h_i for a period of t years after which they'd die; or immediate death. This question determined whether respondents valued the health state as better, worse, or equal to being dead. Subsequently, for health states considered worse than death, respondents were asked to choose between two alternatives: alternative 1 involved immediate death, while alternative 2 involved life in the health state for y years followed by life in full health for x years (with $y + x = t$) followed by death. Years in full health (x) were varied concurrently with years in the health state (y) so that t remained constant, until respondents were indifferent between the two alternatives. The utility value given to the health

state in this case is $-x/y$.[2, 48] However, this formula may produce very low values (in the case of MVH TTO protocol where t = 10 the lowest possible value for a state worse than death can reach -39), which creates problems when modelling valuation data, as values corresponding to states worse than death have a larger impact on the model predictions than values of states better than death.[42] It has been therefore suggested that utility values for states considered worse than death be rescaled, so that they are bounded by a value of -1, and this approach was followed at the valuation of EQ-5D, where utility values of states worse than death were calculated using the formula $-x/t$.[3, 25]

A diagram of the TTO task for a chronic health states is illustrated in Figure 3.

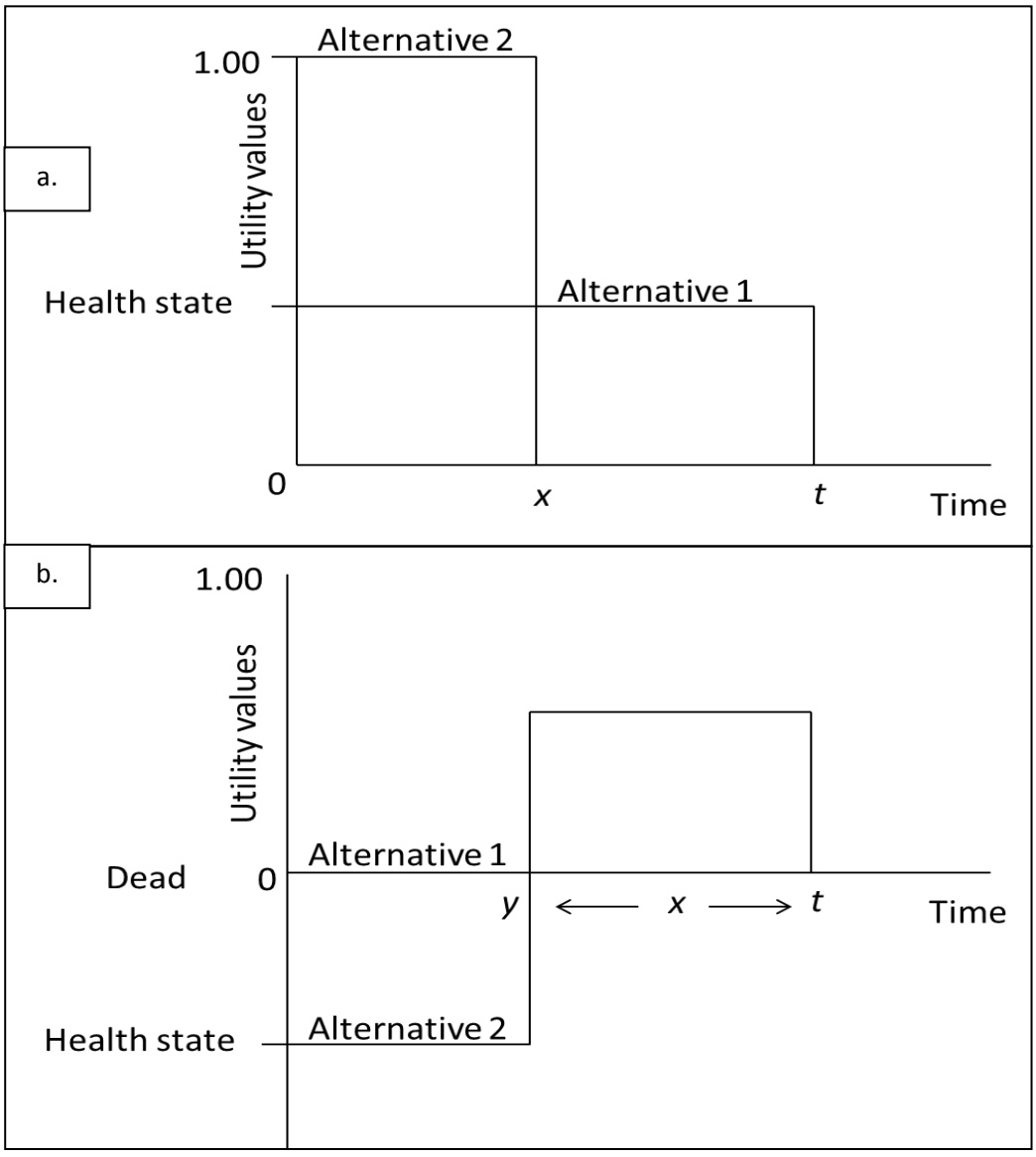


Figure 3: Schematic diagram of time trade-off for a) a health state preferred to death and b) a health state considered worse than death. (Adapted from Brazier et al 2008) [1]

Person trade-off (PTO)

The PTO [1] is a method used to determine the 'societal' value of different health states. Like the SG and TTO, the PTO is choice-based as it asks respondents to choose between options. Rather than asking respondents to value their own health state or imagine being in a health state themselves, the PTO asks respondents to make social value judgements by making choices on behalf of groups of other people. In this method, participants are asked to say how many people in health state "A" are equal to a particular number of people in health state B. For example, if there are 5 people with metastatic lung cancer (health state A) and 10 people with dementia (health state B), and you can only help cure one group, which would you chose? [53] [54] Subsequently, the number of people in health state A is varied until both groups are deemed equivalent regarding need for help. If in the above example the respondent indicated that curing 2 people in health state A (cancer) was equivalent to curing 10 in B (dementia), then metastatic lung cancer is 5 times (10 ÷ 2) as undesirable (disutility) as dementia. This process is then repeated to value other health states. Advocates of the PTO regard this approach as more appropriate for social choice contexts than the traditional individual approach of other valuation methods. Pinto Prades [55] proposed that a hypothetical advantage of the PTO is that by allowing trade-offs between people, it asks the right question from the perspective of economic analysis. Although the PTO is choice-based, it has no theoretical bases. The choices are made in a social context with consequences relating to the wellbeing of others thus conventional consumer theories is not applicable to the choice task. [1] Also, the PTO is very complex and demanding; susceptible to framing effects; and requires a reflective element to allow respondents to consider their responses and so takes longer to complete.

Magnitude estimation (ME)

This valuation method stems from psychometrics and was initially derived as an alternative to the VAS for measuring sensory and non–sensory perception [56]. It asks respondents to indicate the ratio of disutility (undesirability) of pairs of health states e.g. is lung cancer two, three or four times worse than dementia. If lung cancer is deemed two times worse than dementia then the disutility of lung cancer is three times greater than that of dementia. By asking a sequence of such questions,

the relative distances on the disutility scale between all health states for valuation can be determined. In psychometrics literature, M.E. is also called ratio scaling because its questions are worded with the intention of generating data with ratio properties. However, this valuation method is seldom used and so far, its most notable application has been in the valuation of the Rosser disability/distress classification.[57, 58]

Ordinal methods

Discrete choice experiments (DCEs)

DCEs were initiated into health economics in early 1990s to value benefits outside health outcomes[59] and present individuals with a number of choices sets, each of which contains two or more profiles with varying attribute levels. The decision making process in DCEs is akin to comparing indirect utility functions. For each choice, respondents select the option that yields a higher utility. The responses of individuals provide information on the utility of the attributes and how individuals make trade-offs across attributes (marginal exchange rates). Despite being initiated to value non-health attributes, there is growing interest in using DCEs to develop health utilities. DCEs have been used to develop several condition-specific PBMs including the older persons' utility scale (OPUS)[60], and the glaucoma utility index (GUI)[61]; and also generic PBMs including the EQ-5D[62].

Best worst scaling (BSW)

This method includes several choice tasks in which respondents are presented with a health state profile from which they are asked to select the 'best' and 'worst' characteristics. Therefore, choices are made within, not between alternative profiles. Repeating these best and worst decisions over numerous tasks enables utility weights to be estimated for each health profile. BSW has mainly been used to estimates values for capability measures including ICECAP-A, ICECAP-O, CHU-9D, and ICECAP-SCM[63-66].

Comparing valuation methods

Cardinal methods

The three main techniques for valuing health states (VAS, SG and TTO) have demonstrated satisfactory reliability and high acceptability to respondents.[67] However, they have been shown to result in different sets of values for the same health state descriptions.[68, 69] Various arguments in favour or against the use of each of them have been expressed in the published literature:

The VAS method appears to be the simplest to understand and most acceptable to respondents.[67, 70] However, because VAS does not require respondents to make choices by trading-off different attributes of health profiles, it has been criticised theoretically as being incapable of capturing strength of preferences, and thus deemed inferior to the choice-based TTO and SG (Dolan, 2001). Also, VAS is subject to measurement bias, as elicited scores often lack interval.[70] This may explain why VAS values have only poor to moderate correlation with values derived from TTO and SG undertaken at the same time, while TTO and SG correlate reasonably well with each other.[67] Furthermore, the appropriateness of VAS as a measure of utility function has been criticised based on two empirical points: context bias (response spreading), and 'end state aversion'. Context bias implies that VAS values are influenced by the choice of comparators – if a health state is presented alongside many better states, its value is decreased and vice versa. Empirical tests by Bleichrodt et al [71], and Loomes et al [72] demonstrated that VAS values for a given health state depended on the number better and worse health states presented simultaneously, thus yielding inconsistent results. This implies that VAS values are not independent of the context in which they are elicited, as they should be if they elicit points on a measurable value function. Braizer et al further expanded on "context bias" using the concept of 'response spreading' where respondents attempt to distribute (spread) response over the entirety (or specific part) of a given scale; and concluded that there is no theoretical justification for using VAS methods in cost-utility analysis [73]. However, a number of studies have shown a mathematical transformation can be that applied to raw VAS scores in a way that eliminates the inconsistencies that arise due to context bias (as demonstrated by Bleichrodt), thereby overturning Brazier's conclusion about the justification for using VAS. However, this means that transformed rather than raw VAS values ought to be used.

End state is a well-recognised bias affecting continuous scales like the VAS.[74] It is based on the notion that respondents avoid using both ends of the VAS scale, which results in measurement error.[2, 70] This suggests that respondents are unwilling to describe the best health state as being equal to one (full health), or the worst as being equal to zero (dead). The study by Torrance et al demonstrated end state aversion in the VAS at the healthy end of the scale, but found a method to rectify this.[75] The conclusion here is that although VAS has attractive qualities,[76] its scores should be transformed, and it should be used in conjunction with other valuation methods.

The SG has been advocated by economists because it entails making decisions under uncertainty, which also surrounds most decisions about health care.[77] However, the SG may be compromised by probability weighting, where respondents tend to overweight small probabilities and underweight large ones; if the probability weighting function is inverse S shaped as indicated by empirical evidence, and the point where the function changes from overweighting to underweighting probabilities approximates 0.35 as suggested in the literature, then SG tends to overestimate utility values given that the probabilities reported in SG exercises overall tend to exceed 0.35.[78] Moreover, SG is also affected by risk aversion resulting in SG values being pushed upwards, and scale compatibility (this is where respondents assign more weight to attributes that have higher compatibility with the response scale used) resulting on respondents' focusing on the probability rather than the health state valued; and because there are more than one probabilities involved in the task, the direction of bias in estimation of utility values cannot be predetermined.[78]

TTO has been considered the most appropriate valuation method, as it incorporates the relationship between the health state, its duration and its value into a single measure.[79] There is evidence, however, that TTO values are prone to duration and time preference effects; in other words, the period of time spent in a health state and the point in time a health state is experienced (e.g. at the beginning or end of a time period) affect the way the state is perceived by respondents and therefore have an impact on utility values.[80] Moreover, TTO assumes that utility is linear in duration, and given that utility has been empirically shown to be concave, the TTO task tends to systematically underestimate utility values.[78] The assumption of linearity is more strongly violated in end-of-life scenarios.[81] Another issue is that TTO is affected by attitudes such as loss aversion (so that

respondents tend to be more reluctant to give up healthy life-years), and scale compatibility (so that respondents place more weight on the duration of a health state, which is the response scale of the task, rather than to the health state itself); both phenomena result in an overestimation of utility values.[78] Currently, TTO and SG are the most widely used techniques for valuation of health states.[2] Nevertheless, VAS has often been used for respondents' warming-up prior to TTO and SG exercises, to familiarise respondents with descriptions of health states and give them an opportunity to start considering their preferences.[3, 82]

Ordinal methods

Interest in using ordinal valuation methods arose due to the aforementioned limitations of cardinal methods. In both DCE and BWS methods, the utility weights are assumed to represent respondents' trade-offs between dimensions. It is this assumption that allows utility to be estimated for different profiles. Like other choice-based methods (e.g. TTO and SG), DCEs satisfy this assumption as respondents are explicitly asked to make trade-offs between (and within) dimensions.

The BSW is considered a more appealing alternative to the DCE due to its simplicity and lower cognitive burden as it presents a single profile at a time (thereby allowing all profiles to be valued), and it provides more information that the customary "pick one" task of DCEs[83, 84].

However, because BSW only requires respondents to make choices within – and not between – dimensions, opportunity cost (sacrifice) is not integrated in the valuation task. This difference between BWS and DCEs (and indeed other choice-based valuation methods) is important because, based on welfarist theory, utility based preferences can only be derived from trade-offs or choices between dimensions [85]. Indeed in a recent valuation study by Huynh et al in which BSW was used, the authors highlight that BWS tasks elicit only 'values' and not preferences because individuals are not asked to trade one thing for another.[66]

Additionally, it is not possible to determine the absolute value of dimensions using BSW because, relative to the respondent's current situation, selecting the best and worst features of a dimension provides no information about the desirability of the dimension as a whole. For these reasons, BWS is considered unsuitable for measuring preference values.

Conversely, DCEs have two main limitations. First, the DCE task is considered a relatively inefficient way to elicit preferences: considering two or more health states (each with several attributes) at once is likely to be a more difficult task for respondents, leading to more statistical error, thereby decreasing the statistical efficiency of eliciting preferences and increasing the required sample size[84]. Second, the regression constant term is confounded with level scale values and as a result is difficult to interpret. [84] As a means of finding a middle ground, Louviere and colleagues[86] suggested combining the two approaches together by administering the best–worst task as part of a wider choice experiment – in what is now referred to as 'Best Worst Discrete Choice Experiments' (BWDCEs)[87]. BWDCEs, like traditional DCEs, repeatedly ask respondents to make 'between-attribute' choices among alternatives presented in choice sets, each set described by several attributes. "*BWDCEs are designed to elicit extra preference information per choice set by asking respondents not only to choose the best option but also to sequentially choose the worst option, potentially followed by choice of best of the remaining options and so on until an implied preference ordering is obtained over all alternatives in a set*"[87].

Although it's still being developed, BWDCEs is gaining a lot of interest as theoretically it should provide more information on relative preferences between alternatives and more choice data, thus increasing statistical efficiency. This gain in statistical efficiency translates to a reduction in sample size requirements, which would be especially useful in situations where funding is limited or there is a small population from which to sample (e.g. palliative care patients). Work is underway to explore the relevance of BWDCEs in practice.[87, 88]

Modelling valuation data

It would be impractical and resource intensive to value all health states described by an instrument. For example, EQ-5D describes 243 unique health states, while the SF-6D describes 18,000. Alternatively, a sub-sample of the total number of health states described by a measure is selected for valuation. Thereafter, regression models are applied to the utility values obtained for the afore-mentioned sub-sample of health states in order to estimate utility values for all other health states described by the instrument.

Two approaches have been used traditionally for modelling utility values: the composite approach; and the decomposed approach. The composite approach uses statistical modelling to estimate a set of rules (in the form of an equation) for valuing all health states described by an instrument using utility data derived from valuation of a sub-sample of health states. While, the decomposed approach uses Multi-Attribute Utility Theory (MAUT) to determine the functional form underlying the relationship between single dimensions as well as the sub-sample of states to be valued.[2]

However, the HTA have recently recommended using the Rasch approach for the developing a simplified health state classification, selecting a plausible sub-sample of health states for valuation, and modelling the resultant valuation data to derive utility values for all health states.[89]

2.2.2 Generic preference- based measures

The most commonly used generic PBMs are the EuroQol 5-dimension (EQ-5D)[90], the health utilities index mark 3 (HUI-3)[11, 91], and the short form 6-dimension (SF-6D)[92]. A description of each of these measures is provided in what follows.

EQ-5D

The EQ-5D is a 5-item generic preference based measure – and by far the most commonly used – comprising five dimensions as follows: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In the original version (EQ-5D-3L), each item has three response categories ranging from 1 (no problems) to 3 (extreme or severe problems). Consequently, the EQ-5D classification system describes 243 unique health states. Value sets for this version have been derived for the UK (and several other countries).[25, 90, 93] The current UK value set ranges from –0.594 (worst health state) to 1 (best health state with no problems).[25] A new version of the EQ-5D, the EQ-5D-5L, with its accompanying value set is now available.[94] The EQ-5D-5L has five dimensions, each with five response categories. The EQ-5D-5L was developed in response to concerns that the 3-level EQ-5D-3L "*may not adequately capture milder health problems experienced by patients, and smaller changes between different health states.*[94]" While the EQ-5D-3L describes 243 (3^5) distinct health states, the EQ-5D-5L describes 3,125 (5^5). It is yet to be seen whether the EQ-5D-5L has improved sensitivity.

SF-6D

The SF-6D is a 6-dimension preference-based measure comprising physical functioning, role limitations, social functioning, bodily pain, mental health, vitality. The SF-6tD has two versions; the original version derived from the SF-36[26, 82] and a second version derived from the SF-12– (SF-6D [SF-12])[92]. The number of response categories for the original version are 6 for physical functioning and bodily pain; 4 for role limitation; and 3 for the rest; which altogether describe 7,500 distinct health states. The SF-6D (SF-12) comprises 3 response categories for physical functioning,

4 for role limitations, and 5 for each of the rest, which altogether describe 7,500 distinct health states. Value sets for the SF-6D have been derived for the UK (and several other countries) using the standard gamble preference elicitation method.[26, 92]

HUI3

The Health Utilities Index (HUI) is a group of generic health profiles and preference-based systems for measuring health status, health-related quality of life, and generating utility scores.[91] HUI comprises two systems, HUI2 and HUI3, which together describe almost 1,000,000 unique health states. The developers recommend HUI3 as the main instrument for primary analysis. HUI3 comprises 8 dimensions – vision; hearing; speech; ambulation; dexterity; emotion; cognition; and pain – each with 5 or 6 response categories; which altogether describe 972,000 unique health states.

2.2.3 Calculating QALYs using condition-specific measures

There are several reasons why it may be desirable to use a condition specific measure (CSM) to estimate QALYs. First, the CSM may be more widely used than generic PBMs in clinical research in a particular discipline or patient group, e.g. the POS in palliative care studies, and so using it to derive QALYs substantially increases the scope for conducting economic evaluation in such disciplines. Second, CSMs may be regarded as more sensitive or relevant than existing generic PBMs. Despite their widespread use, generic PBMs have been shown to be irrelevant or insensitive in some patient groups including people with hearing problems [95], visual loss from macular degeneration [96], venous leg ulcers [97], urinary problems [98] (Haywood et al., 2008), bladder problems [99], chronic obstructive pulmonary disease [100], and chronic schizophrenia [101].

However, most CSMs are not preference-based, and so cannot be used to derive QALYs for cost-utility analysis. This issue can be addressed using two main approaches. The first is an indirect method called "mapping" [41]. This involves deriving a relationship (commonly a mathematical relationship via statistical association or regression modelling) between a CSM and a generic PBM so that scores from the CSM can be used to predict the scores on the generic PBM from which QALYs are subsequently derived. [41] The second approach involves deriving preference values for

the CSM so that QALYs can be calculated directly from the resultant preference-based CSMs [35, 39, 40, 42, 43, 102, 103]. Details of these two approaches are provided in what follows.

Mapping

Mapping (also known as cross-walking) from a non-PBM onto an existing PBM involves estimating a relationship between the two measures, which can be achieved using expert opinion, or empirically using statistical association.[2] Mapping based on expert opinion relies on the judgements of professionals or researchers and has been criticised for its arbitrariness and lack of validity.[2] Empirically estimating mapping functions between a non-PBM and an existing PBM involves using regression techniques on datasets containing patient-level data on both the non-PBM and the PBM to determine a statistical relationship between the two measures – in the form of a mathematical algorithm. Based on this mapping algorithm, scores on the non-PBM can be used to predict scores on the PBM from which utility values can be estimated. This provides an indirect method of estimating QALYs from datasets that contain only the non-PBM.[2]

The mapping function can be determined using a simple additive model, where the total score of the non-PBM is regressed onto the PBM. The limitation of such a model is that it implicitly assumes that all dimensions of the non-PMB are equally important, all its items carry the same weight, and the item response levels have interval-scale properties.[2] More complex model specifications use sub-scores, item scores or item response levels of the non-PBM as independent variables, and could possibly to introduce interaction terms between dimensions and/or items.[35] The drawback of such approaches is that they can result in a large number of independent variables, although this can be limited by eliminating items with non-significant coefficients. Another complex modelling approach is to estimate separate regression models between the non-PBM and each dimension of the PBM – the so called 'response mapping'.[35]

The advantage of the mapping approach is that it is a cheaper and quicker means of obtaining utilities values for CSMs than developing a preference-based CSM. However, mapping suffers from a number of limitations, such as limited performance in terms of model fit[104] and inability to accurately predict values across the spectrum of symptom severity[105]. Also, a major limitation of

this approach is that it assumes that the PBM covers all aspects of HRQoL captured by the non-PBM. However, where there is insufficient overlap between the two measures the validity of the resulting mapping function is limited. For the above reasons, there has been an increased interest in developing preference-based CSMs for use in calculating QALYs.[35]

Developing preference-based condition-specific measures

Developing a preference-based CSM involves 3 stages as follows: deriving a health state classification; valuing of a selection of health states; and using modelling techniques to predict utility values for all health states described by the classification system based on the results of the valuation survey. Health state classifications amenable to valuation can be developed anew or derived from existing non-preference-based CSMs. The approach to developing a new health state classification involves interviewing patients in order to identify aspects of HRQoL that are important to them and related to the condition examined, followed by a process of testing and refinement using psychometric methods and focus groups, until the final classification system is developed. The new measure needs to be assessed for its psychometric properties, such as its construct validity and responsiveness. The advantage of such a process is that the new measure can be best suited to the purpose it was constructed for; on the other hand, such a task can be time-consuming and costly. A limitation of this approach is that the newly developed measure cannot be used in retrospective economic evaluations using existing datasets.[2]

Deriving a health state classification from an existing instrument relies on selecting a sample of the most representative domains and best performing items within each domain of the original measure and possibly a modifying the item response levels, using a number of psychometric and other statistical methods. This process of selecting items and response levels is essential to ensure that a manageable number of health states are selected for valuation; retaining all items included in the original CSM would likely lead to a large number of health states consisting multiple statements, which would be near impossible to handle in a valuation survey. On the other hand, omitting items of the original measure runs the risk of losing important descriptive information.[2] Deriving a new PBM from an existing CSM is useful when the original measure is more relevant and sensitive to the changes in HRQoL in the study population and more acceptable to patients, clinicians and

researchers than a generic measure. This approach is most useful when the original CSM is a validated measure that is widely used in clinical practice and research. In such cases, deriving a PBM from the original CSM increases the scope for assessing not only the clinical effectiveness of interventions and programmes, but also cost-effectiveness. Nonetheless, concerns have been raised about developing and using condition-specific PBMs – particularly their comparability across different conditions and patient groups.[28-30, 41, 106]

Existing utility measures based on generic descriptive systems are likely to provide an inadequate description of many conditions, and so the values they generate will not fully reflect the impact of the condition. It has been argued that a better approach would be to develop preference-based measures for such conditions.[107]

2.3. Economic evaluations in palliative care

It is important for palliative care interventions to be routinely subjected to economic evaluation for at least two reasons. Firstly, economic evaluation can enable comparisons between palliative care services to determine the most efficient use of currently allocated resources. "*Services that can be shown to be relatively ineffective and costly can be replaced by those that achieve more for less*". [108]

Secondly, and most importantly, palliative care will always compete with other health care services for the same funds. It is the responsibility of health policy makers to consider 'value for money' when deciding what services to fund. Arguing for special consideration based on an intrinsic value of a service is no longer sufficient. Failure to demonstrate the cost-effectiveness of interventions will result in weak arguments in the competition for scarce resources.[108] Therefore, to enable health policy makers to provide the resources required to meet the needs of dying patients, it is necessary for the palliative care community to provide information on the 'value for money' of palliative care. Economic evaluation using cost-utility analysis (CUA) is the recommended means of providing such information.[6]

However, full economic evaluations of palliative care interventions are scarce [8], partly due to the complexities of estimating costs and benefits. *"Economic evaluation of palliative interventions poses some challenges, both for palliative medicine and for economics"*.[108] For example, a 2014 review of the cost-effectiveness of palliative care found only one study reporting cost-effectiveness analysis; but none of the studies found report CUA.[109] There are many challenges with measuring cost and outcomes in economic evaluations of palliative care interventions. Calculating costs in palliative care can be problematic for a number of reasons. First, it is difficult to attribute true costs to a particular service because palliative care patients often receive care from a variety of services in different settings within a single episode of illness. These settings include hospital, home, primary care, and hospice. Measuring the cost of hospice care is particularly challenging as hospices are funded via a mixture of a variety of sources – unlike the other settings, which are primarily funded by the government. Hospices in the UK receive on average 32% of their revenue from the Government, with the remaining 68% coming from local communities via fundraising, hospice charity shops, hospice lotteries, and investments. This is further complicated by a wide variation in the level state funding across the country, and also by that fact that a significant proportion of care is provided by volunteers [110].

The second challenge pertains measuring informal care cost. Friends and family members contribute a great deal to the care of patients with chronic advanced disease. It is vital to include the cost of care provided by friends and family because in their absence, the same amount of care would need to be provided by the government. A recent study conducted by the author during the course of this PhD found that informal care accounted for over 70% of the total cost of care for patients with advanced chronic disease and refractory breathlessness[111] – see details in appendix 8 [publication 5]. One of the challenges of measuring informal care cost highlighted in this study was that most patients had multiple carers (in some cases up to five). An obvious challenge here was locating and interviewing numerous family members/friends per patient. For patients receiving care at home and also living with their carer(s), it is difficult to separate the proportion time carers spend providing care from the time spent on other unrelated activities. For example in the aforementioned study of patients with refractory breathlessness, some informal carers reported that they spent 24

hours a day supervising the patient at home, in addition to bathing, dressing, cooking and cleaning. Consequently, in some instances the total amount of time spent caring for the patient per day exceeded 24 hours.

Several authors[8, 108, 109] have highlighted the challenges of measuring costs in palliative care and the implications for economic evaluations. For example, Haycox[112] suggests "that palliative care leads to increased cost of care at the end of life, "*due to the natural progression underlying disease process*", and that given the limited scope for palliative care patients to generate QALYs, it would be difficult for palliative care interventions to fall within the cost-effectiveness range using conventional methods.[112] Also, the study by Gardiner and Ingleton found that international comparisons of the full economic costs of palliative care are challenging because most of the methods used to derive costs are country specific [8]. Although the problems associated with measuring palliative-care costs are well documented, measuring outcomes poses a far greater challenge for economic evaluations of palliative care interventions.

Understanding the impact of palliative care on health-related quality-of-life (HRQoL) is complex. Palliative care need, disease trajectory and prognosis are often functions of the underlying condition, related symptoms and/ or complications.[20, 113] There has been much debate on the appropriateness of the QALY as an outcome measure in economic analyses of palliative care services.[12-14, 114] Several concerns regarding the use of QALYs in palliative care – such as the 'QALY problem' – have been raised[12, 13 12-14, 114]and alternative methods addressing these concerns have been suggested[12, 14, 115].

Nonetheless, two key areas of uncertainty remain. Firstly, are the concerns being raised valid, and secondly, to what extent do the proposed alternative methods address these concerns? In what follows, a narrative review was conducted to summarise the theoretical literature in order to highlight the specific end-of-life- and palliative-care-based criticisms and defences of QALYs in CUAs of palliative care interventions, and the extent to which proposed alternatives address the different concerns raised.

2.4. Narrative review

Cost-utility analysis in Palliative care: a review of the theoretical literature

Introduction

The appropriateness of the QALY as an outcome measure in cost-utility analyses of palliative care services has been questioned in the theoretical literature.[116] The use of CUA in palliative care has been argued to be a form of discrimination in the theoretical literature. This review focuses on the methodological and ethical challenges of undertaking economic evaluations of interventions for people with advanced chronic illness and approaching the end of life. It summarises the theoretical literature in order to highlight the specific end-of-life- and palliative-care-based criticisms and defences of CUA, and the extent to which alternative methods address the different concerns raised.

Aim

This review summarises the theoretical literature in order to answer the following questions:

- What are the specific arguments for and against the use of QALYs in CUAs of palliative care interventions in the literature?
- To what degree could alternative methods address the different concerns raised by parties within the general debate?

Methods

Literature search

In December 2013 MEDLINE (OVID), and EMBASE (OVID) databases were searched for relevant papers. References of included articles were also hand searched. The key search concepts used were, palliative care / end-of-life care combined with cost benefit terms and quality of life terms. MeSH (Medical Subject Headings) terms used include: 'Palliative Care'; 'Costs and Cost Analysis'; 'Quality-Adjusted Life Years'; and 'Cost-Benefit Analysis' (table 4). The search was kept as broad as possible as there can be quite a lot of overlap between the palliative care and 'end-of-life' literatures. No time limit was placed on searches but searches were restricted to those

published in English. Citations were then reviewed in order to filter out papers that were unlikely to provide useful information for the review. We did not search for empirical cost-effectiveness studies because a recent systematic review of economic evaluations in palliative care found no cost-utility studies [109].

Data extraction and analysis

After removing duplicates from identified records, tiles and abstracts were screened for potentially eligible papers. The full texts of potentially eligible articles were then against the inclusion and exclusion criteria (table 1). Full texts were also retrieved and screened in instances where the relevance of an article was unclear from the title and abstract. Papers were included if they discussed the theory around use of the QALY framework in the context of palliative or end-of-life care including editorials, and opinion pieces. Papers were screened against the eligibility criteria by two researchers (M.D and M.S) independently. The quality of the included papers was not assessed as the main focus was on the opinions of experts in the field.

The papers were summarised in line with the aims as defined above and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [117]. Because the research questions are qualitative in nature, the arguments for and against CUA's were summarised into themes and sub-themes according to the theory or concept underpinning each argument.

Table 1: inclusion and exclusion criteria

Inclusion	**Exclusion**
Theoretical papers (editorials, opinion pieces, etc.)	Systematic Literature reviews
Articles addressing the relevance of QALYs in palliative care	Non-English language
Articles addressing the relevance of CUAs in palliative care	Conference abstracts
Articles on estimating HR-QoL in palliative care	Study protocols
Special reports	
QALYs: quality adjusted life years; HRQoL: health-related quality of life; CUAs: cost-utility analysis	

QALY: quality adjusted life year

Results

A total of 405 records were returned (figure 4) from the initial bibliographic and review database search, of which ninety six duplicates were excluded. Following title and abstract screening, 309 records were excluded. The full texts of the remaining 45 papers were retrieved from which eight were included (table 2) and 37 excluded.

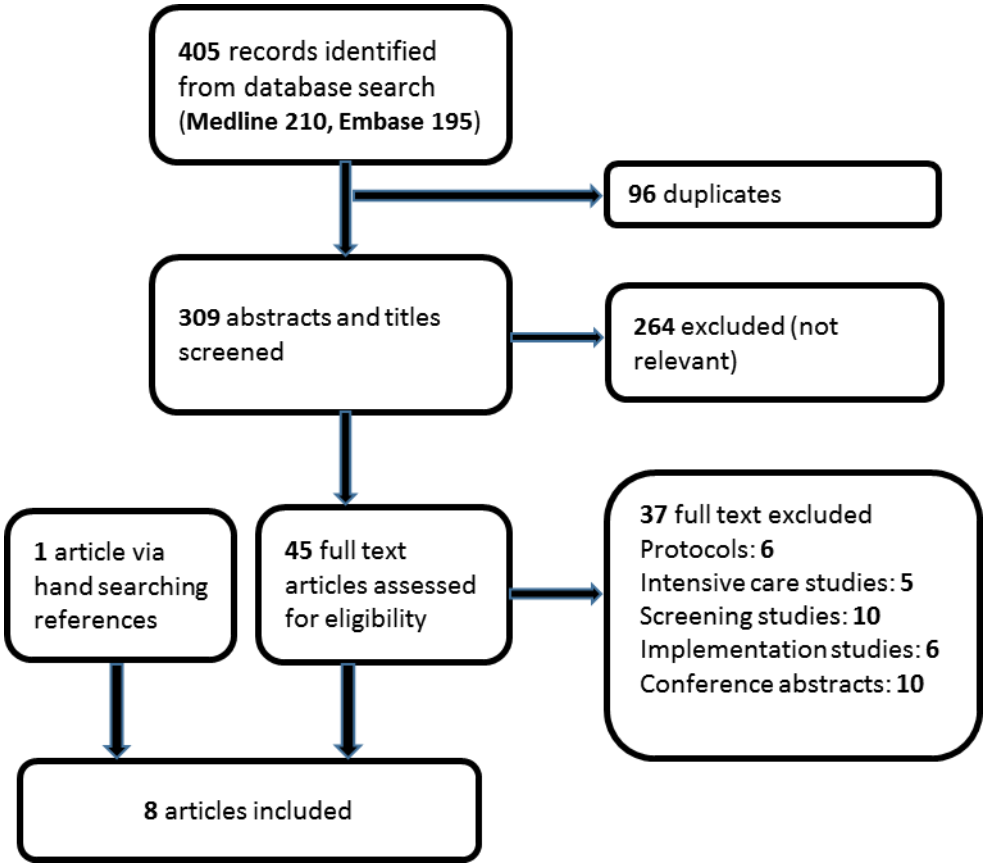


Figure 4: flow chart of search results

Four main themes (table 3) emerged from the literature relating to theoretical arguments for and against using QALYs in palliative care as follows:

1. The QALY problem

2. Non-additivity of time due to the following subthemes:

    - Instability of patient preferences for health states over time

- The heightened value of time at the end of life

3. Imprecision of the QALY – on the basis that the QALY as it stands does not incorporate framework has a narrow focus – i.e. QALYs are measured at the individual (patient)
4. Incompatibility of the QALY maximisation policy with patients' needs/preferences

Table 2: key features of included studies

Authors	Title	Paradigm	Type of article
Hughes; 2005[13]	Palliative care and the QALY problem	**Against QALY**: proposes narrative approach as an alternative	Expert opinion
Round; 2012[14]	Is a QALY still a QALY at the end of life?	**Pro QALY**: admits problems with QALYs but argues against abandoning QALY and suggests problems with QALY can be addressed	Expert review
Yang; 2011[118]	Considerations of quality-adjusted life-year in palliative care for the terminally ill	**Pro QALY**: contingent on using appropriate comparators	Letter
Normand; 2009[12]	Measuring outcomes in palliative care: limitations of QALYs and the road to PalYs	**Against QALY**: proposes developing PalYs as alternative to QALYs	Expert opinion
Chochinov; 2011[115]	Death, Time and the Theory of Relativity	**Pro QALY**: contingent on further adjusting for change	Expert opinion

		in value of time at the end of life (VIP).	
Coast; 2013[119]	Strategies for the economic evaluation of end-of-life care: making a case for the capability approach	**Against QALY**: proposes the capability approach focusing on the opportunity for a good death	Expert review
McNamee; 2008[114]	Incorporation of process preferences within the QALY framework: a study of alternative methods	**Pro QALY**: contingent on incorporating process preferences into QALY calculations	Journal article
Murtagh; 2013[120]	Capturing activity, costs, and outcomes: The challenges to be overcome for successful economic evaluation in palliative care	**Equivocal**; but reiterates potential value of PalYs	Special issue – opinion
QALY: quality adjusted life year; PalYs: palliative care yardstick; VIP: Valuation Index Palliative			

1. Incompatibility of the QALY maximisation policy with patients' needs/preferences

QALY (utility) maximisation is a key health economic principle whereby health resources are allocated in order to achieve the best possible outcomes. It is often assumed by economists that the main aim of health care (and health care systems) is to maximise population health contingent on available resources.[121, 122] This principle dictates that when faced with a choice between two options with equal cost, the option to be chosen is the one expected to yield the most QALYs irrespective of the context or to whom it is accrued. This principle has been criticised for failing to consider differences patients' needs as some groups of patients including palliative care patients will have poorer health than others, or more serious diseases, and so will have a greater need for health care even if the health gain is smaller than that achieved by a different treatment in patients who are less sick.[118 123]

Murtagh suggests that "*Palliative care interventions do not achieve high gains in QALY scores despite having considerably high needs: ... QALY maximization may not be consistent with delivering care according to patient needs or preferences".*[20]

Coast also shares a similar view to Murtagh and proposes for the application of a capability approach focusing on the opportunity for a good death.

- *Applying standard health economics notions of maximising the total health benefit from interventions designed to provide supportive care at the end of life seems inappropriate given that, the objective of care at the end of life is not focused purely on health improvement".*[124]

2. The QALY problem

The most substantial criticism of the QALY framework in palliative care has been attributed to the 'QALY problem'. The 'QALY problem' was first described in the context of palliative care by Hughes[13] in 2005. Hughes suggests that palliative care interventions – when compared with life-saving treatments – do not achieve enough QALY gains to be considered cost-effective because such interventions do extend life, and QoL gains are short lived.

- *"Thus, even when palliative care effects very substantial improvements in its patients' quality of life, the number of additional QALYs generated is small in comparison with*

life-saving treatments… which produce similar improvements in quality of life for patients with longer life expectancy".[13]

Based on the notion that palliative care interventions cannot be expected to achieve high QALYs Hughes proposed the narrative approach as an alternative. This approach entails simply putting forward the argument that palliative care should be treated as a special case because of the QALY problem.

- *"The narrative approach therefore provides a good basis for arguing that palliative care ought to be a higher priority for healthcare funding than its QALY scores would indicate"*[13]

Several other parties in the debate have highlighted the QALY problem.

- *"… the QALY problem is that there are uses of resources that appeal to public and decision makers' preferences, but using conventional measurement of cost per QALY would be clearly outside the ''cost-effective'' range"*[12]
- *"Palliative interventions do not achieve high gains in QALY scores for various reasons … these factors may place palliative care in a dis advantaged position when doing cost-utility analysis to compete for funds with other health care services"*[116]

However, Round[14] suggests that it is difficult to justify a claim of systematic bias (implied by the 'QALY problem'), because QALYs can be generated without life extension, and that more QALYs can be gained from life enhancing interventions (which don't extend life) than from life extending treatments (which do not improve QoL, or which worsen QoL). In essence, that "*the QALY problem rests on a set of assumptions about the decision making process that does not always hold*"[14]. He concludes by highlighting the lack of evidence to support the 'QALY problem'.[14]

Yang[118] suggests that, on the basis of evidence from the study by Temel et.al[125], PC can in fact lead to life extension. He also highlights that PC leads to cost savings by sparing patients the ordeal of aggressive, expensive and non-beneficial treatments. Yang concludes that although PC is compatible with the QALY framework, it is important for decision makers who utilise CUA to

consider the appropriate comparators i.e. should not compare "like (end-of-life treatments) with unlike (none-end-of-life treatments)".[118]

- *"Palliative care for the terminally ill should be compared only with other end-of-life services, including relevant medical inventions … current limited data show that when compared with other end-of-life treatments, end-of-life palliative care is enormously cost-effective".*[118]

3. Imprecision of the QALY

This theme relates to important palliative care domains and benefits that are excluded from the QALY framework as it currently stands including impacts on family members; process factors like information; and spiritual and existential domains. As a result, the QALY is thought to be imprecise and insensitive to changes in palliative care.

Hughes highlighted that the benefits of palliative care are not properly captured by the QALY thereby lacking precision.

- *"…the kinds of benefit that palliative care provides are not measured well by the QALY approach and therefore tend to be under-represented"*[13]

Several parties in this debate have highlighted this issue. For example Murtagh states that domains important palliative care, such as Spiritual/psychosocial wellbeing, are not incorporated in the QALY as it stands.[20]

Also, Normand suggests that the QALY approach itself may not be the problem, but rather that some important palliative care benefits – such as caring externalities and reassurance of access to care – have not been measured.[12] Based on this notion Round asserts that *"…the fact that researchers have not taken advantage of this flexibility* (afforded by the extra-welfarist framework within which the QALY sits) – to incorporate important palliative care benefits into the QALY framework – *is not a criticism of the framework itself".*[14] Round also highlighted that this issue of imprecision has been highlighted in other disciplines including paediatrics, where the response has been to measure what is missing and incorporate it into the QALY framework, rather than

dismissing the framework completely. He asserts that *"… if we agree that maximising the beneficial outcomes from use of scarce healthcare resources should be at least one of the grounds determining their allocation, then a lack of precision should not lead us to abandon the attempt to measure outcomes but rather should prompt us to develop the best ways of estimating them that we can"*[14].

McNamee[114] suggests that preferences for "process-of-care" factors (e.g. information) can be incorporated within the QALY especially where different interventions yield the same outcomes but he does not criticise the framework itself.

- *"Giving greater weight to the process by which care is delivered may lead to a more accurate assessment of the quality of life experienced by the person receiving that care"*[114]

McNamee suggests that the advantage of considering process-of-care in palliative care is that people (family or society) may derive value from the actual processes of providing care, as opposed to achieving some desired level of health or improved health state.

Murtagh highlighted that while the family is the unit of care in palliative care, QALYs are measured at the individual (patient) level. She suggests that the exclusion from the QALY of the effects of palliative on family means that palliative care interventions may be systematically discriminated against in cost utility analysis.

4. Non-additivity of time

Normand[12] suggests that it may be inappropriate to simply add up time – as is done in the QALY calculation – because equal amounts of time will be valued differently, based on contextual factors, even after adjusting along the 'quality dimension'.

- *"QALYs assume that time in a health state can be valued regardless of the context, but there may be circumstances where people put more or less value on time"*[12]

Nevertheless, Normand recognises that the assumption of additivity of time may be satisfactory in most situations.

- *"The assumption of additive time may be acceptable in most circumstances … and these are reasonably assessed in terms of changes in quality-adjusted time"*[12]

The following subthemes emerged relating to Normand's claim that time (particularly at the end of life) is not additive: the value of time at the end of life; and instability of patient preferences for health states over time.

Regarding the value of time at the end of life, Chochinov[115] supports Normand's claim regarding non-additivity of time by highlighting that time is valued higher towards the end of life than at other periods. He supports this claim by referring to evidence from the paper by Lenert et al.[126], which showed that sick patients – though not necessarily those at the end of life – tended to overvalue their current health. Chochinov further explains this heightened value of time at the end of life could partly explain the rise in health expenditures at the end of life. [115]

- *"…time and the value of quality time, changes in proximity to death … there is evidence to support this notion of heightened value of time toward the end of life"*[115]

Chochinov highlighted that *"A standard QALY is the product of quality of life and time, without adjusting for any change in the value of time"* [115]. He proposed that this additional value of time at the end of life can be mathematically quantified as an additional variable – the valuation index palliative (VIP) – which can then be incorporated into Normand's PalY described earlier.

Conversely, Round[14] argues that because the QALY framework sits within the 'extra-welfarist' economic theory, the addition value of time at the end of life can be accommodated within the QALY (rather than the underdeveloped and untested PalY) by applying equity weights to QALY estimates to reflect this 'extra' value of time.

- *"If it were deemed desirable to value time more heavily at the end of life, the most obvious approach would to be incorporate these values into the current estimation of QALYs through the application of an equity weight"*[14]

The second subtheme relates to the instability of patient preferences for health states over time. Coast highlights that preferences of patients at the end of life are unstable and unreliable, thereby

supporting Normand's claim about the non-additivity of time at the end of life.[124] However Round argues that the evidence on this issue is inconclusive, reflecting wide-ranging views about how individuals at the end of life express preferences for both time and health.[14] He also highlights that instability of preferences mainly poses a challenge *"when patients are asked to determine preferences"*[14], and suggests that "*by following consensus and deriving health state values from the general population the practical importance of the problem is removed, even though the conceptual and methodological problems may remain*"[14].

It has also been argued that death is not an

Discussion and conclusion

This review appraised the theoretical literature on the arguments for and against using QALYs in cost utility analysis of palliative care interventions and also identified proposed alternatives to the QALY. Four main themes emerged according to the broad concepts underpinning the arguments: incompatibility of the QALY maximisation policy with patients' needs; the QALY problem; imprecision of the QALY; and non-additivity of time.

All parties in the QALY debate agree that there are problems with the use of the QALY framework in cost-utility analysis of palliative care interventions, such as the omission of important palliative care domains. However, views about how to address these problems differ. While some parties[124] suggest that the appropriate course of action would be to develop a new framework for palliative care to replace the QALY, others[14] suggest that the limitations of the QALY can be accommodated within its current framework.

Theme 1: Incompatibility of the QALY maximisation policy with patients' needs/preferences

The criticisms of QALYs and CUAs in palliative care invariably reflect differences in philosophical perspectives of the parties involved, rather than differences in methodologies. The first theme – the incompatibility of a QALY-maximisation policy with the fundamental palliative-care principle of providing care based on patients' needs and preferences – reflects the conflict between the principles of efficiency and equity in the distribution of healthcare. The principle of QALY-

maximisation (or simply maximisation) appeals more to those interested in allocating resources efficiently, rather than equitably or otherwise [70]. Maximisation sits within the theory of extra-welfarism – which rejects the welfarist view that social welfare is simply the sum of individual welfare (utility) of members of the society [122, 127]. QALY critics have rejected the QALY framework on the grounds that the QALY maximisation objective adopted by health policy makers is incompatible with palliative care objectives of delivering care according to patients' needs or preferences. However, although the efficiency-driven QALY-maximisation policy is an important objective in many health systems, in reality it does not appear to be the only goal of either policy makers or society generally. Many health policy programmes in the UK (including value based pricing) [128] appear to have been driven by concerns for equity and social justice rather than QALY (health) maximisation. Such policies explicitly sacrifice health-maximisation to allow for equity considerations, e.g. severity of illness and unmet need [128]. Maximisation is classed as one of three principles of justice underpinning health-care rationing; others include egalitarian and need principles [129]. Egalitarian principles entail achieving equal distribution of health care (e.g. equal access to hospice) while need principles entail distributing health care according to need [129]. It can therefore be inferred that palliative care would be more aligned with the egalitarian and need principles than with maximising. Each of these principles has a limited focus and so blindly pursuing one over the others inevitably results in winners and losers in society.[129]

However, Cookson and Dolan [129] highlighted that these principles can be combined, either by weighting them together or by activating a secondary principle in instances where the primary principle is either inadequate or inappropriate. For example, in the UK, the National Institute for Health and Care Excellence (NICE) supports QALY-maximisation up to the threshold of £20,000 per QALY gained, beyond which equity concerns are considered relevant[22, 130]. Williams [131] suggested that the best way to combine efficiency and equity considerations is by using societal values to derive equity weights to be attached to QALYs. Several factors contributing to the social value of a QALY have been identified from a number of studies [121] including: patient factors like age (benefits to the young children valued higher), and socio economic status [132]; magnitude and direction of the effect; factors associated with the intervention factors e.g. an innovative treatment;

the way QALYs are distributed e.g. people with self-induced illness receive lower priority [132]; and severity of illness (relevant to palliative- and end-of-life care patients) [133].

Theme 2: the QALY problem

The second theme that emerged from this review was the 'QALY problem' which is based on the idea that palliative care interventions – when compared with life-saving treatments – do not achieve enough QALY gains to be considered cost-effective because such interventions do not extend life, and QoL gains are short lived. However, there are two fundamental problems with this argument. First, it assumes that QALYs cannot be accrued without life extension. In Round's rebuttal to this argument he used a graphical illustration to demonstrate that it is possible to gain QALYs without life extension and conversely that life extension may sometimes yield QALY losses [14].

Second, this arguments assumes that in CUAs, palliative care interventions are (or ought to be) compared with life-saving treatments. Yang (pro-QALY) highlighted the importance of using appropriate comparators in any CUA and in any discipline including palliative care.[118] A comparison between palliative care and curative treatment would not reflect current clinical practice, at least not in the UK, where palliative care is offered in conjunction with life-saving treatments, rather than as an alternative. This is also reflected in the definition of palliative care, which is that palliative care may be initiated early in the course of treatment along with other curative treatments. Furthermore, the World Health Organisation (WHO), at the 67th World Health Assembly, recommended that palliative care be provided in conjunction with potentially curative treatment, and not just as an "*optional extra".*[5] Thus, it would appear that the appropriate comparators in any CUA in palliative care, should be either (1) '*palliative care plus life-saving treatment*' versus '*life-saving treatment only*'; or (2) two alternative palliative care interventions. If this is acceptable, then the QALY problem ceases to be an issue.

Theme 3: imprecision of the QALY

The third theme that emerged from this review relates to the imprecision of the QALY. Several parties in the debate suggest that the QALY framework is imprecise because: it excludes important palliative care domains (e.g. spirituality and psychosocial wellbeing); it focuses solely on health

improvement; and it excludes impacts on family members to whom palliative care interventions are also offered. [120, 124]. For example, Hughes suggests that it would be impossible to account for the experience of dying a good death within the QALY framework[13], and so recommends rejecting the QALY framework in favour of the '*narrative approach*' – the notion that palliative care ought to be treated as a special case and be exempt from traditional principles of economic evaluation[13]. In other words, that palliative care ought to be a higher priority for healthcare funding than its QALY scores would indicate.

However, there are two problems with this argument. First, it fails to recognise the limited availability of health resources and the resultant need for equitable rationing. Second, the narrative approach may be used to justify voluntary euthanasia, which – as acknowledged by Hughes – might be an unintended and unwelcome consequence for those wishing to use it as a basis for expanding palliative care services. However, proponents of the QALY, particularly Round, argue it is possible to incorporate important palliative care benefits that are currently excluded from the QALY including non-health domains, process factors, and impacts on family because the QALY is grounded in the theory of extra-welfarism. Round suggests that a palliative-care specific preference based instrument could be developed which incorporates relevant palliative care domains – as has been done in other disciplines with similar issues. Indeed, besides the imprecision of the QALY, none of the criticisms of the QALY are unique to palliative care. These issues have been highlighted in other areas of health. For example, the QALY has been criticised as being ageist [134], but a review by Round showed that such a claim was not supported by evidence. Similar issues have been highlighted in mental health and paediatrics, and these issues were addressed by determining and incorporating what was missing.[14] For example, McNamee supports suggests that process factors be incorporated within the QALY especially where different interventions yield the same outcomes but he does not criticise the framework itself [114].

Theme 4: non-additivity of time

The fourth theme was around non-additivity of time which is based on the notion that it may be inappropriate to simply add up time – as is done in calculating the QALY– because equal amounts of time will be valued differently, based on contextual factors, even after adjusting along the

'quality dimension'. This is related to two subthemes: the heightened value of time at the end-of-life; and that patient preference at the end of life is unstable and unreliable. Based on these, opponents of the QALY advocate rejecting the framework. In order to incorporate the heightened value of time at the end of life, Normand proposed the PalY as an alternative to the QALY framework, although how this new framework will function remains unclear. Chochinov proposed another alternative framework – the VIP – but similar to the PalY remains undeveloped. Proponents of the QALY argue that instead of developing a new framework altogether, the additional value of time at the end of life can be incorporated into the QALY framework as equity weights [14]. This would be consistent with the aforementioned concept of combining the principles of distributional justice. Indeed current practise suggests that it is possible to do this. For example, in 2011 NICE consulted various stakeholders on applying specific equity weights to QALY estimates[135]. The equity weights considered include burden of illness; whether patients were at the end-of-life; age; time from diagnosis etc. These weights were based on results of a large survey of the preferences of the general public[136] [135]. The results suggest that there is support for valuing time more heavily at the end of life, but on the premise that it gives patients time to settle their affairs, and so would only apply in situations where patients have a short life expectancy (2 years or less) from diagnosis. A correction factor would provide a one-off value for additional time – allowing an individual to put their affairs in order – at the point of diagnosis with a terminal illness.

The second sub-theme of 'instability of patient preferences' refers to the notion that "*as an individual approaches the end of life, they may consider the time/health trade-off for the same health state differently than they would have at previous life stages*" [14]. Round suggests that the evidence for this is inconclusive and that problem pales in significance when general population (rather patient) values are used. Normand further adds that this issue of instability of preferences at the end of life can be addressed by using short time frames (ideally reflecting the average life expectancy of palliative care patients) when valuing health states instead the current time frame of 10 to 20 years. Dolan demonstrated that it is possible to obtain meaningful valuations using time frames as short as one month [80]. Nevertheless, this issue is only a problem with the TTO valuation

method. Other valuation methods like standard gamble and DCEs are unlikely to be affected by this.

It is clear from this review that the QALY – like any other outcome measure – has limitations most which can be addressed within the current framework. However, the arguments for abandoning the QALY are weak at best for several reasons. First, the QALY problem in reality is unlikely to be a problem provided the right comparators are used in CUAs of palliative care because QALYs can be accrued with or without life extension. Moreover, at least two studies have shown that palliative care can lead to life extension.[125, 137]

Second, the criticism of the QALY on the basis that a QALY-maximisation policy is incompatible with the goals of palliative is not enough justification for abandoning as maximisation principles can be used alongside other considerations including equity and need. The issue here is not the framework as such, but the way in which value judgements are applied to it.

Finally, although the arguments about the imprecision of the QALY are sound, they do not seem to justify abandoning the QALY. Indeed the QALY's imprecision is mainly attributed to using imprecise generic preference-based measures like the EQ-5D. Nevertheless, it is remarkable that there are currently no CUAs of palliative care interventions.

Limitations of this review

This review was based on a small body of literature and was appraised subjectively. We did not search for empirical studies, however, a recently published systematic review on the cost and cost-effectiveness of palliative care found no CUAs [109]. It is also possible that our search strategy did not capture all relevant publications, as we did not search the grey literature.

Recommendations for future research

Despite numerous parties contributing to this debate, it is surprising that none of the arguments, either for or against, is based on empirical evidence. It would seem worthwhile and feasible to demonstrate the aforementioned issues empirically. For example, a validated palliative care measure could be mapped [138] onto a generic preference measure using statistical methods to assess

the extent to which it captures palliative care concerns. This would be a fairly simple study using secondary data from studies that have included both a palliative care measure and a generic preference-based measure. It would also be useful to have CUAs of palliative care interventions, ideally alongside clinical trials. Such studies would substantiate most if not all of the criticism against the QALY by comparing the sensitivity of a generic preference-based measure against a validated palliative car measure, and prospectively exploring the implication of using the QALY in palliative care evaluations.

Further research is also needed to incorporate important palliative care domains into the QALY framework. This can be achieved by developing a palliative-care-specific preference based measure, either anew or from a currently existing non-preference-based palliative care measure. This approach has been used in other disciplines where similar QALY limitations have been highlighted.[39, 40, 61] This approach can also be used to address some of the criticisms of the QALY (e.g. instability of patient preferences) by using short time frames during the valuation phase. However, this approach would only partially address the issue of non-additivity of time as it would not be possible to incorporate into this, the purported added value of time at the end of life. Nevertheless, the added value of time can be addressed using equity weights as discussed earlier.

In summary, all parties in the QALY debate agree that there are problems with the use of the QALY framework in cost-utility analysis of palliative care interventions, such as the lack of inclusion of domains important to palliative care patients (and their family). However, views differ as to how these problems should be addressed. While some parties suggest that a new framework should be developed to replace the QALY, others suggest that the limitations of the QALY can be accommodated within the framework.

Although substantive concerns have been raised regarding the use of QALYs in palliative care, it appears such concerns can be addressed within the QALY framework. We believe that the QALY framework should not be abandoned for the following reasons:

- There is currently no better alternative;

- The QALY has proved to be a serviceable vehicle for quantifying joint mortality-morbidity impacts at individual and population level;
- To abandon the QALY now is to sever links to hundreds of published studies and multiple ongoing investigations – including many capitalizing on data now collected in national surveys, clinical trials, observational studies;

A more productive pathway would be to pursue a program of research that takes the QALY as a starting point for continuous QALY improvement over time, for example developing a palliative-care-specific preference based measure.

These conceptual and methodological issues signal opportunities for making important incremental improvements in the QALY – rather than discarding the framework. However, until such a time when CUAs of palliative care interventions are available, these debates will continue.

Table 3: main theoretical arguments for and against using the QALY in palliative-care evaluations

Theme	Against QALYs	Pro QALYs	alternative
1	QALY problem: palliative care interventions – when compared with life-saving treatments – do not achieve enough QALY gains to be considered cost-effective because such interventions do extend life, and QoL gains are short lived[12-14]		
	"even when palliative care effects very substantial improvements in its patients' quality of life, the number of additional QALYs generated is small in comparison with life-saving treatments… which produce similar improvements in quality of life for patients with longer life expectancy"[13]	*"it is difficult to justify a claim of systematic bias because QALYs can be generated without life extension"*[14]	
	"the QALY problem is that there are uses of resources that appeal to public and decision makers' preferences, but using conventional measurement of cost per QALY would be clearly outside the ''cost-effective'' range"[12]	*"more QALYs can be gained from life enhancing interventions (which don't extend life) than from life extending treatments"*[14]	

	"Palliative interventions do not achieve high gains in QALY scores for various reasons … these factors may place palliative care in a disadvantaged position when doing cost-utility analysis to compete for funds with other health care services"[120]	*"the QALY problem rests on a set of assumptions about the decision making process that does not always hold"*[14]	The narrative approach
		"There is evidence that palliative care can lead to life extension"[118]	
		"Palliative care for the terminally ill should be compared only with other end-of-life services, including relevant medical inventions … current limited data show that when compared with other end-of-life treatments, end-of-life palliative care is enormously cost-effective"[118]	Use appropriate comparators
2	Non-additivity of time: that it may be inappropriate to simply 'add-up' time because equal amounts of time will be valued differently, based on contextual factors, even after adjusting along the 'quality dimension. E.g. due to heightened value of time at the end of life, and instability of patient preferences for health states over time)[12, 14]		

	"QALYs assume that time in a health state can be valued regardless of the context, but there may be circumstances where people put more or less value on time"[12]	*"If it were deemed desirable to value time more heavily at the end of life, the most obvious approach would to be incorporate these values into the current estimation of QALYs through the application of an equity weight"*[14]	VIP, PalY, Capabilities
	"time and the value of quality time, changes in proximity to death … there is evidence to support this notion of heightened value of time toward the end of life"[115]	*"the evidence is inconclusive on this issue* [of instability of preferences], *reflecting wide-ranging views about how individuals at the end of life express preferences for both time and health"*[14]	
			general population valuations, equity weighting; DCE; BWS
3	Imprecision of the QALY: benefits of palliative care are not properly captured by the QALY		
	"the kinds of benefit that palliative care provides are not measured well by the QALY approach and therefore tend to be under-represented"[13]	*"QALY approach itself may not be the problem, but rather that some important palliative care benefits, such*	

		as caring externalities and reassurance of access to care, have not been measured"[12]	
	"important palliative care domains, such as Spiritual/psychosocial wellbeing, are not incorporated in the QALY as it stands"[120]	*"the fact that researchers have not taken advantage of the flexibility afforded by the extra-welfarist framework* [by incorporating important palliative care domains] *within which the QALY sits is not a criticism of the framework itself"*[14]	Better measure of valuing benefits e.g. a palliative care specific PBM
	"Assessment of a good death seems unlikely to be fully captured for the dying person in terms of improvements in morbidity and/or mortality; it seems even less relevant to the loved ones of the dying person"[119]	*"Giving greater weight to the process by which care is delivered may lead to a more accurate assessment of the quality of life experienced by the person receiving that care"*[114]	Incorporating process measures
4	Incompatibility of the QALY maximisation policy		
	"*Palliative interventions do not achieve high gains in QALY scores for various reasons: ... QALY maximization may not be consistent with delivering care according to patient needs or preferences"*[120]		
	"Applying standard health economics notions of maximising the total health benefit from interventions designed to provide supportive care at		Capability approach

	the end of life seems inappropriate given that, the objective of care at the end of life is not focused purely on health improvement"[119]		
	"palliative care fares badly under a policy of QALY-maximisation, since procedures which prevent premature death (provided the life is of reasonable quality) or improve quality of life for those with longer life expectancy will produce more QALYs"[13]		

QALY; quality adjusted life year; DCE: discrete choice experiment; BSW: best worst scaling; PalY: palliative care yardstick; VIP: valuation index – palliative; PBM preference-based measure; QoL: quality of life

Search terms

Table 4: Search terms

Medline	Embase
((“Quality-Adjusted Life Years” [MeSH]) OR (“Quality of Life” [MeSH])) AND ((“Cost-Benefit Analysis” [MeSH]) OR ("Costs and Cost Analysis"[MeSH)) AND ((“Hospice Care” [MeSH]) OR (“Terminal Care” [MeSH]) OR “Palliative Care” [MeSH]))	((terminal care/) OR (hospice care/) OR (palliative therapy/)) AND ((cost benefit analysis/) OR (cost effectiveness analysis/)) AND ((quality of life/) OR (quality adjusted life year/))

2.5. UK health policy considerations

2.5.1 NICE and its social value judgements

The National Institute for Health and Clinical Excellence (NICE) gives guidance and advice to improve health and social care in the NHS in England and Wales. Established in 1999 as a special health authority under the Department of Health, it aims to decrease variation in access and quality of NHS treatments and care. In 2013, the UK parliament established NICE as a Non Departmental Public Body (NDPB), making it operationally independent of – but still accountable to – the department of health. At the same time NICE became tasked with developing guidance and quality standards in social care, thereby changing its name to the National Institute for Health and Care Excellence to reflect this.

NICE’s has several programs of activities including; technology appraisals (mainly appraising patented drugs); medical technologies evaluation (mainly diagnostic devices); and clinical guidelines (mainly assessing clinical interventions and unpatented medicines [139]

NICE's guidelines are informed by clinical and cost-effectiveness analyses, usually cost-utility analysis using QALYs with the EQ-5D stipulated as the preferred PBM [130]. For an intervention to be recommended for adoption by the NHS, it should have an incremental cost-effectiveness ratio (ICER) below or at a range of £20,000 to £30,000 per QALY gained. The likelihood of a given technology being rejected on grounds of cost-ineffectiveness increases as its ICER increases. An intervention with an ICER below £20,000 per QALY gained is likely to be approved solely based on its cost-effectiveness, whereas approvals for interventions with ICERS above £20,000 will depend on other factors including equity considerations as discussed in section 2.4. To approve interventions with ICERS above the £30,000 threshold a much stronger argument regarding the relevance of these factors would be required [130].

NICE's guideline development groups (independent advisory groups) have sometimes applied social value judgements and 'special weighting' in recommending interventions with ICERs exceeding the stipulated threshold. For example, in appraising multi-disciplinary (MDT) care in the management of motor neurone disease (MND), the guideline development group took into account the 'disease severity and short life expectancy' of MND patients, and recommended MDT care despite high ICER estimates ranging from £28,000 to £57,000 per QALY gained [140] [141]. The guideline group also considered the fact that QALY gains in MND patients may have been underestimated because "*generic measures of health utility may fail to detect differences in quality of life that are important to patients particularly at the end of life*" [141].

2.5.2 End-of-life treatments – where does NICE stand?

In 2009 NICE introduced flexibility in its methods and process for considering treatments for patients at the end-of-life [142]. This was because of prominent refusals of new treatments the previous year, which led to criticisms from key stakeholders including patients and industry. This flexibility assigned more weight to QALYs achieved at the end of life in particular instances where: patients have a life expectancy of less than two years; and the treatment extends life by at least 3 more months [142]. Paulden suggests that this effectively equates to raising the threshold to £50,000 per

QALY for this group [143] gained for 'end-of-life' treatments, thereby enhancing the chance of a favourable recommendation [144]. Additionally, in the process of weighting QALYs gained at the end-of-life, NICE's guideline development groups are requested to assume that the quality of life experienced in this additional period of life extension is at the maximum expected for a healthy person of equal age. This policy assumes that society values life extension for people at the end of life more heavily than quality of life gains thereby decreasing the likelihood of accepting palliative-care interventions, as they do not seek to extend life. Noticeably, there was little evidence supporting this assumption. It is conceivable that this policy may have contributed to some of the criticisms of QALYs framework in palliative care discussed in section 2.4. However, the problem here is not the framework per se, but the way in which value judgements are applied to it.

This led to a lot to criticism and in 2014, NICE proposed two additional considerations that would warrant a higher threshold: 'burden of illness' and 'wider societal impact' [144]. Although these proposals are likely to have a favourable impact on palliative care interventions, at the time of writing this thesis these have not yet been implemented.

2.6. Rationale for this thesis

Palliative care is a broad discipline where the appropriateness of the use of generic PBMs in order to generate QALYs for use in economic evaluation has been questioned.[12, 13, 112] This is because generic measures have been primarily designed to capture physical health problems and may miss important aspects of HRQoL of palliative care patients. For example, the EQ-5D does not incorporate domains important to palliative care patients, such as Spiritual and psychosocial wellbeing. This may explain their limited use in clinical practice and research.[109] These concerns have led to proposals for developing a palliative care-specific PBM (in CUAs), which will be appropriate for palliative care patients with a variety of diagnosis, and sensitive to changes in their HRQoL status.[14]

However, to the best of our knowledge, none of the palliative care-specific outcome measures are preference-based (that is, they are not linked to utility values) and so cannot be used to estimate QALYs in CUAs. Given this gap between the need for economic evaluations of palliative care and the lack of an appropriate PBM that captures important aspects of HRQoL of palliative care patients, the main objectives of this thesis are: 1) to assess the feasibility of deriving a palliative-care-specific utility values via the mapping approach; 2) depending on the outcome of the mapping study – to develop a palliative care-specific PBM either as a new tool or by adapting an existing measure.

A new preference-based measure or a modification of an existing measure?

A survey of 311 palliative-care researchers and clinicians across Europe found nearly 200 different palliative care measures with respondents indicating their preference for a reduced number of tools[145]. Thus, this raises the question of the appropriateness of adding to an already oversaturated field. However, there are many advantages of developing a PBM from an existing palliative care instrument. In particular, the validity of existing instruments in palliative care patients may have already have been established, and so it would be extremely beneficial to harness this property rather than having to 'reinventing the wheel'. Furthermore, deriving a PBM from a pre-existing

measure will enable wider assessment of the 'value for money' palliative care interventions, both prospectively and retrospectively – using historical data.

Given the large pool of palliative-care measures[146], it seemed more appropriate to derive a PBM from an existing palliative-care measure. But which measure should be used? A systematic review of QoL measures used in palliative care by Albers et al[146] identified 29 palliative care-specific QoL instruments. The following criteria were considered in selecting the most appropriate instrument for the derivation of a PBM:

- Broad coverage of aspects of HRQoL, including psychological, spiritual and physical health aspects;
- Applicable across a broad range of diagnoses, including cancer and non-cancer;
- Psychometric properties: established construct validity and responsiveness;
- Widely used in clinical practice and in research (international coverage desirable);
- Applicable across primary and secondary settings;
- Free to use;
- Patient-reported;
- Accessible secondary data (for mapping purposes);

Of the 29 instruments, the McGill Quality of Life Questionnaire (MQOL) and the palliative care outcome scale (POS) appeared to fulfil all or most of the set criteria. The POS is free use and data set were readily accessible, whereas, the MQOL is not free to use. For these reasons, the POS was selected as the base measure for deriving a palliative care-specific PBM. Moreover, the POS has been suggested elsewhere as suitable for this purpose.[12]

2.7. Palliative Outcome Scale (POS)

The Palliative Outcome Scale (POS) is a short easy-to-use clinical outcome measure originally developed and validated in eight end of life and palliative care settings in the UK, including hospital, community, in-patient hospice, outpatient, day care and general practice.[147] It was developed to measure domains that impact on the quality of life of palliative care patients. The POS was based on a systematic literature review of existing scales and it has ten items including physical

and psychological symptoms, information and spiritual needs, family and practical problems plus an open field for additional reports.[147] It has been designed to reflect patient- centred care and addresses problems for patients and families. Recent comparisons of patient and caregiver POS ratings showed substantial agreement for pain, moderate for four items, and fair for three and slight for two.[148] There is extensive evidence on the descriptive validity of the POS as a measure of health status of palliative care patients across a wide range of medical conditions. It has become one of the most widely used measures of health status in palliative and EOL care. However, the POS currently cannot be used to derive QALYs, as its scoring system is not preference-based. The number of items in the POS also means that it is not amenable to health-state valuation in its current form. Therefore, it would be extremely useful to be able to adapt it for use in economic evaluation. Given its widespread use in palliative care clinical practice, service evaluation, and research;[111, 137, 149-156] deriving a preference-based measure from the POS would considerably extend the scope for conducting economic evaluations in palliative care.

2.8. Theoretical foundations of thesis

Utilities and QALYs are interrelated but distinct concepts that can be used separately or together. Utilities are based on the theory of 'expected utility' which was developed in the 1940s by mathematician, John von Neumann, and economist, Oscar Morgenstern.[50] This theory was developed as a normative (prescriptive) model which specifies how a rational individual should make decisions when outcomes are uncertain.[157] This model is applicable to policy and decision-making in all fields, including health care.[158] The expected-utility theory is based on three fundamental principles that dictate an individual's preferences in the face of uncertainty. These principles, as presented by Bell and Farquhar, are that preferences are transitive, independent, and continuous.[158]

Utilities as defined by von Neumann and Morgenstern (VN-M utilities), are the numbers that represent the strength of a person's preferences (or desirability) for certain outcomes in the face uncertainty.[157] The measurement of utilities on patients and their use in the expected utility model is the underlying paradigm of clinical decision analysis[159], which is increasingly being applied in

health care.[160] VN-M utilities are considerably different from utilities that underpin both current microeconomics and nineteenth-century economics.[161] However, it is worth noting that the utility theory does not describe how people make decisions under uncertainty in reality, but rather, it describes how they should make decisions if they wish to act rationally. The evidence as to whether or not people follow this principle is mixed.[157]

In economic evaluation, the QALY framework is generally associated with cost-utility analyses, where the incremental cost-effectiveness ratio (ICER) is expressed in terms of cost per QALY gained. In the particular case of utility-weighted QALYs, the relevant ratio is still cost per QALY gained. To distinguish this special case, the analytic model is known as cost-utility analysis. [70]

The concept of QALYs was first developed in the 1970s by Fanshel and Bush, who initially called it "function-years gained", and then two years later referred to it as "additional quality-adjusted years of life".[162, 163] It was designed as a method that could integrate within an individual, the health improvements from changes in both the quality and quantity of life, and could also aggregate these improvements across individuals.[163, 164] The fundamental ethical judgment inherent in this approach to aggregation is that a gain of one year in full health counts as 1, irrespective of any characteristics the individual (such as age or disease severity). In other words, a QALY gained is valued the same, regardless of how, or for whom, it is attained. [157] For example, over a specified time frame, a gain in quality of 0.6 for an individual is equal to a gain of 0.2 each for three people. Likewise, a gain of 0.6 for a year is equal to a gain of 0.2 for three years, assuming equal time preference.

The QALY framework is based on the wider extra-welfarist economic theory of health care evaluation. [14, 122, 165]The QALY framework requires the assignment of quality-adjustment weights to various health states. However, the framework itself does not specify how the weights should be determined, and so a number of credible approaches could be used. These weights may reflect the preferences of patients, providers, planners, government officials, or any other group or individual. For example, Bush used the Index of Well Being (and not utilities), obtained from the general public as weights, whereas, Torrance used health-state utilities measured on patients.[166] More recently, Bleichrodt et al. used capabilities as quality-adjustment weights.[167] Other groups have used a variety of weights for quality adjustment.[168] However, because the QALY model is used to

support decision-making about appropriate treatment or interventions for groups of individuals, it seems appealing to use weights that reflect the preferences of the individuals – i.e., utilities.[157]

In the discipline of palliative care, a major criticism of the use of utilities as quality-adjustment weights for QALYs is that they do not capture important aspects of palliative care, although this has not been demonstrated empirically. [12, 13, 124] However, because the QALY framework sits within the extra-welfarist theory, it is possible to include domains and attributes that are important to palliative- and end-of-life care patients.

2.9. Summary of gaps and prioritization

This section summarises the key issues from the literature and other considerations and makes the case that a new or modified palliative care preference-based measure is needed for use in economic evaluations of palliative care interventions.

What is known about economic evaluations in palliative care?

- *High-quality economic evaluations are crucial in identifying the comparative clinical and cost-effectiveness of competing palliative-care interventions.*
- *There is a dearth of economic evaluations (particularly cost-utility analysis) of palliative care interventions.*
- *Current palliative care instruments are not preference-based, and so cannot be used to calculate QALYs for cost-utility analysis*
- *The dearth of cost-utility analysis has mainly been attributed to the limitations of the QALY in palliative care (e.g. the inappropriateness of generic preference-based measures in palliative care) and this has generated a lot of debate amongst palliative-care researchers and clinicians.*
- *While some parties in the debate advocate replacing the QALY framework entirely due to its limitations in palliative care, others recommend persisting with the framework and addressing the limitations therein.*

- *The criticisms of the QALY framework have been theoretical and not supported by evidence.*
- *The response to similar issues with the QALY in other disciplines suggests that the limitations of the QALY can be addressed within its framework.*

Why is this important?

- *The lack of economic evaluations deprives decision makers of the basic information required to best meet the needs of dying patients.*

3. Aim and objectives

3.1. Aim

To develop a palliative-care-specific preference-based outcome measure (POS-E) for use in economic evaluations of palliative care.

3.2. Objectives

1. To assess the feasibility of mapping the Palliative Care Outcome Scale (POS) onto the EQ-5D
2. To derive and validate a simplified health-state classification from the POS
3. To conduct a valuation exercise to elicit health-state values for a sample of states
4. To model valuation results to produce utility values for all health states using regression / econometric models
5. To integrate results and produce an algorithm for estimating utilities for use in cost-utility analysis of palliative care interventions

4. Overview of methods and methodological considerations

This chapter describes the study design, and the rationale for the chosen methods.

The overall study design was a secondary analysis of cross-sectional data followed by a cross-sectional valuation survey.

As previously discussed in section 2.2.3 above, the vast majority of the available CSMs are not preference-based, and so cannot be used to derive utility values for estimating QALYs in CUAs. Mapping from CSMs directly onto a generic PBM[35] is one of the ways to address this issue.[169] A second approach to addressing the issue is to derive preference weights for the CSM as discussed in chapter 2.1.2 above. The approach for this thesis comprises two main stages as follows: 1) mapping the POS onto the EQ-5D; and 2) developing a palliative-care specific preference-based measure comprising six sequential steps grouped into three stages – 2A, 2B, and 2C (figure 5). For the mapping analysis, the main methodological considerations are discussed in section 4.1 below, with further details of methods and results provided in chapter 5 (publication 2). The main methodological considerations for stages 2A, 2B, and 2C are discussed in section 4.2 below. However, because the methods used in stages 2B and 2C were partially dependent on the results of stage 2A, the methods and results for stage 2A are reported separately in chapter 6 (publication 3), while those of 2B and 2C are reported together in chapter 7 (publication 4).

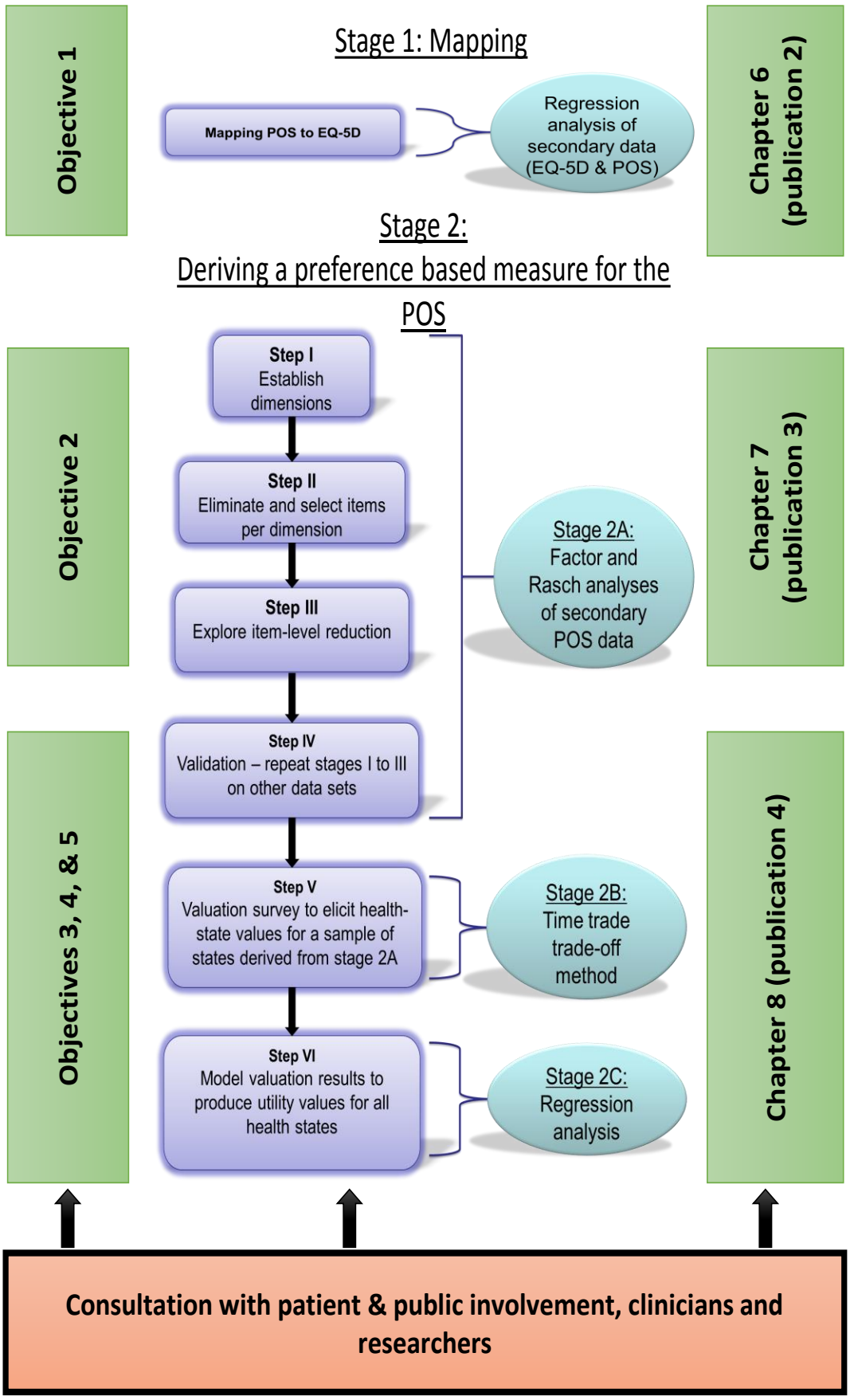


Figure 5: overview of thesis methods

4.1 Stage 1: Mapping POS onto the EQ-5D

The first stage of this thesis explores the feasibility of mapping a CSM – the Palliative Care Outcome Scale (POS) – onto a generic PBM; the 3-level EQ-5D. The EQ-5D was chosen because it is the most commonly used generic PBM and has been recommend by the National Institute for Health and Clinical Excellence (NICE) as the reference measure for cost-utility analyses of health care in the United Kingdom.[22] Likewise, NICE endorses the use of mapping to obtain utility values. [169] The design here was a secondary analysis of cross-sectional data. This analysis was informed by the MAPS Reporting Statement for Studies Mapping onto Generic Preference-Based Outcome Measures[170].

4.1.1 Methodological considerations

Mapping (or cross walking) onto generic preference-based measures is a commonly used process for deriving health utilities for QALYs within cost-utility analysis.[171, 172] Mapping involves assessing the association between a preference-based instrument and a non-preference-based instrument and then using this association to determine conversation rates between both measures, thereby enabling the conversion of scores from one measure to the other.[35] Mapping can be achieved either through statistical techniques or via expert judgement, however, the latter is seldom used due to its ambiguity and inability to account for variability in the outputs [173]. For mapping to be useful a degree of conceptual correspondence is required between both measures [169]. The feasibility of mapping is contingent on the same patients providing data on both instruments.

The main advantages of mapping are that it can be used to: predict utility scores in studies where a generic PBM has not been used; and to assess the extent to which utility scores may be impacted by potential conceptual differences between two instruments. This property of mapping is crucial to this thesis as it provides the first evidence on the extent to which the EQ-5D – the most commonly used generic preference-based measure – captures palliative care concerns, thereby substantiating (or refuting) some the criticisms discussed in section 2.4.

Mapping requires two datasets: a development dataset to which regression models are applied to derive a statistical relationship (a mathematical algorithm) between the POS and the EQ-5D in this instance; and a validation dataset on which the aforementioned algorithm is tested.[170]

Model specification

The regression models used in mapping studies can be specified in various ways (table 5). The simplest of these is the additive model, which uses regression techniques to assess the relation between the EQ-5D utility scores and POS total scores. However, this model is limited by its assumption that all items on the POS have equal weight (e.g. that the intervals between 'all of the time', 'most of the time' and 'some of the time', etc., are equal). This can be addressed via a number of approaches such as: using item responses instead of total scores; and including squared and interaction terms. This analysis assessed the relationship between the EQ-5D and: POS total scores; POS sub-scale scores; and individual POS items where appropriate. Total and sub-scale scores were treated as continuous variables, while item responses were modelled as discrete dummy variables. Another more complex alternative – response mapping [169] – was also used which will be discussed in the following section on modelling techniques.

The more complex procedures require large datasets, which is problematic as palliative care studies often, have small sample sizes. In order to address this issue data from three studies that included both POS and EQ-5D were pooled together and the subsequently split into two random halves – one for development and the other for validation. This split-sample approach to validation has been recommended in the literature.[174, 175] Details of the data use for mapping are discussed later in section 4.3.

Choice of modelling technique

Models were fitted to the overall EQ-5D index using linear regressions estimated by OLS and CLAD. Further models were fitted to the individual dimensions of the EQ-5D (response mapping) using multinomial logistic regression (table 5).

Ordinary least squares (OLS)

OLS was chosen because it is the commonest model used for mapping between instruments. The OLS models assumes that the relationship between the dependent variable (EQ-5D index values) and the independent variable(s) (POS) can be expressed as a linear function of the parameters.

However, OLS models are poor at predicting scores for people at extreme ends of scales (i.e. those in full health and poor health) [35, 169]. As a considerable proportion of palliative care patients would be expected to have extreme scores, it was necessary to explore other models.

Censored least absolute deviations model (CLAD)

Censored least absolute deviations (CLAD) regression methods take into account the ceiling effect (right censoring) of the EQ-5D. It also accounts for the bimodal distribution of the EQ-5D index score which occurs as a result of the large gap in the valuation space between full health (which has a score of 1) and the nearest dysfunctional health state (maximum of 0.883) defined by the EQ-5D descriptive system. CLAD employs a median regression procedure that minimizes the sum of absolute residuals, and so is not as sensitive to deviations from normality and homoscedasticity [176].

Response mapping

An alternative to modelling the EQ-5D index is to fit models to the individual dimensions of the EQ-5D using ordinal or multinomial logistic regression models known in the literature as response mapping [105, 171] Multinomial logistic regression models fitted to each of the five dimensions of the EQ-5D – to account for the ordinal nature of the dimensions. Subsequently, the predicted EQ-5D dimensions were transformed into EQ-5D values using the UK population tariff as follows.

Expected EQ-5D utility score =

$$1-(\text{P-mob2}\times 0.069)-(\text{P-mob3}\times 0.314)-(\text{P-care2}\times 0.104)-(\text{P-care3}\times 0.214)$$

$$-(\text{P-uact2}\times 0.036)-(\text{P-uact3}\times 0.094)-(\text{P-pain2}\times 0.123)-(\text{P-pain3}\times 0.386)$$

$$-(\text{P-anx2}\times 0.071)-(\text{P-anx3}\times 0.236)-(1-\text{P-Perfect})\times 0.081-\text{P-N3}\times 0.269 \qquad (A)$$

Where P-mob2 is the probability of affirming mobility at level 2 on EQ-5D, P-mob3 is the probability of affirming mobility at level 3 on EQ-5D, P-care2 is the probability of affirming self-care level 2 on EQ-5D, P-care3 is the probability of affirming self-care at level 3 on EQ-5D, P-uact2 is the probability of affirming usual activities at level 2 on EQ-5D, P-uact3 is the probability

of affirming usual activities at level 3 on EQ-5D, P-pain2 is the probability of affirming pain at level 2 on EQ-5D, P-pain3 is the probability of affirming pain at level 3 on EQ-5D, P-anx2 is the probability of affirming anxiety or depression at level 2 on the EQ-5D and P-anx3 is the probability of affirming anxiety or depression at level 3. P-N3 is the probability of affirming any EQ-5D dimension at level 3.

P-Perfect (the probability of living in perfect health)

$$= P\text{-}mob1 \times P\text{-}care1 \times P\text{-}uact1 \times P\text{-}pain1 \times P\text{-}anx1 \qquad (B)$$

And P-N3 (the probability of affirming any EQ-5D dimension at level 3)

$$= 1 - (1 - P\text{-}mob3) \times (1 - P\text{-}care3) \times (1 - P\text{-}uact3) \times (1 - P\text{-}pain3) \times (1 - P\text{-}anx3) \qquad (C)$$

Where P-mob1 is the probability of affirming mobility at level 1 on EQ-5D, P-care1 is the probability of affirming self-care at level 1 on EQ-5D, P-uact1 is the probability of affirming usual activities at level 1 on EQ-5D, P-pain1 is the probability of affirming pain at level 1 on EQ-5D, and P-anx1 is the probability of affirming anxiety or depression at level 1 on EQ-5D.

Model selection

Mapping models that we fitted between POS and EQ-5D were:

1. OLS

a. Model 1: EQ-5D Index = Total POS score

b. Model 2: EQ-5D Index = POS dimensions

c. Model 3: EQ-5D Index = POS dimensions + squared terms

d. Model 4: EQ-5D Index = POS Items

2. CLAD

a. Model 1: EQ-5D Index = Total POS score

b. Model 2: EQ-5D Index = All POS dimensions

c. Model 4: EQ-5D Index = POS Items

3. Response mapping

a. Model 1: EQ-5D Dimensions = Total POS score

b. Model 2: EQ-5D Dimensions = POS dimensions

c. Model 4: EQ-5D Dimensions = POS Items

Table 5: Modelling Approach

Model type	Dependent variables	Independent variables	Performance	Validation
Linear OLS[a]	EQ-5D index	Total POS score	MAE[b]	Application and assessment
		Dimension summary scores	Adjusted R^2	of mapping algorithm using
		Dimension scores + squared terms	RMSE[c]	validation dataset
		Item level models	AIC[d]	
			BIC[e]	
			Ramsey Reset test	
CLAD[f]	EQ-5D index	Total POS score	Pseudo R^2	Application and assessment
		Dimension summary scores	MAE[b]	of mapping algorithm using
		Item level models		validation dataset
Response	EQ-5D dimensior levels	Total POS score	MAE[b]	Application and assessment
Mapping		Dimension summary scores		of mapping algorithm using
		Item level models		validation dataset

a: ordinary least squares, b: mean absolute error, c: root mean square error, d: akaike information criterion, e: Bayesian information criterion, f: censored least absolute deviations

Further details of the mapping methods are provided in publication 2 (chapter 5).

4.2 Stage 2: deriving a palliative-care preference-based measure (POS-E) from the POS

The second stage involved deriving preference weights for the POS. The approach here consists of six sequential steps, which are broadly divided into three stages (see Figure 5):

Stage 2A: the aim here was to construct a simplified health state classification containing a subset of items that are most representative of the POS. This involved conducting secondary analysis of POS datasets using factor analysis, Rasch analysis, and other standard psychometric techniques.

Stage 2B: this stage involved primary data collection in a cross sectional survey. The aim here was to elicit health-state utility values/weights for a *sub-sample* of health states derived from stage 2A. These health states were valued by asking patients and healthy volunteers, 'Time-Trade-Off' (TTO) questions in a 'valuation' survey. We used a modified version of the TTO questionnaire developed by the MVH group (more details provided in chapter 6 below).

Stage 2C: the aim here is to derive utility values for *all* other health states that were not included in stage 2B using regression analysis

4.2.1 Methodological considerations for stage 2A: deriving a simplified health-state classification from the POS

This stage is the first of a three-part process of developing a preference-based measure from a pre-existing instrument. It consists of four steps as follows:

- Step 1: establishing the dimensions of the POS;
- Step 2: selecting and eliminating items in each dimension;
- Step 3: reducing item categories; and
- Step 4: validation.

Some of the methodological considerations for this stage are discussed in what follows; further details are provided in section 5 (paper 3).

<u>Step 1: establishing the dimensions of the POS using factor analysis</u>

Previous research by Seigert and colleagues [177] found that the 10-item Palliative Care Outcome Scale (POS) captures two factors – psychological status and quality of care. However, because

three items (family anxiety, symptoms and pain control) did not load significantly on any of the factors, the multi-dimensional structure of the POS remains unclear. Other limitations of this study include a small sample size and a preponderance of cancer patients. As a result, the authors suggest that it would be "*desirable to replicate the present findings with a larger sample, with samples from other countries, and with non-cancer samples*".[177]

For these reasons, it was deemed necessary to further explore the dimensionality of the POS using a larger dataset of palliative care patients with a variety of diagnoses, in order to identify major domains within the POS that should be ideally represented in the final preference based measure. The objectives of factor analysis at this stage were to:

a) examine the correlations between underlying domains of the POS; and
b) group the POS items into distinct domains so that, at subsequent stages, the most suitable items from each domain were candidates for inclusion in the new health state classification

The dimensionality of the POS was explored using principal component analysis (PCA). Tennant and colleagues suggest that when a new instrument, PCA can be used to get early indications of dimensionality, prior to conducting Rasch analysis [178]. The resultant dimensions will then form the domains of the health state classification. Traditional preference-based measures use a health-state classification system wherein the dimensions are independent to avoid producing illogical health states.[102] Factor analysis can also show where dimensions are not sufficiently independent by identifying underlying factors that explain patterns of correlation within a set of observed variables.[38, 102] However, the results of factor analysis require cautious interpretation as the items it groups into dimensions may not always be conceptually coherent. Following PCA, Rasch analysis can be used to assess the extent to which items belonging to a single dimension meet the criteria for unidimensionality.[179]

Steps 2 and 3: selecting and eliminating items in each dimension; and reducing item categories

These two steps together are required for developing a health state classification from the POS. A health-state classification is a multidimensional framework that can be used to define health states. Such classifications define a set of health states by selecting one level from each dimension. The

EQ-5D, for example, has five dimensions each comprising three levels of response (1-3) and defines a total of 243 health states (3 × 3 × 3 × 3 × 3) which were deemed too many to directly obtain values for, and so only 45 health states were selected for valuation. The POS has 10 items, of which eight have five response categories per item (0 – 4), while the remaining two items have 3 response categories each. Based on this, the POS defines a practically unmanageable number of 3,515,625 (5 × 5 × 5 × 5 × 5 × 5 × 5 × 5 × 3 × 3) health states. This is notably too large and not amenable to valuation using preference elicitation techniques such as standard gamble or time-trade-off. Therefore, the objective here was to construct a simplified descriptive system (health state classification) containing a subset of items that are most representative of the POS. A health-state classification system based on the POS would be designed to capture the range of palliativecare-related problems that can occur with different diagnosis with minimum loss of information and the ability map the original POS to map onto it.

The item reduction process aims to identify the most important items to form the health-state classification system. Rasch analysis was used in selecting and eliminating items in each dimension; and reducing item categories. This method is recommended for developing preference-based measures form pre-existing measures.[102, 179, 180]

Rasch analysis has been shown to be useful in reducing instruments into a simpler descriptive health-state classification system by identifying the severity levels captured by its items. [102, 180, 181] Rasch analysis is a mathematical modelling technique which transforms categorical data (POS item categories in this instance) to continuous data on a latent scale using a logit model [182]. Certain attributes present in people (e.g. pain, anxiety, and intelligence) are not directly measureable hence the term 'latent'.[182] The underlying principle of the Rasch model is that the likelihood of affirming an item is entirely a '*logistic function (on a linear scale)'* of the difference between the level of severity expressed by the item (item location) and the severity of the respondent's ill-health (person location).[180] Using the example of POS items, a person with severe depression is more likely to affirm an item that is highly associated with depression (e.g. '*I feel good about myself*') than a person with less depression. Likewise, a person with severe depression is more likely to affirm an

item that is highly associated with depression (e.g. '*I feel good about myself*') than one that is less associated with depression (e.g. an item on '*information needs*').

The specific criteria used in this stage for selecting and eliminating items are reported in chapter 6 (publication 3).

Step 4: Validation

Conducting steps 1–3 resulted in a simplified health state classification that is small enough for valuation. However, before proceeding to the valuation stage the newly derived health state classification will need to be validated. This was achieved by repeating steps 1 – 3 on the validation dataset. There were no specific methodological considerations here. Details of this process are reported in chapter 6 (publication 3).

4.2.1 Methodological considerations for stage 2B: valuation survey

Having derived and validated a simplified health state classification system from the POS (POS-E), the next stage was to generate value sets for the POS-E. This was achieved through a cross-sectional valuation study.

In light of some of the limitations of the QALY framework discussed in section 2.4, there were several methodological considerations at this stage including whose values to include (i.e. patients or the general public), what preference elicitation technique to use, and which health states to include. These methodical considerations are discussed in what follows – further details are also provided in chapter 7 (publication 4).

Study organisation and management

An advisory group was convened for this study. The study research team and wider advisory group included the study's patient and public involvement (PPI) group; experts in patient-reported outcomes, health economics, palliative medicine, statistics, epidemiology, psychometrics, and data management; and research nurses. The questionnaire used in this study was developed in consultation with the advisory group and piloted with patients and healthy volunteers to: determine whether the questions were appropriate for the intended participant groups; explore the

acceptability of the questions; determine the completion time of the questionnaire; and assess the overall risk of harm including participant distress and cognitive burden. Further details of the inputs from the advisory group are provided in chapters seven and eight.

Which health states should be included in the valuation survey?

It is often infeasible for respondents to value all health states derived by most health state classification systems, which normally describe several thousands of health states. Consequently, a sample of health states was selected for valuation from the health state classification system derived from stages 1–3. In this study, the sub-sample of health states to be valued was selected using the 'Rasch vignette approach'[89]. This approach was developed by Brazier and colleagues for use in deriving preference-based measures from condition-specific outcomes measures[89]. The Rasch approach, as well as providing a method for reducing the content of the original measure, can be used to select health states for valuation that represent different levels of severity (by examining item threshold maps). "*When all items are ordered the item threshold map shows the most likely item response combinations, 'health states', across the Rasch logit scale that increases as symptom/disease severity increases*" [42, 89]. This generates logical health states based on the natural occurrence of health states in the data set and reduces the risk of generating infeasible combinations of health states, as is often the case when conventional statistical designs (e.g. orthogonal arrays) are used. Conventional statistical methods for selecting health states for valuation assume that items and domains in a health classification system are uncorrelated[103], and so are inappropriate for health classification systems with correlated items like the POS-E. For example, a person who is '*severely affected by pain*' is highly like to also be '*feeling anxious or worried about their illness*', and so it would be implausible to define a health state with severe pain and no anxiety. However, the Rasch vignette approach has been criticised for generating a small subset of health states for valuation thereby leaving a large number unvalued [183]. This can be resolved regressing the health-state preference values (obtained from the valuation survey) on their corresponding Rasch logit score (location of the health state on the Rasch scale) in order to derive a relationship between preference values and Rasch logit scores (in the form of an algorithm). This

algorithm can then be used to predict preference values for health states that were not included in the valuation survey.

Whose values should be included?

This was a critical issue in this study. Valuation raises the issue of whose values to be included, those of the general public or those of patients? Seeking the general public's values has the important advantage that the preferences of members of the general public will be largely free of the influence of or adaptation to the circumstances of service users, particularly where those circumstances are affected by services. Also, from a public policy perspective, it might be regarded as essential to establish preferences for the general population on the grounds that the population pays for health care through taxes, and decisions about funding (ultimately) are made at the ballot box. The problem with using general population rather than patient preferences is that the general public may have to imagine what it is like to have advanced life limiting illness [184]. However, there is also an argument that whose preferences should be addressed depends on why those preferences are being sought[185] and, in the field of palliative care, patients' views and preferences increasingly play a fundamental role in policy and practice development. It remains unclear whether the views of palliative care patients are systematically different to those of the general population and, if so, in what way. Moreover, the important effects of palliative care interventions are experienced by the sicker (and often older) patients. However, no valuation study to date has included palliative care patients. Therefore, a secondary aim of this valuation study was to assess whether patient values differ from those of health volunteers.

Valuations for the selected health states were obtained from a survey of a convenience sample of healthy volunteers and palliative care patients. The healthy volunteers were not intended to be representative of any one group in society, but selected to reflect the variety of groups that are conventionally used in valuation exercises.

What valuation method should be used?

As discussed in section 2.2.1 there are advantages and disadvantages to using any of standard preference elicitation methods. After consulting with the study's 'patient and public involvement'

(PPI) group and the study advisory group, the time-trade-off (TTO) method was chosen on the condition that some alterations were made to reflect some of the concerns of the QALY framework raised in section 2.4 and also to incorporate ethical concerns of including patients nearing the end of life in research. Current protocols for valuation studies have been designed for use with members of the general public, and so have not considered ethical and methodological issues associated with conducting research in patients. The time-trade-off (TTO) developed by the Measurement and Valuation of Health group (MVH) [25] was modified and used obtain preference values for the POS-E (appendix 10.3.9).

In choosing the TTO, the PPI and advisory group considered the following: that the TTO was likely to impose the least cognitive burden on patients; that the developers of the MVH questionnaire had indicated their willingness for researchers to make appropriate adjustments to the protocol; that the TTO was the preferred method by many reimbursement agencies including NICE[130], and that evidence suggests that it is feasible to elicit valid TTO values for durations as short as 10 weeks.[186, 187]

Based on the advisory groups' recommendations the following adjustments were made to the MVH protocol:

1. A shorter time frame: The advisory group agreed that it would be inappropriate to ask palliative care patients to make trade-offs of up to 10 years as stipulated in the MVH protocol because patients will be aware that they do not have that long to live. It was agreed that a more appropriate time frame would be one that reflected the average life expectancy of palliative care patients. Although there was no evidence on the average life expectancy of palliative care patients, the PPI and advisory group which also comprised clinicians agreed that 10 months (rather than 10 years) would be a more realistic reflection of life expectancy for palliative care patients. It was noted that this would enable utility values to be calculated in an identical manner to the original protocol. The groups also suggested incorporating into the valuation survey a question about the appropriateness of the time frame used. Based on this the MVH questionnaire was modified to a 10 month horizon with intervals of two weeks, and questions on whether participants felt that '*the duration*

used was too short (or tool long) to be meaningful' were included as shown in appendix 10.3.5.

2. Using the words 'dead' and 'die': the PPI and advisory group noted that the MVH protocol contained too many references to 'death' which they felt could potentially cause distress among patients at a sensitive time in their lives. For example, the MVH protocol contained statements like *"...* ***this means you would either live in life A for 10 years and then die, or you would live in life B for 10 years and then die*** *..."* Such statements were changed to ***"… imagine that you had only 10 months to live. Would you prefer to live in life A, or life B, or are they the same****?* It was noted that although these changes were not guaranteed to prevent patient distress, they were somewhat more sensitive to the situation of patients than the original phrasing. The advisory group further recommended the inclusion of a distress protocol as part of the study to address any distress that may arise as a result of participation in the study. A copy of the distress protocol used for the valuation of POS-E is provided in appendix 10.3.3.

Recruiting at external sites

In order to maximise the chances of recruiting sufficient patients into the valuation study, it was necessary to recruit several sites including hospital, hospice, and primary care. In order to achieve this, the study applied for and obtained approval for inclusion in the UK National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio [188]. There are many benefits to inclusion on the CRN portfolio e.g. all sites (including NHS and non-NHS sites) are reimbursed for participating in research studies based on the number of patients recruited from each site, and also the study design [188]. This serves as an incentive for NHS (and non-NHS) health service providers to participate in, and actively recruit into, research studies nationally. Studies that have received CRN approval are included on the Central Portfolio Management System (CPMS) – a cloud-based data management system. NHS service providers across the UK are then able to access the CPMS through which they can identify and contact studies that are open to recruiting at external NHS sites. Non-NHS sites including hospices are also able to access this service as long as they can demonstrate that the patients that use their services are also registered on the NHS [188]. Many

service providers employ dedicated research nurses to facilitate patient recruitment at these sites. Therefore inclusion on the CRN portfolio meant that the POS-E valuation study could recruit from a larger pool of patients and also that research nurses could help with recruitment at sites that were far away (e.g. one of the POS-E sites was based in Newcastle). However, it was necessary to train research nurses prior to commencing recruitment. Two training sessions on the TTO method and on using the MVH protocol, each lasting 5 hours, were provided by the author to all research nurses that recruited into the study. The training manual developed by the MVH group was used to facilitate this (appendix 10.3.9). In addition, the author and all researcher nurses completed the Good Clinical Practice training. Research participants were mainly recruited by the author with the assistance of research nurses where there were multiple referrals at around the same time.

Identification and consent

Patients: it was crucial to ensure that patients were not unduly burdened given that they were already having to deal with their illness. Therefore, it was necessary that only stable patients were approached about participating in the study. In this study, potential patient participants were screened against the inclusion and exclusion criteria in the first instance by a member of their clinical team (specialist palliative care team), at the participating NHS sites or hospice. For example, patients who were too ill or cognitively impaired, as determined by their clinical team, were excluded. If screened as appropriate and eligible, potential participants were given an information sheet by a clinician and had further discussions about the study, with the opportunity to ask questions. A member of the research team (either the author or a research nurse) then visited patients who had expressed an interest in taking part at least 24 hours after initial identification. If they were still willing to take part, full-informed written consent was obtained. Patients were allowed to participate in a way comfortable to them, and were offered flexibility around the time and place of interviewing.

Furthermore, to ensure consistency in screening and identifying patients, clinicians were provided with the following guide:

POS–E study: Guide to screening patients and introducing the study

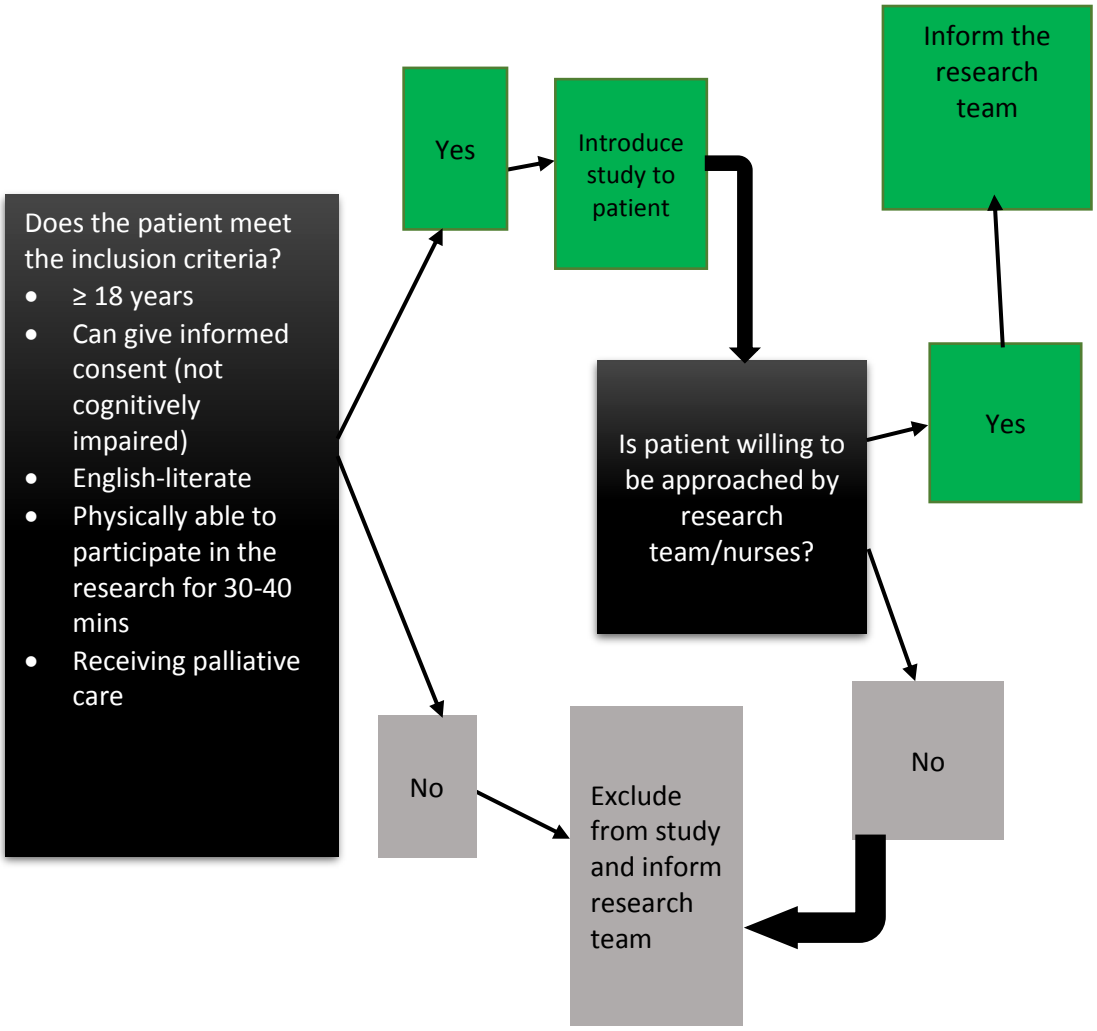


Figure 6: Guide to screening patients and introducing the POS-E study

If able to consent & participate, what information should be provided?

- This study involves exploring the importance (or value) of different aspects of health (such as pain, anxiety, depression etc.). For example, is treating moderate pain more important than treating severe anxiety, and if so, how much more important is getting treatment for moderate pain over treatment for severe anxiety?
- Your participation will help in making decisions about how to provide resources to meet the needs of patients.
- Are you happy to be approached by a member of our research team?
- Would you like a copy of the information leaflet?

Healthy volunteers: healthy volunteers were recruited via the volunteer services at each of the study sites. Volunteers were contacted about participation in the study via the leads of the respective volunteer departments through e-mail or directly in person. Volunteers who expressed interest in participating in the study were then contacted by a member of the research team who explained that participation was entirely voluntary, and provided more details about the study.

Steps to prevent harm to participants

All participants were advised that they were under no obligation to participate. The purpose of the study was explained. Participants were given the choice of not answering any question. They may skip the question and move on, return to the question later, omit the question altogether, or discontinue the questionnaire. Patients informed that they can withdraw from the study at any time, and that this would have no impact on their clinical care.

Ethical considerations for the valuation study

Protocol, procedures, information sheets, consent forms, and questionnaires were developed by the author with input from supervisors and the study advisory group to ensure that the wording was appropriate and that the safety and wellbeing of participants were considered in all the study procedures. All study documents and procedures were approved through the independent UK Integrated Research Approval System via the National Research Ethics Service (ref. 15/LO/1774). NHS Research and Development approval was obtained for all participating sites through the Health Research Authority (HRA). Additional approval was sought for non-NHS sites though their respective internal processes. Ethics application forms, accompanying documents, and approval letters are provided in appendix 10.4.

Other methodological and ethical considerations for the valuation study are detailed in chapter 7 (paper 4).

4.3 Description of datasets and data merging procedure

Secondary analyses for steps 1 and 2 were performed on six different datasets collected in several studies of palliative care patients (N=1011) as follows:

1. a cross-sectional study on symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer in Germany(N109);[189]
2. a study of Parkinson's disease (longitudinal community study of predictive factors N=82);[190]
3. a randomised phase II trial of dignity therapy (N=45, UK);[191]
4. a longitudinal study on trajectories of illness of stage 5 chronic renal disease (N=74, UK);[113]
5. a cancer mortality follow-back survey (N=596) from 2009 to 2010 in London (The QUALYCARE study);[192] and
6. a study of the development, effectiveness and cost-effectiveness of a breathlessness support service for the management of breathlessness in patients with advanced disease in the UK (N=105). [137]

Data sets were selected based on availability. All datasets contained longitudinal collected assessment data using different measurement tools but for the purposes of this thesis's objectives, only baseline estimates were used. Data sets 1, 3, and 4 contained only POS data, whereas, datasets 2, 5, and 6 contained both POS and EQ-5D data. Datasets that contained both POS and EQ-5D (2, 5, and 6; N=783) were used for mapping analysis, while all six datasets were used for the development of a health classification (factor and Rasch analyses).

For factor and Rasch analyses, a random subsample of 400 respondents (estimation data) was used, as there is evidence that some Rasch fit statistics for polytomous scales such as the POS are sensitive to sample size and larger samples can have a higher chance of type 1 errors. [193] The results were validated on an additional random subsample of 400 respondents (validation data). Similarly, for the mapping analysis, the three data sets containing both POS and EQ-5D data were pooled into a single data set (N=783) which subsequently was randomly split into development (N=392) and validation (N=391) datasets.

More information on the background of each dataset can be found in the already published papers on the datasets.[113, 137, 189-191, 194] Table 6 presents the characteristics of the datasets, summarizing the patients samples, their personal characteristics (i.e. age, gender and ethnicity), and the number of patients in each dataset.

Table 6: Summary of characteristics of POS and EQ-5D datasets

	Dataset 1 (POS)		Dataset 2 (POS and EQ5-D)	Dataset 3 (POS)	Dataset 4 (POS)	Dataset 5 (POS and EQ5-D)	Dataset 6 (POS & EQ5-D)
Diagnosis:	COPD:	Lung cancer	Parkinson	Cancer	Chronic Kidney Disease stage 5 (CKD5)	Cancer	Cancer, COPD, CHF ILD, Other
Number (N) of patients:	60	49	82	45	74	596	105
Demographics:							
Mean Age(SD)	64.7 (9.56)	63 (8.99)	67 (8.82)	67 (16.73)	80 (6.74)	74 (12.8)	67 (9.87)
Sex (% female)	51.7	49.0	37	51.1	48.6	48.5	41.9
Ethnicity (frequencies in valid percentages)	Missing		78.0 % White (English, Welsh, Scottish)/ 2.4% White (Irish)/ 3.7% Black (Caribbean)/ 2.4%Pakistani; 1.2% Chinese; 2.4% Anglo Indian; 6.1% Any Other Group	80% White/ 2.2% Black/ 4.4% White-Italian/ 2.2% Asian-Sri Lanken/ 4.4% Black-Carribean/ 4.4% Black African/ 2.2% Black British	68.9% White/ 16.2% Black/ 8.1% South Asian/ 6.8% Other Ethnicities	92.% white/ 2.8% Black/ 1.7% south Asian/ 0.5% Chinese/ 2.6% other	77.1% white/ 14.3% Black/ 1.7% south Asian/ 0.0% Chinese/ 5.7% other
Total number of cases with missing data = 162 (16%) Total number of cases with complete data = 849 (16%)							

Data cleaning and merging

Before merging the data, the response labels and the codes of variables in each dataset and the version of the POS questionnaire that was used to collect the data were examined. These characteristics were then compared and adjustments (e.g. recoding of variables into different variables) were made in order to obtain standardize the variables. For the purposes of the planned analysis, the following variables were selected: diagnosis; age; gender; ethnicity, EQ-5D scores and POS scores. After standardising the data, datasets 2, 5, and 6 were merged and used for the analysis in stage 1 (mapping analysis). Subsequently all six datasets were merged into one for the analysis in stage 2A. The merged dataset was further examined for missing data and for inconsistencies such as unexpected large or small counts for variables or implausible values. Details of the merging procedure (including procedures for recoding variables) are provided in appendix 10.1.

The results and methods of stages 1, 2A, and 2B are presented in detail in chapters five, six, and seven respectively. For each stage, the methods and results are presented together. This is because the results of each stage (apart from the first) determined the methods for the next stage.

A full description of the data sets used in this thesis (including data merging methods) can be found in Appendix 1: Description of datasets and data merging procedure.

The methods used for stage 2 are based on recommendations in the Health Technology Assessment (HTA) guidance document on "developing and testing methods for deriving preference based measures of health from condition-specific measures (and other patient-based measures of outcome)".[89]

Ethical considerations for secondary data analysis

Following consultation with the Senior Research Ethics Officer of the Research Ethics Office at King's College London, it was agreed that further ethical approval would not be required for the proposed secondary data analysis as all the six studies had received ethical previously approval for secondary data analysis. The ethical flow diagram for further analysis of pre-existing data is presented below.

Guidance

The following guidance (figure 7) was developed by the Research Ethics Office at King's College London.

This guidance refers to the re-analysis of primary data, such as interview transcripts, questionnaires, etc. It does not refer to secondary data that is in the public domain, such as books, journals and other literary resources.

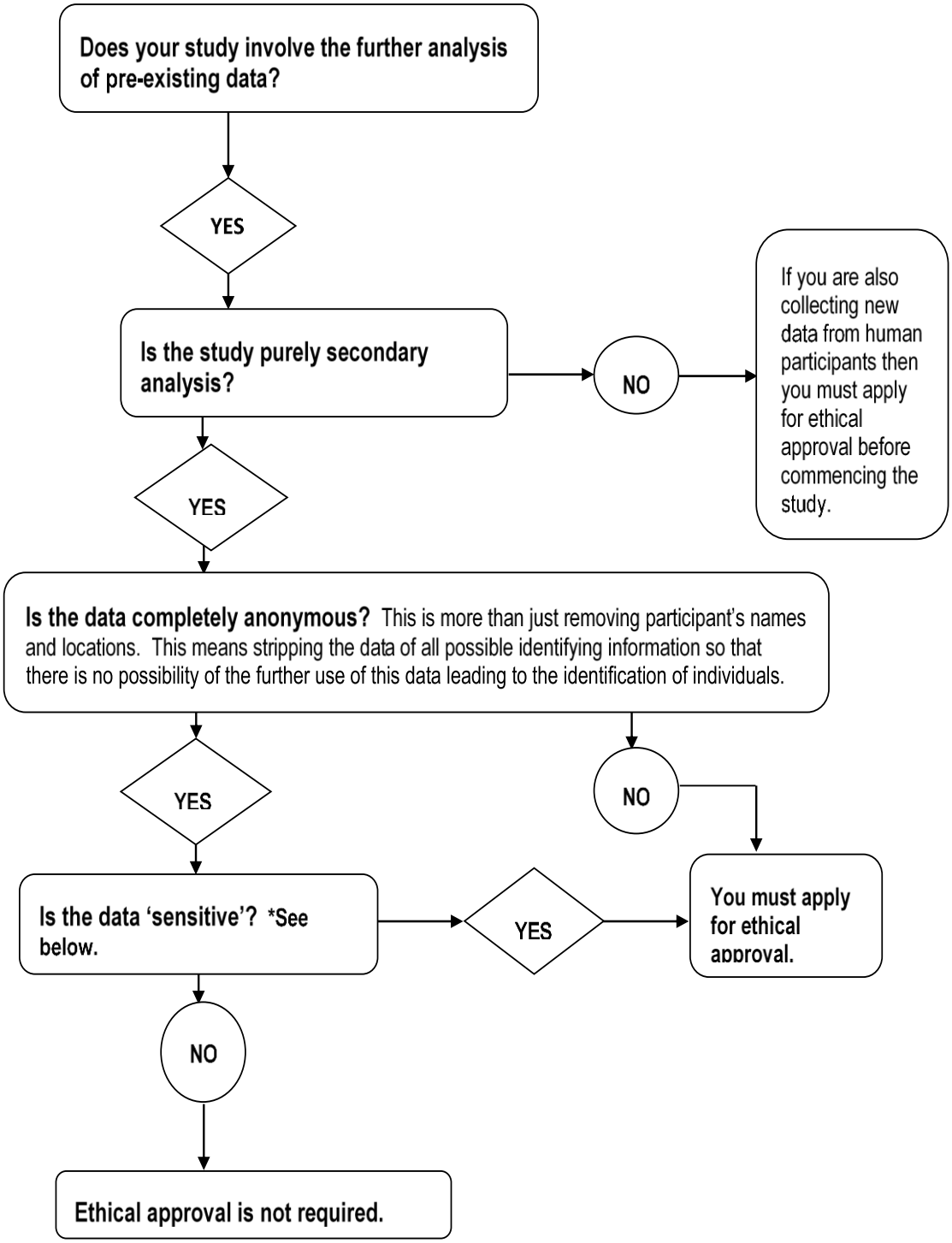


Figure 7: Steps for assessing requirements for ethical approval for secondary data

***Sensitive Data**

Whether data is deemed sensitive is not always clear-cut and researchers are advised to use their common sense when deciding if the data they will be using is sensitive. In addition, there are sometimes cases where data relating to individuals at first sight might not seem to be sensitive, but

due to cultural or social reasons could be deemed as such. A good rule of thumb would be to assess whether you would consider the data sensitive if it was your personal data being used. You may also wish to consider the following list, taken from the Data Protection Act 1998, as a starting point for determining what sort of data might be considered 'sensitive' in this way:

Data that relates to a person's:

- racial or ethnic origin;
- political opinions;
- religious beliefs or other beliefs of a similar nature;
- membership of a trade union (within the meaning of the Trade Union and Labour Relations (Consolidation) Act 1992);
- physical or mental health or condition
- sexual life

And also information about:

- The commission or alleged commission by him/her of any offence;
- Any proceedings for any offence committed or alleged to have been committed by him/her, the disposal of such proceedings or the sentence of any court in such proceedings."

Application of guidance – decision making process

The above flow diagram was applied to the characteristics of six datasets used in this thesis, and following discussion with supervisors it was decided that no further ethical approval was required for secondary data-analyses.

The decision-criteria that were used were:

- there is no identifying information in the datasets while the data are completely anonymised and the identity of the respondents is untraceable;
- there are existing ethical approvals for secondary analysis for all the six datasets;

None of the datasets contained sensitive information.

5. Methods and results for stage 1: mapping POS onto the EQ-5D using secondary data [paper 2]

The following publication reports the methods and results of stage 1 of this thesis: a secondary analysis of quantitative data exploring the conceptual correspondence between the Palliative care Outcome Scale (POS) and the most commonly used generic preference-based measure (EQ-5D). The article explores the feasibility of mapping the POS onto the EQ-5D using statistics methods.

This chapter addresses objective 1 of this thesis: to assess the feasibility of mapping the Palliative Care Outcome Scale (POS) onto the EQ-5D

Original Article

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Does the EQ-5D capture the concerns measured by the Palliative care Outcome Scale? Mapping the Palliative care Outcome Scale onto the EQ-5D using statistical methods

Mendwas D Dzingina[1], Paul McCrone[2] and Irene J Higginson[1]

Abstract

Background: The main measure to generate utility data for economic evaluations is the EQ-5D, but no study has tested whether or how to map from palliative care measures to the EQ-5D.

Aims: To assess the level of conceptual overlap between palliative outcomes and the EQ-5D, and the feasibility of mapping between them to obtain utilities for the Palliative care Outcome Scale.

Design: A cross-sectional secondary analysis of data from three studies.

Setting/participants: Patients receiving palliative care and bereaved relatives, recruited from three tertiary National Health Service hospitals in South London.

Methods: The overlap between both measures was assessed using principal component analysis. The Palliative care Outcome Scale was mapped onto the EQ-5D using three regression models.

Results: Spearman's correlations between both instruments were low (mean rho = 0.11). The principal component analysis showed the Palliative care Outcome Scale is associated with only two EQ-5D dimensions (pain; and anxiety/depression). No Palliative care Outcome Scale items loaded onto the mobility, self-care and usual activities dimensions of the EQ-5D. The mapping models performed poorly at predicting utilities from Palliative care Outcome Scale data (mean absolute error >0.3 and R^2 <0.10). Hence, none of the models can be recommended as acceptable for calculating utilities from Palliative care Outcome Scale responses.

Conclusion: Differences between the Palliative care Outcome Scale and the EQ-5D do not undermine the qualities of either instrument when used for their own purposes. However, due to conceptual differences, the EQ-5D does not capture some of the concerns measured by the Palliative care Outcome Scale, and therefore, mapping onto the EQ-5D is unlikely to provide an appropriate basis for estimating utilities for conducting economic evaluations in palliative care studies.

Keywords

EQ-5D, health-state utility, modelling, patient-reported outcomes, palliative care outcome scale

What is already known about the topic?

- The Palliative care Outcome Scale (POS) captures palliative outcomes as indicated by various validation studies and its extensive use in palliative care research and clinical practice. However, the POS cannot be used directly in cost–utility analysis because it does not incorporate preference/utility weights.
- The EQ-5D is the most commonly used preference-based measure for cost–utility analysis and has been recommended by the National Institute for Health and Clinical Excellence (NICE). But, we do not know how relevant it is for palliative care and the extent to which it captures palliative care outcomes.

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- Mapping can be used to address this issue by estimating a statistical relationship between the POS and EQ-5D which can then be used to predict utility weights from POS scores. However, the appropriateness of a mapping function depends on the degree of overlap between both instruments and has never been tested for any palliative care measure.

What this paper adds?

- This study provides the first evidence on the degree of conceptual overlap between a measure commonly used in cost–utility analysis – the EQ-5D – and the POS, and the feasibility of mapping between them to obtain utilities.
- Results showed low correlations and low conceptual overlap between the two instruments and that mapping algorithms had unacceptably high errors.

Implications for practice, theory or policy

- Due conceptual differences, the EQ-5D does not capture some of the concerns measured by the POS, and therefore, mapping is unlikely to provide an appropriate basis for estimating utilities for conducting cost–utility analyses in palliative care studies.

Introduction

Palliative care is a public health issue because the problems faced by patients and their families represent a substantial burden of illness and cost to society. As the world's population continues to age, palliative care will become even more important.[1]

Palliative care, like other health care services, is faced with the task of competing for limited resources for health. The remit of health policy makers is to maximize 'value for money' when deciding what services to fund. In order to make a case for funding palliative care services, the palliative care community needs to demonstrate that its interventions represent good value for money in comparison to competing alternatives, and also to provide evidence that the resources currently allocated are being used efficiently. Economic evaluations are commonly conducted to support this. Cost–utility analysis is a key component of economic evaluations in comparative effectiveness research.

In this, a standard preference-based utility measure is used to compare interventions and to estimate quality-adjusted life years (QALYs) as a part of the cost–utility analysis. The EQ-5D is the most commonly used preference-based measure (PBM) for cost–utility analysis and has been recommended by the National Institute for Health and Clinical Excellence (NICE).[2] It has been validated in several disease groups,[3,4] but not in end-of-life and palliative care patients. Furthermore, although the EQ-5D has been used in a number of palliative care studies (nine economic evaluations according to the recent literature review by Wichmann et al.[5]), often these are instances where the interventions focus on domains that have a large impact on health-related quality of life (HRQoL) of patients such as pain.[5,6] However, we do not know the extent to which the EQ-5D captures 'small but important changes' in palliative care outcomes (which perhaps have a moderate impact on HRQoL), and how relevant it is for palliative care as a whole. We know that the Palliative care Outcome Scale (POS) captures palliative outcomes as indicated by various validation studies[7,8] and its extensive use in palliative care research and clinical practice.[9–11] However, the POS cannot be used directly in economic evaluations because it does not incorporate preference/utility weights.

Mapping is one approach that can be used to address this issue. Mapping involves estimating the statistical relationship between a generic PBM and a non-PBM using regression techniques.[12,13] The statistical relationship is expressed in the form of an algorithm (mathematical formula) which can then be used to predict health-state utility values for a non-PBM. However, because mapping assumes that there is considerable similarity between what is being measured by the two instruments and also that all domains of the non-PBM are captured by the target PBM, the viability of a mapping function depends on the degree of overlap between the target PBM and the non-PBM.[12]

The objective of this study was to assess the level of conceptual overlap between a palliative care–specific outcome measure – the POS – and the EQ-5D, and the feasibility of mapping between them to obtain utilities for use in economic evaluations.

Methods

Measures

Target measure: EQ-5D. Our target measure for mapping was the EQ-5D (3-level). The EQ-5D consists of a general health descriptive system based on five dimensions.[14] The dimensions cover mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and are characterized by three levels (i.e. no problems, some problems and extreme problems). The instrument can be used to describe 243 possible health states, which are assigned utilities based on country-specific algorithms. The most widely

used utility algorithm was based on a time trade-off (TTO) survey of 2997 UK respondents.[15] Utility scores derived from the EQ-5D range from –0.594 (worst possible state) to 1 (full health). Details of the validity and reliability of the EQ-5D have been published elsewhere.[4]

Source measure: POS. The source measure was the 10-item POS. The POS is a short easy-to-use clinical outcome measure originally developed and validated in eight end-of-life and palliative care settings in the United Kingdom, including hospital, community, in-patient hospice, outpatient, day care and general practice.[8] It was developed to measure domains that impact on the quality of life of palliative care patients. The questionnaire consists of 10 items scored using a 0–4 (Likert) scale except for items 9 and 10 ('time wasted 'and 'practical matters') both of which are scored on a 3-point scale (0, 2 and 4). The summary score ranges from 0 to 40 with higher scores indicating a worsening condition. The POS is a multidimensional tool which comprises psychological well-being, quality of palliative care and physical domains. Details of POS validation and reliability have been published elsewhere.[8,16]

Data sets

Baseline data from three studies, each containing both POS and EQ-5D data, were pooled into a single data set and used for the mapping analysis (there was no missing data). Pooled data are available for 783 patients; 52.8% were male; 88% had a cancer diagnosis (mixed cancer type) while 12% non-cancer patients; and the average age was 72.7 years. EQ-5D responses from the pooled data were converted to utilities using the EQ-5D UK value set. The pooled data set was subsequently randomly split into two halves; one half (392) was used to develop the mapping function and the other half (391) for validation. The following is a brief description of the studies:

1. A cancer mortality follow-back survey (N = 596) from 2009 to 2010 in London (The QUALYCARE study);[17]
2. A study of Parkinson's disease (longitudinal community study of predictive factors N = 82);[18]
3. A study of the development, effectiveness and cost-effectiveness of a breathlessness support service for the management of breathlessness in patients with advanced disease in the United Kingdom (N = 105).

Data analysis

Exploratory data analysis. We started our analyses by exploring the data to find the (dis)similarities of the instruments using the combined correlation matrix of the POS and EQ-5D. The correlation matrix comprised the inter-item correlations for all items on both questionnaires. Exploratory principal component analysis (PCA) was applied to explore and compare the underlying dimensional structure of the POS and EQ-5D evident in these data. We evaluated the PCA results by first considering Scree plots and selecting components with eigenvalues >1,[19] according to the criteria by Kaiser.[20] To confirm these findings, we subsequently conducted Monte Carlo analysis according to the method of parallel analysis described by Horn[21] and Walkins.[22] We explored both Orthogonal (Varimax) and Oblique (including Direct Oblimin) rotation methods in order to enhance differentiation and interpretability of the extracted factors.[23]

Prior to assessing the predictive performance of mapping models between the POS and EQ-5D, Spearman's rank correlations of the independent variables were used to determine whether any variables were collinear and therefore not recommended for inclusion in the same regression model. A threshold for collinearity was defined as a correlation coefficient $>|0.7|$.[24] The distribution of the EQ-5D was also examined to determine the distribution of the scores. This was used to determine the appropriate model specifications for the regression equations mapping the POS onto EQ-5D.

Modelling techniques. We first estimated direct utility mapping models by regressing responses to individual POS questions directly onto EQ-5D utility using ordinary least squares (OLS) and censored least absolute deviations (CLAD).[25] Further models were fitted to the individual dimensions of the EQ-5D (response mapping) by fitting a separate multinomial logistic (MLogit) model for each EQ-5D dimension, as explained previously.[26,27] We started with OLS as it is the most commonly used model in mapping studies.[28] However, the OLS model does not restrict the range of values and therefore may lead to implausible predicted values outside the existing range of EQ-5D values (bounded by an upper limit of 1).[28] Thus, we extended this to the CLAD model which accounts for censored or bounded data and is also robust to heteroscedasticity and can also be used for skewed data.[12,29] Because the aim of mapping is to derive a predictive (rather than an explanatory) model,[12,30,31] we included all items even if they were insignificant, as has been recommended.[32–34]

Model specification. We started with simple models (OLS and CLAD) that predicted the EQ-5D utility value (dependent variable) from the total POS score, POS sub-scale scores and individual items of the POS. We also investigated models that predicted the responses of each of the five dimensions of the EQ-5D from the total POS score, POS sub-scale scores and individual items of the POS using ordinal or multinomial logistic (MLogit) regression – a technique commonly referred to in the literature as response mapping.[26,27] The predicted EQ-5D dimensions

Table 1. Patient characteristics and average EQ-5D and POS scores in the estimation and validation data sets.

	Estimation data (N = 392)	Validation data (N = 392)
Age (mean, SD)	74 (12.3)	71 (12.6)
Male (%)	212 (54)	201 (51)
Ethnicity (%)		
White	90	89
Black	2.6	5.2
South Asian	2.6	1.6
Chinese	0.3	0
Other	4.5	5.2
Diagnosis (%)		
Cancer	95.5	81
Non-cancer	4.47	19
EQ-5D index score (mean, SD)	0.370 (0.368)	0.378 (0.373)
% reporting EQ-5D index = 1	6	4
% reporting EQ-5D index <0	20	20
POS total score (mean, SD)	13.6 (6.75)	14 (6.77)
POS domains (mean, range)		
Psychological well-being	8.9 (0–20)	8.8 (0–19)
Quality of care	2.3 (0–12)	2.5 (0–11)
Physical domain	2.9 (0–8)	2.2 (0–8)

POS: Palliative care Outcome Scale; SD: standard deviation.

were then transformed into EQ-5D utility values using the UK population tariff. We further tested whether the model improved when including polynomial terms.

Model performance and validation. The predictive validity of the mapping models was assessed in the validation data set using three approaches: (1) goodness of fit was assessed using adjusted/pseudo R^2 (OLS and CLAD) in the estimation sample, (2) the predictive performance of the models in the validation sample was assessed using the mean absolute error (MAE) and (3) the distributions of the observed and predicted utility values were compared by visual inspection of predicted versus observed scatter plots. This split-sample or internal approach to cross-validation has been recommended in the literature.[35,36]

PCA was conducted in SPSS version 21.0 and mapping in STATA 12 software (StataCorp, College Station, TX, USA).

Results

There were 783 patients in the combined data set (Table 1). The mean EQ-5D index score for estimation data set was 0.378 (standard deviation (SD) = 0.368), scores ranged from –0.594 to 1, 6% of responders are in full health and 20% scored less than 0. Figure 1(b) presents the distribution of the EQ-5D index which appears to be somewhat different from those published in most studies. Patients with very poor HRQoL were included in our sample and, therefore, the data set spans the full range of EQ-5D (Table 1).

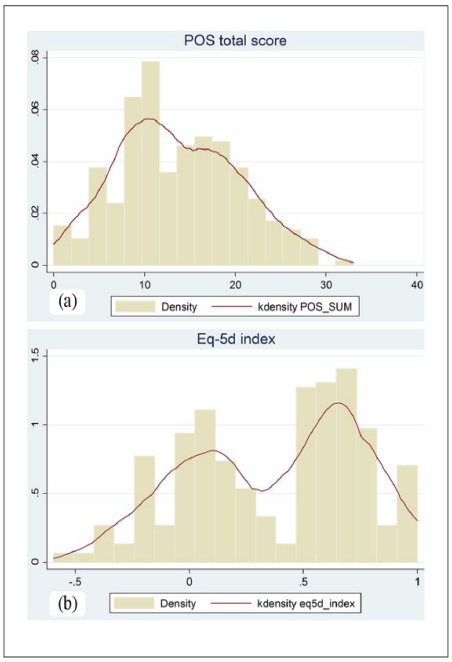


Figure 1. (a) Distribution of total POS scores and (b) EQ-5D index in estimation data set.

As shown in Figure 2(b), the EQ-5D data have a bimodal distribution with one peak around 0.7 and another

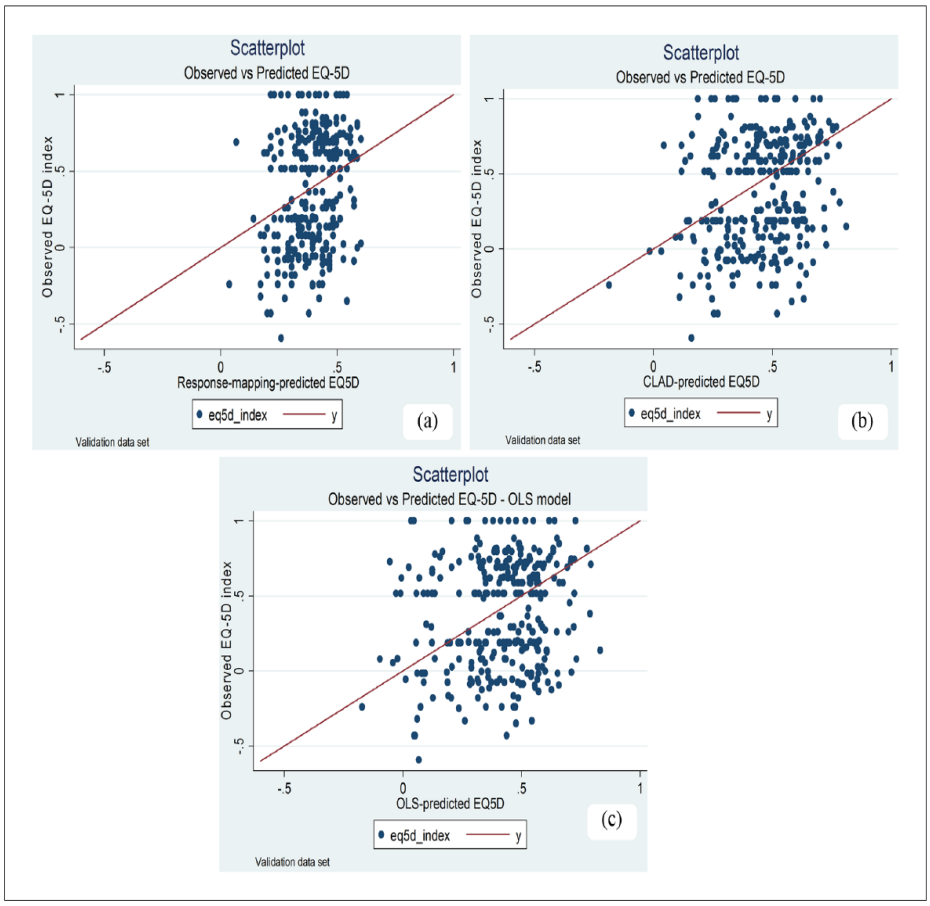


Figure 2. Scatter plots comparing observed versus predicted EQ-5D (item levels) for (a) OLS, (b) CLAD, and (c) response models in validation data set.

around 0.1. This binomial distribution was evident in each of the three data sets (supplementary file 1). The mean total POS score was 13.6 (range, 0–40) in the development data set and 14 (range, 0–38) in the validation data set, with responders spanning the full range of the POS score, similar to the EQ-5D (Table 1).

Correlation between the EQ-5D and POS

The Spearman correlations between the POS items and the EQ-5D items tended to be low (mean = 0.11, range = 0.001–0.41). The highest correlation (0.414) was found between POS item 7 (I have been feeling depressed) and the anxiety/depression item of the EQ-5D (see supplementary file 3). The mean of the correlations between the EQ-5D index and the POS items was −0.150 (range, −0.07 to −0.24). The lowest correlations were those between any of the POS items and the mobility dimension of the EQ-5D. The overall correlation between the EQ-5D index and POS (total score) was −0.25 (see supplementary files 3 and 4).

Exploratory PCA

When the number of components was limited to those with an eigenvalue >1, using Oblimin rotation, four constructs emerged that explained 54.4% of the total variance: physical function, psychological function, pain and other symptoms, and quality of care (see Table 2). Horn's parallel analysis also confirmed four significant constructs (supplementary file 2).

Two of the 15 items (POS item 3 and EQ-5D item 4) had a loading ⩾0.4 on more than one construct. Four EQ-5D dimensions mobility, usual activity, self-care and pain – all relating to physical function – loaded onto the same construct. However, the pain dimension of the EQ-5D also loaded (almost equally) onto the 'pain/other symptoms'

Table 2. Overview of items associated with the four constructs derived from Exploratory principal component analysis ($N = 783$).

Item	Construct 1: Physical function	Factor loading
EQ-5D 1	Mobility	0.81
EQ-5D 2	Self-care	0.81
EQ-5D 3	Usual activity	0.83
EQ-5D 4	Pain/discomfort	0.47
	Construct 2: Psychological function	
POS 8	Have you felt good about yourself as a person?	0.77
POS 3	Have you been feeling anxious or worried about your illness or treatment?	0.55
POS 4	Have any of your family or friends been anxious or worried about you?	0.40
POS 7	Have you been feeling depressed?	0.73
POS 6	Have you been able to share how you are feeling with your family or friends?	0.56
EQ-5D 5	Anxiety/depression	0.60
	Construct 3: Pain/other symptoms	
POS 1	Have you been affected by pain?	0.76
POS 2	Have other symptoms, for example, nausea, coughing or constipation seemed to be affecting how you feel?	0.70
POS 3[a]	Have you been feeling anxious or worried about your illness or treatment?	0.40
EQ-5D 4[a]	Pain/discomfort	0.44
	Construct 5: Quality of care	
POS 10	Have any practical matters resulting from your illness, either financial or personal, been addressed?	0.78
POS 5	How much information have you and your family or friends been given?	0.61
POS 9	How much time do you feel has been wasted on appointments relating to your health care, for example, waiting around for transport or repeating tests?	0.34

POS: Palliative care Outcome Scale.
Extraction method: principal component analysis; rotation method: Oblimin with Kaiser normalization. KMO = 0.766; Bartlett's test $X^2 = 2270$, significance = 0.000.
[a]Item is associated more strongly with one of the other constructs.

construct. None of the POS items loaded onto physical function construct – which comprises the mobility, self-care, usual activities and pain dimensions of the EQ-5D. The anxiety/depression dimension of the EQ-5D loaded together with POS items 3, 4, 6, 7 and 8 – all of which relate to psychological function. POS item 3 which relates to patient anxiety loaded on both the psychological function and the pain/other symptoms constructs. POS items 5, 9 and 10 loaded together on the same construct. These items describe activities that relate to the quality of palliative care.

Mapping models (estimation data set)

Model performance statistics indicate that models that use individual POS items as dummy variables (item-level models) consistently performed better than the domain-level models and the total score models as indicated by higher R^2 and lower MAE values when compared to models that used the total POS score or POS domain scores. Therefore, this model was chosen as the best model. Table 3 summarizes the predicted EQ-5D scores and model performance of the models that were undertaken. Inclusion of squared terms did not improve the models, and so were only reported for the OLS regression for descriptive purposes.

None of the predicted values were above 1 (full health) or below −0.594 (worst possible state).

The total POS-score models and the domain models did not predict any values less than 0. All OLS models predicted mean EQ-5D values that were higher than the mean EQ-5D observed in the data set. The OLS model had the largest range of predicted scores as shown in Table 3.

The results for the response mapping models (Table 3) were similar to OLS in terms of model performance statistics with item-level models also performing better than the other models. The CLAD models had consistently better model fit (lower MAEs) than OLS models. However, OLS models were better at predicting the mean EQ-5D value and covered a wider range than the CLAD models. For response mapping, the mean EQ-5D predicted values were lower than the observed values. Similar to the OLS and CLAD models, the best fitting response mapping model was the item-level model. This model gave the closest estimate of the mean observed

Table 3. Summary of observed and predicted values for all models in estimation data set ($N = 392$).

	Observed EQ-5D utility	Predicted EQ-5D utilities			
		OLS Model 1 Total POS score	OLS Model 2 POS domain scores	OLS Model 3 Domain scores and squared terms	OLS Model 4 POS items
Mean	0.3704	0.3996	0.3991	0.3986	0.4033
Minimum	−0.5940	0.1116	0.1113	−0.0202	−0.3289
Maximum	1.0000	0.6021	0.6146	0.5278	0.8491
Range	1.5940	0.4906	0.5033	0.5480	1.1780
MAE		0.3124	0.3113	0.3096	0.2815
Adjusted R^2		0.0666	0.0657	0.0639	0.0981
		CLAD Model 1	CLAD Model 2		CLAD Model 4
Mean	0.3704	0.4518	0.4567	–	0.4530
Minimum	−0.5940	−0.0142	0.0175	–	−0.0977
Maximum	1.0000	0.7794	0.7681	–	0.7832
Range	1.5940	0.7936	0.7506	–	0.8808
MAE		0.3048	0.3034	–	0.2936
Pseudo R^2		0.0474	0.0539	–	0.0831
		Response mapping Model 1	Response mapping Model 2		Response mapping Model 4
Mean	0.3704	0.3550	0.3531	–	0.3615
Minimum	−0.5940	0.0556	0.0738	–	−0.3360
Maximum	1.0000	0.5375	0.5409	–	0.7626
Range	1.5940	0.4819	0.4670	–	1.0986
MAE		0.3184	0.3172	–	0.2802
Adjusted R^2		0.0716	0.0743	–	0.2449

MAE: mean absolute error; OLS: ordinary least squares; CLAD: censored least absolute deviations; POS: Palliative care Outcome Scale.

EQ-5D, and the lowest MAE, when compared with all other models in the estimation data set.

Model validation

In the validation data set, models which predicted EQ-5D score using POS items consistently performed better than those which used total and sub-scale POS scores.

Table 4 shows the model performance statistics of the three regression models in the validation data set. It can be seen that all three regression models had high – and fairly similar – MAEs although the MAE for the CLAD model was marginally lower than those for OLS and response mapping models (MAE = 0.3037, 0.3124 and 0.3157 for CLAD, OLS and response mapping models, respectively). Also, while the response mapping model approximated the mean EQ-5D the closest, the predicted scores from the OLS model covered the largest range (−0.1723 to 0.8326).

Discussion

To the best of our knowledge, this is the first time that a palliative care outcome measure has been mapped to the EQ-5D. Our analysis of POS and EQ-5D data shows clear differences in the underlying constructs of these two measures. The PCA showed that at least four constructs relating to physical function, psychological function, pain and other symptoms, and quality of care can be used to summarize the data. We found low correlations between the POS and the EQ-5D index. Similar to other studies,[12,37,38] we found that the mapping models underestimated the utilities for the mild health states and overestimated those for severe health states. We found that the models which used individual POS items as independent variables consistently performed better than the domain-level models and the total score models. All three regression models performed poorly in using POS data to predict utilities as indicated by MAE values greater than 0.3 – much higher than published minimally important differences for the EQ-5D index of between 0.06 and 0.12.[30,39–41] These large MAE values suggest a minimum prediction error of 30% of the entire utility scale. Also, R^2 values for all models were found to be <0.1 which are much lower than the range of R^2 values (0.4–0.6) reported by Brazier et al.,[12] in their systematic of studies mapping non-PBMs to generic PBMs. Consequently, none of the models can be recommended as an acceptable basis for calculating utilities from the POS responses for use in cost–utility analyses.

Table 4. Summary of observed and predicted values for best performing models in validation data set ($N = 391$).

	Observed EQ-5D utility	Predicted EQ-5D utilities			
		OLS Model 1 Total POS score	OLS Model 2 POS domain scores	OLS Model 3 Domain scores and squared terms	OLS Model 4 POS items
Mean	0.3631	0.3904	0.3930	0.3923	0.4142
Minimum	−0.594	0.0372	0.0570	−0.1224	−0.1723
Maximum	1.00	0.6021	0.6146	0.5278	0.8326
Range	1.5940	0.5649	0.5576	0.6503	1.0049
MAE		0.3167	0.3158	0.3171	0.3124
Adjusted R^2		0.0666	0.0657	0.0639	0.0981
		CLAD Model 1	CLAD Model 2		CLAD Model 4
Mean	0.3631	0.4369	0.4424	–	0.4521
Minimum	−0.594	−0.1344	0.0961	–	−0.1863
Maximum	1.00	0.7794	0.7681	–	0.8103
Range	1.5940	0.9138	0.8642	–	0.9966
MAE		0.3092	0.3087	–	0.3037
Pseudo R^2		0.0474	0.0539	–	0.0831
		Response mapping Model 1	Response mapping Model 2		Response mapping Model 4
Mean	0.3631	0.3460	0.3470	–	0.3742
Minimum	−0.594	0.0140	0.0366	–	−0.1306
Maximum	1.00	0.5375	0.5409	–	0.7898
Range	1.5940	0.5515	0.5043	–	0.9204
MAE		0.3183	0.3171	–	0.3157
Adjusted R^2		0.0680	0.0704	–	0.0253

MAE: mean absolute error; OLS: ordinary least squares; CLAD: censored least absolute deviations; POS: Palliative care Outcome Scale.
All three models underestimated EQ-5D values above the mean observed values and overestimated values below the mean (Figure 2).

Furthermore, it appears unlikely that a mapping model with acceptably low MAE will be obtained because of differences in the underlying constructs of the POS and EQ-5D, such as the absence of information and practical matters on the EQ-5D. Moreover, palliative care is targeted at patients with advanced disease and/or patients at the end of life – at which stage the goal of treatment is no longer cure[42] – thus, mapping to a generic measure may leave a substantial degree of the palliative care–specific impact unaccounted for.

The POS items are multidimensional such that the same aspect of health status is picked up by different items. Therefore, the POS items are conceivably more likely to be sensitive to change than the items of the EQ-5D. Moreover, because the POS items have five response categories, the potential for respondents to indicate an improvement is higher.

Another difference between the instruments is that the EQ-5D extracts the changes in health separately for each dimension, whereas the POS combines information on several dimensions in a number of items. Also, in the POS, a mixture of response categories is used. Some of the response categories are similar to those of the EQ-5D (i.e. they range from no problems to overwhelming) and thus describe levels of severity. Other items in the POS have response categories based on frequency or quantity (e.g. ranging from 'not at all' to 'always'). Such items are not present in the EQ-5D; hence, improvements in these attributes as measured by POS may not be reflected by a corresponding change in the EQ-5D.

To adequately map condition-specific instruments to PBMs, a certain degree of overlap is required between the two descriptive systems.[12] Our analysis shows that, due conceptual differences, the EQ-5D does not capture some of the concerns measured by the POS, and therefore, mapping onto the EQ-5D is unlikely to provide an appropriate basis for estimating utilities for conducting economic evaluations in palliative care studies. The review by Longworth et al.[28] suggests that where 'there is no overlap in content between the measures of interest, mapping is unlikely to be able to appropriately capture the relationship to estimate health-related utility. Alternative methods for estimating health-related utility data should be considered in these circumstances'.

Furthermore, our analysis contributes to the wider debate in which the appropriateness of standard economic

methods in palliative care has been questioned, with some researchers proposing that the QALY framework be either modified or completely substituted.[43–45] However, wider question of the appropriateness of standard economic methods and tools in palliative care is a much bigger question – beyond the scope of this analysis – and will require further research. Such research would, for example, involve a careful examination of other generic health economic instruments, in addition to the EQ-5D, to assess their ability to detect changes in palliative care populations when compared with palliative care–specific instruments.

Our study had some limitations. First, although we tested three models, there are several other models that were not tested. However, due to the poor conceptual overlap between the two measures, it is unlikely that other models would have performed better. Second, the mapping functions in our analysis are based on pooled data from three studies; this was necessary in order to give a large enough sample to produce more reliable and representative mapping estimates. Moreover, because patients with a variety of cancer and non-cancer diagnoses were included, the data set can perhaps be considered an appropriate reflection of the diverse diagnoses of palliative care patients.

Conclusion

Differences between the POS and the EQ-5D do not undermine the qualities of either instrument when used for their own purposes. However, our results suggest that due to conceptual differences between these two instruments, mapping onto the EQ-5D is unlikely to provide an appropriate basis for estimating utilities for conducting economic evaluations in palliative care studies. Further research is needed to address the wider question of the appropriateness of standard economic approaches in palliative care.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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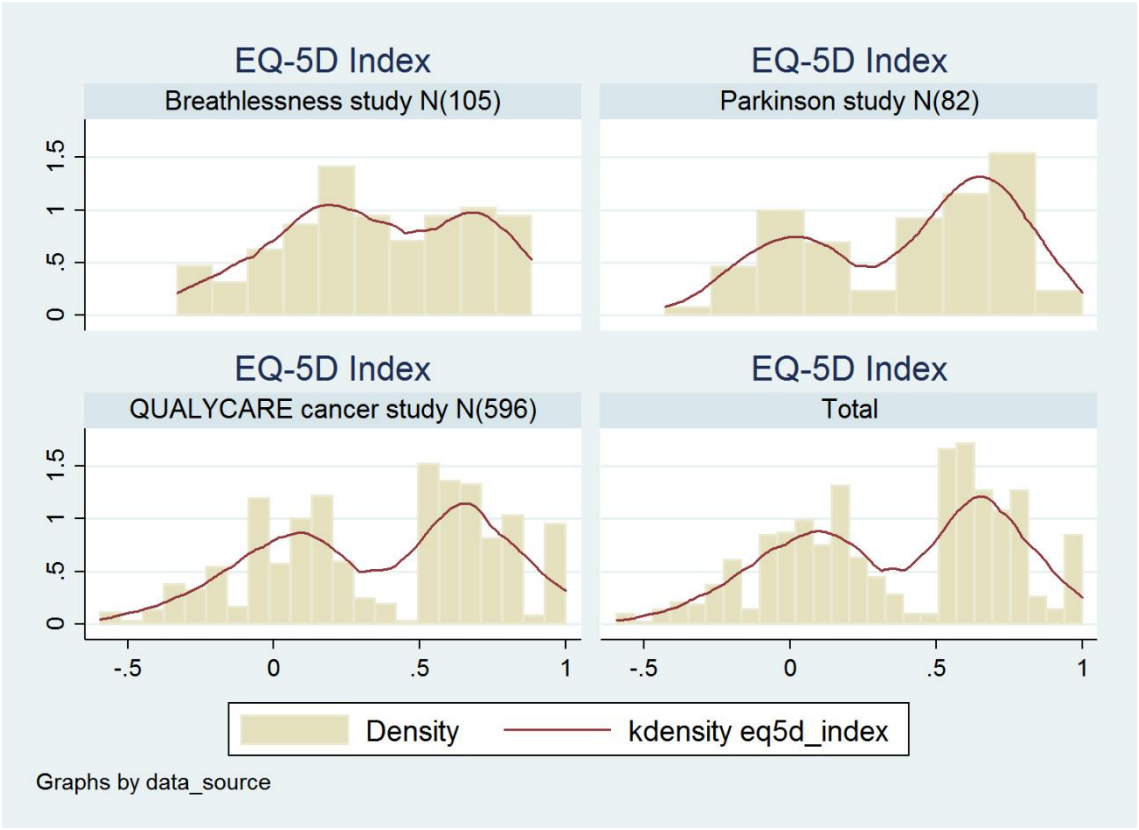
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Supplementary Material

Supplementary file 1



Supplementary file 1: Distributions of EQ-5D scores by data source

Supplementary file 2

```
Monte Carlo PCA for Parallel Analysis.

Number of variables:     15
Number of subjects:     783
Number of replications: 100

++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
Eigenvalue #     Random Eigenvalue     Standard Dev
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
      1               1.2410               .0304
      2               1.1913               .0218
      3               1.1513               .0184
      4               1.1121               .0165
      5               1.0831               .0145
      6               1.0497               .0127
      7               1.0219               .0139
      8               0.9955               .0140
      9               0.9669               .0128
     10               0.9395               .0132
     11               0.9114               .0131
     12               0.8847               .0142
     13               0.8526               .0142
     14               0.8198               .0159
     15               0.7792               .0204
++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
Monte Carlo PCA for Parallel Analysis ©2000 by Marley W. Watkins. All rights reserved.
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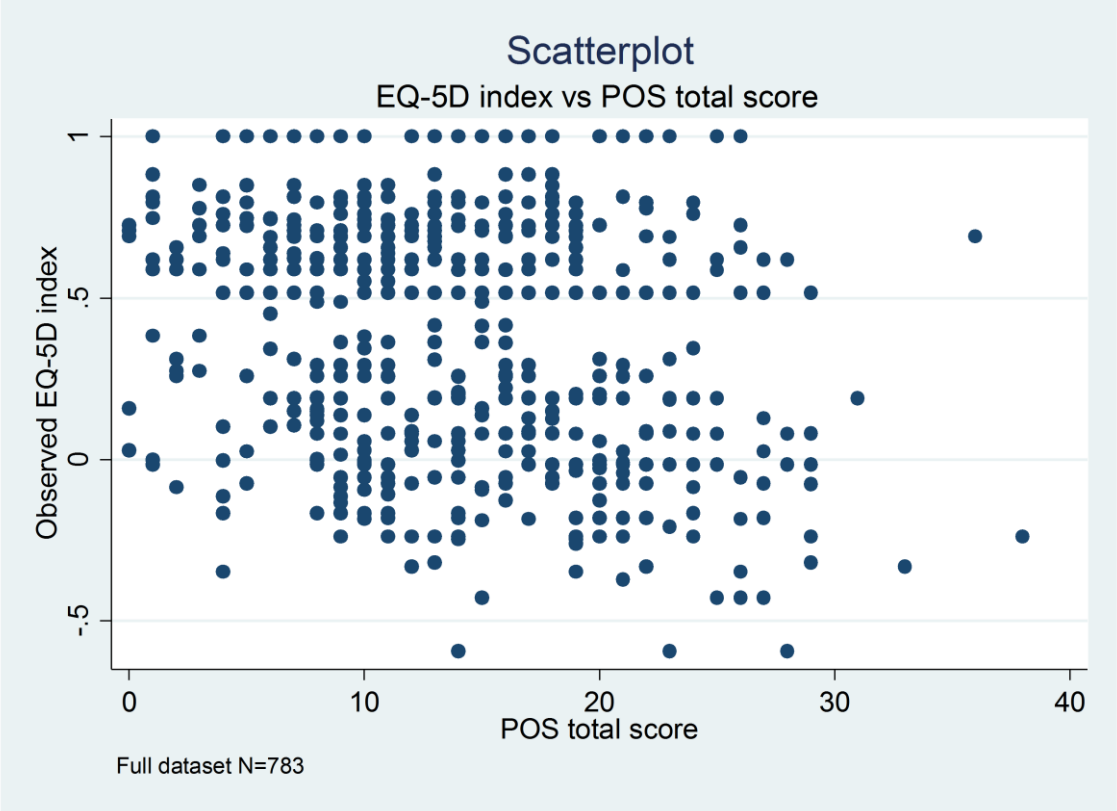
Supplementary file 2: Monte Carlo PCA for (Horn's) parallel analysis

Supplementary file 3

Supplementary file 3: Pearson's correlation coefficients of POS items with EQ-5D index and items (N=783)

		EQ-5D items				
POS Items	EQ-5D index	Mobility	Self-care	Usual activities	Pain	Anxiety/ depression
Pain	– 0.241	0.117	0.084	0.035	0.380	0.120
Other symptoms	– 0.111	0.004	0.056	– 0.055	0.170	0.101
Patient anxiety	– 0.155	0.032	0.072	0.101	0.091	0.303
Family anxiety	– 0.142	– 0.026	0.053	0.005	0.179	0.222
Information needs	– 0.044	0.028	0.026	0.149	– 0.044	0.001
Sharing feelings	– 0.139	0.050	0.132	0.086	0.098	0.165
Depression	– 0.214	0.047	0.080	0.124	0.121	0.414
Feeling good	– 0.196	0.048	0.142	0.128	0.143	0.324
Time wasted	– 0.102	0.030	0.094	0.038	0.089	0.051
Practical matters	– 0.072	0.047	0.102	0.058	0.063	0.060
Total POS score	– 0.252	0.067	0.152	0.142	0.239	0.342

Supplementary file 4



Supplementary file 4: Scatter plot of EQ-5D index vs POS total score

Supplementary file 5: Checklist of items to include when reporting a mapping study

Section/topic	Item number	Recommendation	Reported on page number/line number
Title and abstract			
Title	1	Identify the report as a study mapping between outcome measures. State the source measure(s) and generic, preference-based target measure(s) used in the study	Page 1
Abstract	2	Provide a structured abstract including, as applicable: objectives; methods, including data sources and their key characteristics, outcome measures used and estimation and validation strategies; results, including indicators of model performance; conclusions; and implications of key findings	Page 2
Introduction			
Study rationale	3	Describe the rationale for the mapping study in the context of the broader evidence base	Page 4, lines 12-23
Study objective	4	Specify the research question with reference to the source and target measures used and the disease or population context of the study	Page 4, lines 24-26
Methods			
Estimation sample	5	Describe how the estimation sample was identified, why it was selected, the methods of recruitment and data collection, and its location(s) or setting(s)	Page 4, lines 20-28 & page 5, lines 1-2
External validation sample	6	If an external validation sample was used, the rationale for selection, the methods of recruitment and data collection, and its location(s) or setting(s) should be described	Not applicable
Source and target measures	7	Describe the source and target measures and the methods by which they were applied in the mapping study	Page 4, lines 2-19
Exploratory data analysis	8	Describe the methods used to assess the degree of conceptual overlap between the source and target measures	Page 5, lines 4-16

Section/topic	Item number	Recommendation	Reported on page number/line number
Missing data	9	State how much data were missing and how missing data were handled in the sample(s) used for the analyses	Page 5, line 22
Modelling approaches	10	Describe and justify the statistical model(s) used to develop the mapping algorithm	Page 6, lines 18-26
Estimation of predicted scores or utilities	11	Describe how predicted scores or utilities are estimated for each model specification	Page7, lines 2-7
Validation methods	12	Describe and justify the methods used to validate the mapping algorithm	Page7, lines 8-14
Measures of model performance	13	State and justify the measure(s) of model performance that determine the choice of the preferred model(s) and describe how these measures were estimated and applied	Page7, lines 8-14
Results			
Final sample size(s)	14	State the size of the estimation sample and any validation sample(s) used in the analyses (including both number of individuals and number of observations)	Page7, lines 18
Descriptive information	15	Describe the characteristics of individuals in the sample(s) (or refer back to previous publications giving such information). Provide summary scores for source and target measures, and summarise results of analyses used to assess overlap between the source and target measures	Page 7, line 18 to page 9 line 12
Model selection	16	State which model(s) is(are) preferred and justify why this(these) model(s) was(were) chosen	Page 11 lines 11-17
Model coefficients	17	Provide all model coefficients and standard errors for the selected model(s). Provide clear guidance on how a user can calculate utility scores based on the outputs of the selected model(s)	Not applicable

Section/topic	Item number	Recommendation	Reported on page number/line number
Uncertainty	18	Report information that enables users to estimate standard errors around mean utility predictions and individual-level variability	Tables 3 and 4
Model performance and face validity	19	Present results of model performance, such as measures of prediction accuracy and fit statistics for the selected model(s) in a table or in the text. Provide an assessment of face validity of the selected model(s)	P 10, lines 12-13 & tables 3 and 4
Discussion			
Comparisons with previous studies	20	Report details of previously published studies developing mapping algorithms between the same source and target measures and describe differences between the algorithms, in terms of model performance, predictions and coefficients, if applicable	Not applicable
Study limitations	21	Outline the potential limitations of the mapping algorithm	Page 14, lines 2-7
Scope of applications	22	Outline the clinical and research settings in which the mapping algorithm could be used	Not applicable
Other			
Additional information	23	Describe the source(s) of funding and non-monetary support for the study, and the role of the funder(s) in its design, conduct and report. Report any conflicts of interest surrounding the roles of authors and funders	Page 14, lines 14-20

6. Methods and results for stage 2A: using Factor and Rasch analysis to deriving a simplified health-state classification for the POS [publication 3]

The following publication reports on stage 2A of this thesis: developing and validating a simplified health state classification system (POS-E) from the POS via secondary analysis of quantitative data.

It was considered better to develop the POS-E from the POS rather than developing a new measure, so as to benefit from the extensive development work of the POS. This paper reports on the first of three stages of developing a preference-based based measure from an existing measure, which involved using psychometric and Rasch analysis to reduce the content of the original measure and produce a simplified health state classification that is small enough for valuation. The findings from the mapping analysis [publication 2] indicated that mapping is unlikely to be a viable approach for deriving utilities in palliative care as the EQ-5D misses important palliative care concerns.

This chapter addresses objective 3: to derive and validate a simplified health-state classification from the POS.

Patient
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ORIGINAL RESEARCH ARTICLE

Development of a Patient-Reported Palliative Care-Specific Health Classification System: The POS-E

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Abstract

Background Generic preference-based measures are commonly used to estimate quality-adjusted life-years (QALYs) to inform resource-allocation decisions. However, concerns have been raised that generic measures may be inappropriate in palliative care.

Objective Our objective was to derive a health-state classification system that is amenable to valuation from the ten-item Palliative Care Outcome Scale (POS), a widely used patient-reported outcome measure in palliative care.

Methods The dimensional structure of the original POS was assessed using factor analysis. Item performance was assessed, using Rasch analysis and psychometric criteria, to enable the selection of items that represent the dimensions covered by the POS. Data from six studies of patients receiving palliative care were combined ($N = 1011$) and randomly split into two halves for development and validation. Analysis was undertaken on the development data, and results were validated by repeating the analysis with the validation dataset.

Results Following Rasch and factor analyses, a classification system of seven items was derived. Each item had two to three levels. Rasch threshold map helped identify a set of 14 plausible health states that can be used for the valuation of the instrument to derive a preference-based index.

Conclusion Combining factor analysis and Rasch analysis with psychometric criteria provides a valid method of constructing a classification system for a palliative care-specific preference-based measure. The next stage is to obtain preference weights so the measure can be used in economic evaluations in palliative care.

Key Points for Decision Makers

We propose a new palliative care health-state classification system termed Palliative Care Outcome Scale (POS)-E.

POS-E classifies palliative care states as a combination of seven dimensions.

The dimensions are pain, other symptoms, anxiety, depression, family anxiety, feeling good about oneself and practical matters.

1 Introduction

Economic evaluations are performed to inform the allocation of resources between competing healthcare interventions. A commonly used method is cost-utility analysis, which compares interventions in terms of their cost per quality-adjusted life-years (QALYs) gained. The QALY combines life expectancy (in years) and quality of life (QOL; expressed in the form of 'health state values') into a single metric based on people's preferences [1]. The QOL portion is estimated by assigning a numerical value to each health state experienced by a person on a scale ranging

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from 1 (equivalent to full health) to 0 (dead) [2]. A common way of estimating health-state values is to use a 'generic' preference-based measure (PBM) such as the EuroQol five-dimensional questionnaire (EQ-5D) [3], Health Utilities Index Mark 3 (HUI3) [4], or Short-Form 6-Dimensions (SF-6D) [5]. Each generic PBM, e.g. EQ-5D, has a preference-based algorithm for assigning values to each health state. These preference weights are obtained by asking members of the general public to value the health states using a choice-based valuation technique such as standard gamble [6, 7] or time trade-off [6].

These generic PBMs are deemed appropriate for all patients, irrespective of their medical condition, because they concentrate on broad aspects of health-related QOL (HRQoL). However, debate has focussed on the degree to which the broad nature of these PBMs incorporates attributes of HRQoL that are particularly relevant to specific health conditions and health disciplines [8]. The estimation of QALYs in palliative care is one such case.

Palliative care is "the active holistic care of patients with advanced progressive disease, aimed at achieving the best possible QoL for patients and families, through the management of pain and other symptoms, as well as provision of spiritual, psychological and social support; which may be initiated early in the course of treatment along with other curative treatments" [9]. In the discipline of palliative care, there are concerns that generic PBMs do not incorporate many aspects of HRQoL important to patients receiving palliative care and rather are heavily focused on function (e.g. mobility, self-care and usual activities) [10–12]. This has led to proposals for the development of a condition-specific PBM (CSPBM) that would be appropriate for patients receiving palliative care [10, 13]. Furthermore, the likely dominant nature of palliative care needs in determining HRQoL arguably justifies the development and use of a CSPBM in palliative care. Presently, no such measure exists. The Palliative Care Outcome Scale (POS) has been suggested as suitable for this purpose [10]. The POS is a validated palliative care outcome measure [14] that has been used in many studies, including randomized controlled trials (RCTs) and observational studies, as well as for service evaluation [15–22]. Given the dearth of economic evaluations in palliative care [23], developing a CSPBM from a widely accepted and commonly used instrument such as the POS enables retrospective analysis of existing datasets and increases the likelihood that the measure will be used in future studies [24].

The process of developing a PBM from an existing condition-specific outcome measure involves three stages [8]. This paper reports on the first stage; the second and third stages will be addressed in a separate paper.

2 Methods

2.1 Design

This study was a secondary analysis of baseline data from several studies of patients receiving palliative care.

A health-state classification is a multidimensional framework that can be used to define health states. Such classifications define a set of health states by selecting one level from each dimension. For example, the EQ-5D has five dimensions, each comprising three levels of response, and defines a total of 243 states (3^5). This presents a more manageable number to value (and even then only a sample of states were directly valued). The POS has ten items, eight of which have five levels, and two items have three levels each. Given the number of items and their corresponding levels, the POS would define a practically unmanageable number of 3,515,625 health states ($5 \times 5 \times 5 \times 5 \times 5 \times 5 \times 5 \times 5 \times 3 \times 3$). This would result in unreasonable cognitive demands on respondents to the valuation exercise required to estimate quality weights. Therefore, the first stage of deriving a health-state classification that is amenable to valuation from an existing measure involves using Rasch analysis to reduce the size of the existing measure while minimizing the loss of descriptive information [8]. This classification system would be designed to capture the range of palliative care-related problems that can occur with different diagnosis with minimal loss of information and the ability to use the responses from the original instrument to map onto it. Although some studies have derived and valued health-state classifications using standard methods (e.g. factorial and orthogonal block designs) that do not require a reduction in the size of the existing measure, such methods are inefficient because they treat items as independent (uncorrelated) statements and so are likely to result in deriving (and valuing) implausible health states. It is unlikely that the types of problems seen in palliative care are unrelated (as is implied in orthogonal and factorial designs). For example, it makes no sense to define a health state where a person feels 'good about themselves always' but also feels 'depressed always' as they are both likely to have the same primary cause. This approach of developing a health-state classification by using Rasch to reduce a larger instrument has been applied to numerous non-preference-based measures, including the SF-36 [25], SF-12 [26], menopausal health questionnaire [27], a preference-based measure for atopic dermatitis [28], King's Health Questionnaire [29], Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM) [30] and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) [31].

This study used a four-stage process as recommended by Brazier et al. [8] as follows:

1. Identify the most relevant dimensions of the POS for use in the POS-E, giving an initial descriptive system.
2. Identify item response levels that could be removed from the new descriptive system.
3. Identify item response levels that can be merged without loss of information.
4. Validate the new instrument by repeating steps 1–3 above in a separate dataset.

2.2 Datasets

We merged the following baseline POS data from six studies of patients receiving palliative care.

1. A cancer mortality follow-back survey ($N = 596$) from 2009 to 2010 in London (The QUALYCARE study) [32].
2. A study of Parkinson's disease (longitudinal community study of predictive factors; $N = 82$) [33].
3. An RCT on the effectiveness of an integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness in 2014 in the UK ($N = 105$) [12].
4. A longitudinal study on trajectories of illness of stage 5 chronic renal disease in the UK ($N = 74$) [34].
5. A cross-sectional study on symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer in Germany ($N = 109$) [15].
6. A randomised phase II trial of dignity therapy in the UK ($N = 45$) [35].

We then randomly split the data into a development dataset ($N = 504$) and a validation dataset ($N = 508$), providing suitable sample sizes for Rasch analysis. There is evidence that some Rasch fit statistics for polytomous instruments (e.g. POS) are sensitive to the sample size, and larger samples can have a higher chance of type 1 errors [36]. The development dataset was used to develop the health classification, and this was validated by repeating the analysis on the validation dataset. See the appendix (Table 7) for the descriptive statistics for each dataset. All datasets were anonymized prior to analysis.

2.3 The Palliative Care Outcome Scale (POS)

The ten-item POS is a short easy-to-use clinical outcome measure originally developed and validated in eight end-of-life and palliative care settings in the UK, including hospital, community, inpatient hospice, outpatient, day care and general practice [14, 37]. It was developed to measure domains that impact on the QOL of patients receiving palliative care. The questionnaire consists of ten items, each item scored on a 5-point Likert scale ranging from 0 to 4, except items 9 and 10 ('time wasted' and 'practical matters'), both of which are scored on a 3-point scale (0, 2 and 4) as shown in the Electronic Supplementary Material (ESM) 1. The POS has been well validated and is widely used in clinical practice and research regionally and nationally in the UK to evaluate and improve the quality of care, and has been culturally adapted for use in 20 EU countries, Africa and other countries around the globe [15–22]. Two systematic reviews (in 2011 [39] and 2015 [38]) on the use of the POS found it was used in 78 published studies in both patients with and without cancer.

2.4 Analysis

The objective of the analysis was to derive a multi-dimensional health-state classification system amenable to valuation by reducing the number of items and item levels in the POS.

2.4.1 Step 1: Establishing Dimensions

Principal component analysis (PCA) was used to assess the dimensions of the POS. PCA is commonly used in the development of new instruments to provide early indications of possible dimensions before Rasch analysis is attempted [40]. First, the Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy was used to assess the appropriateness of POS data for PCA (the KMO value should be >0.5 if the data are appropriate) [41]. In addition, Bartlett's test of sphericity was used to test whether the correlations between POS items were significant [42]. Significant factors (dimensions) were identified using Horn's parallel analysis [43] incorporated into an online facility by Watkins [44]. Next, the rotated factor matrices were examined to assess correlations of every item with each of the main factors of the instrument. We used both orthogonal and oblique rotation methods and compared the results of both, as recommended in the literature [45]. In all matrices, loadings with coefficients $\geq|0.400|$ were considered to reveal strong correlations between an item and a factor. Items loading on the same factor were considered to belong to the same underlying dimension captured by the POS.

2.4.2 Step 2: Eliminating Items Per Dimension

Rasch analysis was used to reduce the POS to a simpler descriptive health-state classification system by identifying POS items that did not fit the Rasch model and therefore were potentially unsuitable for inclusion in the

classification system. Rasch analysis is a mathematical technique used to convert categorical data to continuous data [46]. Rasch methods can be used to assess the extent to which individual items represent the underlying construct that an instrument intends to measure, thus enabling the assessment of the appropriateness of items for a classification system.

The following criteria were considered for item exclusion, in line with recommendations for multidimensional measures [8]:

- Item-level ordering (disordered thresholds): we examined threshold maps to identify items that had disordered thresholds. For instance, ordered thresholds indicate that a person with a high level of an attribute, such as pain, is more likely to endorse a high level on an item that measures pain than is a person with less pain. Disordered thresholds suggest that respondents are unable to differentiate between adjacent item categories [47]. In such instances, adjacent response categories were merged to obtain ordered thresholds. Items were excluded if their thresholds remained disordered despite merging of adjacent response categories. Furthermore, if the only way to obtain an ordered threshold for an item was by merging adjacent response categories in a way that did not make clinical sense, then such an item was eliminated. For example, it was deemed clinically meaningless to merge response categories 'moderately' and 'severely', as these indicate significantly different levels of severity.
- Rasch goodness of fit: following threshold re-ordering, overall and item-specific fit statistics were inspected to assess the extent to which the entire instrument, as well as individual items, fit the Rasch model. Items were excluded if fit residuals were >2.5 or less than −2.5 and/or chi-squared statistics were significant at the 0.001 level after Bonferroni adjustment [8].
- Differential-item functioning (DIF): items that demonstrate significant DIF are items with response patterns that vary according to specific patient factors such as diagnosis, age group, sex or ethnicity. Such items were excluded from further consideration because DIF can be a source of misfit in the Rasch model and because items forming a PBM should ideally express the same aspects of HRQoL across the whole patient population (and not distinguish significantly among subgroups with different baseline characteristics).

2.4.3 Step 3: Item Level Reduction

Rasch analysis can identify response levels that may be merged without losing descriptive information, offering further means of simplifying the classification system [8]. We identified potential item categories for merging by examining Rasch category probability curves and response frequencies. Visual inspection of respective category probability curves determined which adjacent response categories to merge. We also sought expert opinion about the clinical and psychometric meaningfulness of the merged item levels. These experts included a professor of psychology (Dr. R. Siegert, Auckland University of Technology, New Zealand) and two palliative care clinicians (Dr. P. Edmunds, King's College Hospital, London, and Dr. P. Kane, Beaumont Hospital, Dublin).

We also assessed the unidimensionality of the new classification system by using the test proposed by Smith [48], which involves conducting paired t tests of the final models. Unidimensionality is confirmed when $\leq$5% of the tests are significant at the $p < 0.05$ level [49]. We also examined the person separation index (PSI) to assess how efficiently the final set of items was able to separate those people measured. PSI values range from 0.0 to 1, with higher values indicating better separation and a more precise measure [49].

2.4.4 Step 4: Validation of Classification System

The health-state classification was validated by repeating steps 1–3 of the analysis using the validation data. We inspected the examining overall and item fit statistics, DIF, unidimensionality and item–response combinations.

RUMM2020 was used for all Rasch analysis and STATA version 12 for all other statistical analysis.

3 Results

3.1 Step 1: Factor Analysis

The KMO measure of sampling adequacy reached 0.79, suggesting that factoring of data was appropriate and meaningful. Bartlett's test of sphericity demonstrated the statistical significance of the findings ($p < 0.0001$). Although the analysis identified three factors with eigenvalues above 1, which explained 52% of the total variance (see Table 8 in the appendix for details), Horn's parallel analysis indicated two significant factors (Table 1). The scree plot (Fig. 1) appears to support a two-factor solution as the slope of the line flattens after the second factor.

In line with results of parallel analysis, a two-factor solution was extracted for rotation. Table 2 shows two rotated factors, one comprising six items (primarily about psychological and physical wellbeing) and the other comprising three items (two relating to the standard of care and one relating to psychological wellbeing). One item (time wasted) did not load above 0.40 on either of the two factors. Results were very similar between the two methods of

Table 1 Significant components of the Palliative Care Outcome Scale identified by principal component analysis (N = 504), and comparison of components with eigenvalues >1 with significant components identified by Horn's parallel analysis

Component	PCA: initial eigenvalues			Horn's parallel analysis: significant mean eigenvalues (SD)	
	Total	% of variance	Cumulative %		
1	**2.908**	29.080	32.807	**1.2609**	(0.0359)
2	**1.269**	12.693	41.773	**1.1833**	(0.0355)
3	1.013	10.128	51.901	**1.1134**	(0.0242)

Bold formatting indicates the significant eigenvalue levels identified using each approach

PCA principal component analysis, *SD* standard deviation

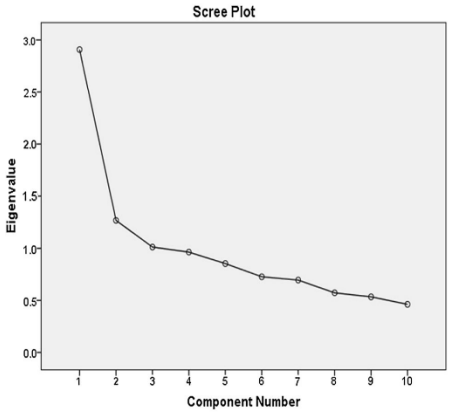


Fig. 1 Scree plot of principal component of POS items ($N = 504$)

Table 2 Rotated two-component matrix (orthogonal; $N = 504$)

POS items	Component		Conceptual domain of item
	1	2	
Anxiety	**0.772**		Psychological wellbeing
Depression	**0.658**	0.230	Psychological wellbeing
Family anxiety	**0.644**	–0.226	Psychological wellbeing
Pain	**0.585**	0.292	Physical
Symptoms	**0.575**	0.244	Physical
Feeling good	**0.567**	0.368	Psychological wellbeing
Time wasted	0.260		Quality of care
Information		**0.737**	Quality of care
Practical matters		**0.640**	Quality of care
Share feelings		**0.525**	Psychological wellbeing

Principal component analysis. Rotation: varimax with Kaiser normalization. Bold formatting indicates loadings ≥|0.400|

rotation (orthogonal vs. oblique), with all the items loading on the same components.

The results of PCA indicated that the POS consists of two domains that are moderately correlated. These domains do not appear to be consistent with predefined conceptual domains of the POS. Our findings suggest that the POS constitutes a measure with no clear multidimensionality. Thus, it was deemed necessary to conduct Rasch analysis on the whole instrument, rather than on any specific domain, in the next stage of the analysis.

3.2 Steps 2 and 3: Use of Rasch Analysis and Expert Opinion to Merge Categories, Eliminate Items and Develop a Unidimensional Scale

3.2.1 Item-Level Ordering

A total of nine items (items 1, 2, 4, 5, 6, 7, 8, 9 and 10) were disordered in the initial Rasch model. For two of the nine disordered items (item 1 'pain' and item 2 'other symptoms'), 'slightly' and 'moderately' were collapsed into a single category, as were 'severely' and 'overwhelmingly', resulting in three categories per item. Similarly, 'family anxiety', 'shared feelings', 'depression' and 'feeling good' (items 4, 6, 7 and 8, respectively) were converted to three-level items by merging 'occasionally' with 'sometimes' into a single category and 'most of the time' with 'always'. Wasted time (item 9) and practical matters (item 10), which have three levels in the original questionnaire, were converted to two-level items by merging 'half a day' with 'more than half a day' (item 9), and 'practical problems being addressed' with 'no practical problems' (item 10). The threshold probability curves for item 5 (information) suggested that this item would only work with two categories. Therefore, 'full information', 'information given but hard to understand', 'information given on request' and 'very little information given' were collapsed into a single category. However, because this merging was not deemed to be clinically meaningful, item 5 was eliminated from further analysis.

3.2.2 Rasch Model Goodness of Fit

After all thresholds were ordered, we assessed goodness of fit by examining overall and individual item statistics.

Table 3 Results of initial Rasch analysis of Palliative Care Outcome Scale (POS)-E (all items included)

Item		Threshold	Statistics after threshold re-ordering			
			Residual[a]	*X*-square	*p* value[b]	DIF
1	Pain	**Disordered**	−0.574	8.352	0.499	No
2	Other symptoms	**Disordered**	−1.410	21.811	0.010	No
3	Anxiety	Ordered	**−3.254**	40.843	**0.000**	No
4	Family anxiety	**Disordered**	−0.046	10.655	0.300	No
5	Information	**Disordered**	**3.442**	46.423	**0.000**	**Yes**
6	Shared feelings	**Disordered**	**3.758**	34.484	**0.000**	No
7	Depression	**Disordered**	−1.237	9.849	0.363	No
8	Feeling good	**Disordered**	−1.048	8.598	0.475	No
9	Time wasted	**Disordered**	2.177	25.787	0.002	**Yes**
10	Practical matters	**Disordered**	1.118	11.222	0.261	No
Overall model statistics after threshold re-ordering			Total item *X*-square = 218.025; $p = 0.0000$			
			Person-separation index: 0.657			

All statistics showing item misfit into the Rasch model are presented in bold

DIF differential-item functioning

[a] Residuals >2.5 or <−2.5 are considered high

[b] $p < 0.01$ indicates items that do not meet Rasch item fit criteria

Initial overall fit statistics of the items indicated poor fit to the Rasch model, with items 3, 5 and 6 showing misfit (a fit residual beyond ±2.5 and a chi-squared probability significant at the 0.001 level). Items 5 and 9 also exhibited DIF. Results of the initial analysis on all items are shown in Table 3. Based on the results of Rasch analysis, a number of items were consecutively excluded from further analysis according to our exclusion criteria until a good model fit was achieved.

Successive Rasch analyses led to the exclusion of items 5, 6 and 9 as they persistently had a poor fit to the Rasch model. For example, item 5 (information) had the poorest fit when compared with other items, it exhibited DIF, and its thresholds could only be ordered by combining adjacent levels in a way that was neither cognitively nor clinically meaningful. Items were excluded one at a time and both Rasch statistics and the PSI were constantly checked. This resulted in a final scale consisting of seven items (1, 2, 3, 4, 7, 8 and 10). With the exception of item 10, all other items had three response levels (e.g. 'not at all', 'occasionally or sometimes' and 'most of the time or always'). Item 10 (which originally had three levels) was collapsed to two levels: 'no problems or problems resolved' and 'problems in the process of being resolved or problems exist' (Table 4). The scale demonstrated a good model fit (X^2 probability 0.047). All items had a reasonable fit, as shown in Table 5, and no DIF was observed. The PSI reached a reasonable level of 0.678.

Table 4 Items and levels in final Palliative Care Outcome Scale (POS)-E scale

Item	Categories	Score
Family anxiety	No, not at all	0
	Occasionally/sometimes	1
	Most of the time/always	2
Other symptoms	No, not at all	0
	Slightly/moderately	1
	Severely/overwhelmingly	2
Pain	No, not at all	0
	Slightly/moderately	1
	Severely/overwhelmingly	2
Depression	No, not at all	0
	Occasionally/sometimes	1
	Most of the time/always	2
Anxiety	No, not at all	0
	Slightly/moderately	1
	Severely/overwhelming	2
Practical matters	Addressed	0
	Not addressed	1
Feeling good	Always/most of the time	0
	Occasionally/sometimes	1
	Not at all	2

Figure 2 shows the threshold map with items arranged in order of increasing difficulty from top to bottom, and with severity levels increasing from left to right.

Table 5 Rasch statistics of the Palliative Care Outcome Scale (POS)-E measure

Item		Rasch analysis statistics		
		Residual	*X*-square	*p* value
1	Pain	0.452	5.586	0.694
2	Other symptoms	–0.424	11.073	0.198
3	Anxiety	–2.090	20.088	0.010
4	Family anxiety	1.221	11.423	0.179
7	Depression	0.247	10.893	0.208
8	Feeling good	1.084	6.422	0.600
10	Practical matters	2.951	9.339	0.315
Overall model statistics		Total item *X*-square = 74.825; $p = 0.0472$		
		Person-separation index: 0.678		

As shown in Fig. 3, the item map demonstrates that the new instrument is well targeted to the study population as it is able to capture the whole range of severity of palliative-care symptoms, with minimal floor or ceiling effects and good spread of items across the full range of respondents' scores.

3.2.3 Deriving Plausible Health States From the POS-E for Utility Measurement

The threshold map (Fig. 2) was used to derive plausible health states. This map illustrates the most likely combinations of item responses expected to be obtained by the study population at various levels (locations) of symptom severity. Items have been ordered from the easiest (item 4 'family anxiety') to the most difficult (item 8 'feeling good'), as indicated by their average location in the Rasch model. Shaded areas 0 (blue), 1 (red) and 2 (green) correspond to the three levels 'not at all', 'occasionally or sometimes' and 'most of the time or always', respectively, with the exception of item 10, which has two levels: 0 (no problems or problems resolved) and 1 (problems in the process of being resolved or problems exist). The threshold map allows prediction of the most likely responses at various levels of severity. For example, a person whose symptom severity corresponds to location 0 on the logit scale is expected to most likely respond 0011112 (to items 8, 10, 3, 7, 1, 2, and 4, respectively).

Each combination of item responses represents a plausible health state likely to be observed in people with common palliative care problems. As illustrated in Table 6, a total of 14 distinct health states can be identified.

The results of the test for unidimensionality proposed by Smith [48] showed that the proportion of independent *t* tests that were significant at the 0.05 level was 1.52% (well below the 5% level), thus supporting the unidimensionality of the classification system.

3.3 Step 4: Validation of the Classification System

The POS-E was validated on the validation sample ($N = 508$): the scale had satisfactory overall and item fit statistics and no DIF was observed. The post hoc unidimensionality test also verified the scale's unidimensionality in this sample, and the threshold map indicated the same most likely item–response combinations (reflecting plausible health states) with those demonstrated by the analyses on the estimation sample. In total, the POS-E describes 1458 health states.

4 Discussion

We describe the first stage in developing a health-state classification for palliative care: the POS-E. Using rigorous research methods [8], we have derived the POS-E

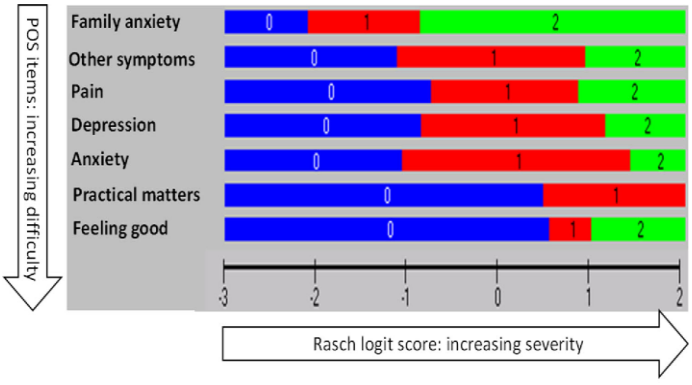


Fig. 2 Threshold map illustrating plausible health states obtained by Rasch analysis. *POS* Palliative Care Outcome Scale

Rasch threshold map illustrating items in order of increasing difficulty from top to bottom, and severity levels increasing from left to right

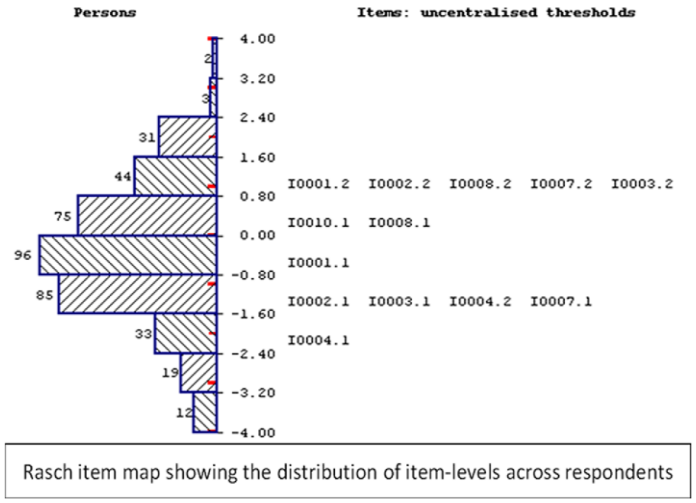


Fig. 3 Item map of the Palliative Care Outcome Scale (POS)-E showing the distribution of items across respondents

Table 6 Health states (and coverage) of the Palliative Care Outcome Scale (POS)-E as identified by the threshold map

Item		Health states ($N = 504$)													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
4	Family anxiety	0	1	1	1	2	2	2	2	2	2	2	2	2	2
2	Other symptoms	0	0	1	1	1	1	1	1	1	1	2	2	2	2
1	Pain	0	0	0	0	0	0	1	1	1	2	2	2	2	2
7	Depression	0	0	0	0	0	1	1	1	1	1	1	1	2	2
3	Anxiety	0	0	0	1	1	1	1	1	1	1	1	1	1	2
10	Practical matters	0	0	0	0	0	0	0	1	1	1	1	1	1	1
8	Feeling good	0	0	0	0	0	0	0	0	1	1	1	2	2	2
Coverage (N)		40	79	13	49	17	8	128	35	14	13	27	14	21	46

classification system from an existing palliative care measure, the POS. The next stage of the research will involve preference elicitation and related regression-based statistical modelling to derive preference weights for all health states described by the POS-E. This will result in a CSPBM capable of generating QALYs for use in economic evaluations in palliative care.

POS-E is a unidimensional seven-item scale able to capture the full range of severity of palliative care needs. Six of the items have three levels each, and one item (measuring practical matters) has two levels. The PSI of this scale was approximately 0.68, which is somewhat lower than the 0.70 value generally considered acceptable for group comparison [50]. Nevertheless, 0.68 was deemed adequate for our purpose, given the ability of the scale to discriminate amongst different respondent groups needed to be traded off with its conciseness and convenience in a valuation survey, wherein respondents need to process a combination of individual statements rather than a summated scale score.

One limitation of our approach, similar to the methodology proposed by Sugar et al. [51], is that the number of generated health states is limited and does not capture the whole range of plausible combinations of responses. Despite generating a limited number of health states, application of this approach allows for the valuation of all potential health states described by the POS-E. An advantage of Rasch analysis over the clustering-based approach is that it assigns all potential health states (i.e. all combinations of item responses including those not illustrated in threshold maps) to different locations along the scale according to their level of severity. The relationship between the location of the health states across the latent variable and the respective utility values obtained in a valuation exercise can be estimated and used to generate utility values for all patients completing POS-E. This

solution has been explored using regression techniques in a subsequent application of this approach on the Flushing questionnaire [52]. The findings of this latter study showed it is possible to assign appropriate utility values to all potential health states of a measure based on their location along the latent variable as estimated by Rasch analysis. However, it is conceivable that the Rasch approach we used would be best suited to a unidimensional instrument.

Developing a CSPBM from an existing palliative care measure has numerous advantages. Adapting a widely accepted and commonly used instrument such as the POS enables retrospective analysis of existing datasets and increases the likelihood that the measure will be used in future studies [24].

However, a major disadvantage of CSPBMs is that they may be prone to focusing effects where the effect of the condition is overrated because respondents to the valuation survey focus solely on the areas of health included in the classification system rather than viewing them in a broader perspective. Another disadvantage of CSPBMs is the correlation between perfect health and the best possible state described by a classification system. It is conceivable that a person could endorse the best possible health state based on a specific instrument but still have other problems not covered by its classification system. Thus, it becomes challenging to compare results between different PBMs because 'best possible' health states are instrument specific [8].

Nevertheless, these disadvantages are perhaps less crucial when the condition of interest is the overriding factor in determining HRQoL, as is likely to be the case for patients receiving palliative or end-of-life care. Furthermore, because advanced life-limiting conditions affect people's HRQoL in a wide variety of ways, the POS-E classification system covers a wider range of dimensions than many other CSPBMs. The decision on whether to use a CSPBM or a generic PBM will always involve a trade-off between the pros and cons of CSPBMs relative to the condition of interest [8]. In the case of palliative and end-of-life care, the potential limitation of existing generic measures [13], the wide range of the POS-E classification system, and the likely dominant nature of palliative care needs in determining HRQoL all favour the development and use of a CSPBM. The argument in favour of CSPBMs for palliative care is further strengthened by research around the role of capabilities and wellbeing in end-of-life care, which highlights that the objectives of end-of-life care do not always focus solely on health but may also include impacts on wellbeing [53]. This is particularly evident in the development work for the ICECAP Supportive Care Measure (ICECAP-SCM) [54], which is a CSPBM that measures capability at the end of life for use in economic evaluations. The POS-E relates to the ICECAP-SCM in that both instruments seek to incorporate important aspects of palliative and end-of-life care into economic evaluations. Standard economic instruments have been criticised for failing to do this [10, 11] However, there are important differences between the two instruments, mainly due to conceptual differences in their respective evaluative frameworks. The POS-E measures impact on health (or utility), whereas the ICECAP-SCM gives more attention to broader impacts on capability and wellbeing and is particularly important where health outcomes are not the focus of evaluation, such as social care interventions [55]. Nevertheless, because palliative and end-of-life care include aspects of both health (e.g. pain) and wellbeing (e.g. availability of social support), among other things, the POS-E and ICECAP-SCM can be regarded as complementary rather than mutually exclusive. Our analysis is based on pooled data from six studies, which was necessary to obtain a large enough sample to produce reliable and representative estimates. However, because the data were from patients with different types of cancer and those without cancer, it is perhaps a reasonable reflection of the diverse diagnoses of palliative care patients and therefore arguably more generalizable.

5 Conclusion

This study has shown that reducing the POS to a health-state classification system for palliative care (POS-E) is possible and that the results are robust. The POS-E classifies palliative care states as a combination of seven items: pain, other symptoms, anxiety, depression, family anxiety, feeling good about oneself, and practical matters. We also identified 14 plausible health states that can be used to value the HRQoL of patients receiving palliative care.

6 Further Research

The next step for this study is to undertake a valuation survey to attach appropriate utility values to all health states of the POS-E and thus convert it into a preference-based index. Our aim is that the new PBM will be suitable for cost-utility analyses of palliative care interventions where the use of generic PBMs such as the EQ-5D has been shown to be problematic [56–58]. Since this measure has been derived from the POS, an instrument routinely used for outcome monitoring in patients receiving palliative care in the UK and beyond, this study is expected to enable wider assessment of healthcare interventions for managing patients receiving palliative care in the form of cost-utility analysis.

Compliance with Ethical Standards

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Conflict of interest MD, IJH, PM and FM have no conflicts of interest.

Ethical approval Formal ethical approval was received for all the original studies; this secondary analysis did not require further formal consent.

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Appendix

See Tables 7, 8 and 9.

Descriptive Statistics of Datasets

Dataset 1: a cancer mortality follow-back survey ($N = 596$) from 2009 to 2010 in London (The QUALY-CARE study).

Dataset 2: a cross-sectional study on symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer in Germany ($N = 109$).

Dataset 3: a study of Parkinson's disease (longitudinal community study of predictive factors; $N = 82$).

Dataset 4: a randomised phase II trial of dignity therapy ($N = 45$, UK).

Dataset 5: a longitudinal study on trajectories of illness of stage 5 chronic renal disease ($N = 74$, UK).

Table 7 Descriptive statistics for development and validation datasets

Characteristic	Development ($N = 504$)	Validation ($N = 508$)
Female	53%	52%
Male	47%	48%
Age <60 years	16%	12%
Age >60 years	84%	88%
Cancer	79%	77%
Non-cancer	21%	23%
Mean total POS score	13.03	13.14

POS Palliative Care Outcome Scale

Table 8 Rotated three-component matrix[a] ($N = 504$)

Item	Component			Conceptual domain of item
	1	2	3	
Anxiety	**0.764**			Psychological wellbeing
Depression	**0.707**			Psychological wellbeing
Feeling good	**0.645**	0.207	–0.265	Psychological wellbeing
Family anxiety	**0.625**	–0.305		Psychological wellbeing
Pain	**0.600**	0.259		Physical
Symptoms	**0.543**	0.309	0.327	Physical
Information		**0.755**		Quality of care
Practical matters	0.211	**0.697**		Quality of care
Share feelings	0.240	0.283	**–0.667**	Psychological wellbeing
Time wasted			**0.602**	Quality of care

Extraction method: principal component analysis. Rotation method: varimax with Kaiser normalization. Bold formatting indicates loadings $\geq |0.400|$

[a] Rotation converged in five iterations

Table 9 Descriptive statistics of datasets according to study

Characteristic	Dataset 1	Dataset 2	Dataset 3	Dataset 4	Dataset 5	Dataset 6
N	596	109	82	45	74	105
Mean age ± SD	74 ± 12.8	65 ± 9.56	67 ± 8.82	67 ± 16.73	80 ± 6.74	67 ± 9.87
Female (%)	49	52	37	51	49	42
Ethnicity (%)						
White	92	95	80.4	84.4	68.9	77.1
Black	2.8	1	3.7	13.2	16.2	14.3
South Asian	1.7	2	4.8	2.4	8.1	1.7
Chinese	0.5	0	1.2	0	2.5	0
Other	2.6	2	6.1	0	4.3	5.7
Diagnosis (%)						
Cancer	100	45	0	100	0	20
Non-cancer	0	55	100	0	100	80
Mean POS total score ± SD	13.5 ± 6.72	10.3 ± 5.9	13.9 ± 6.2	11.7 ± 6.7	11.2 ± 7.1	15.0 ± 6.6

SD standard deviation

Dataset 6: an RCT on the effectiveness of an integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness in the UK in 2014 ($N = 105$).

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Supplementary files

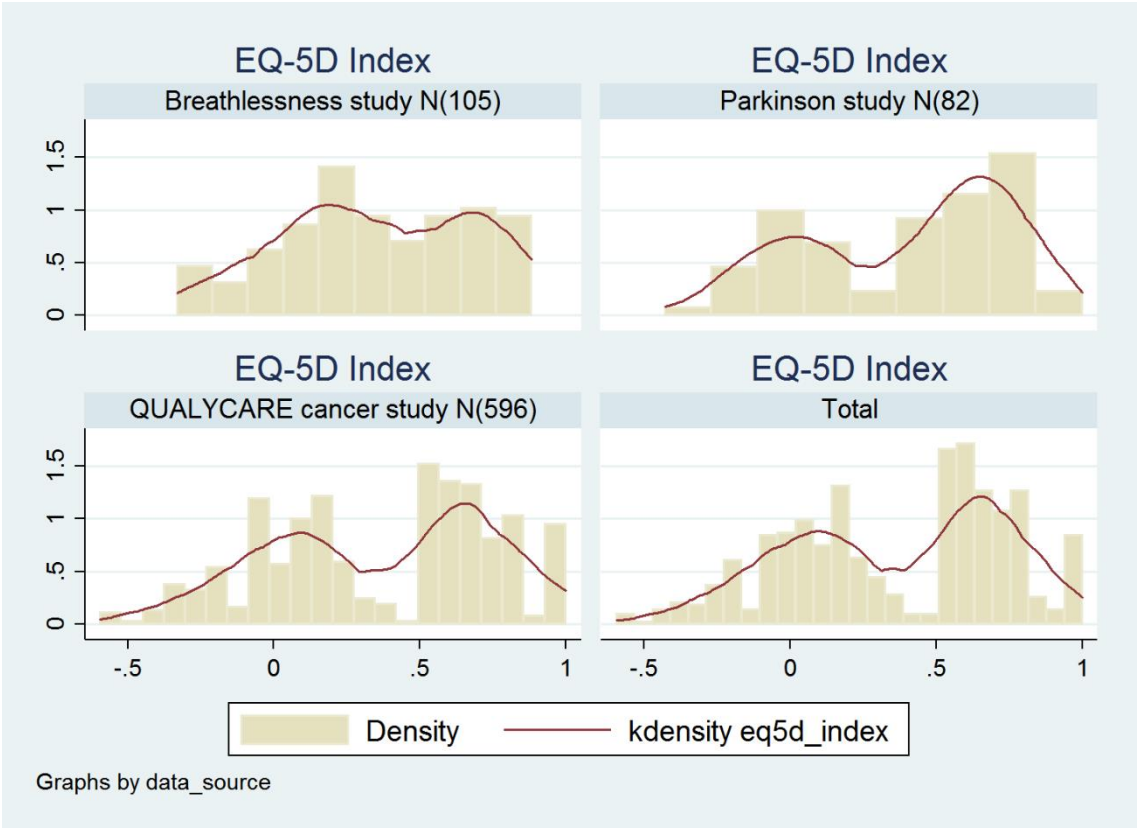


Figure 4: Supplementary file 1 (distributions of EQ-5D scores by data source)

Monte Carlo PCA for Parallel Analysis.

Number of variables: 15
Number of subjects: 783
Number of replications: 100

Eigenvalue #	Random Eigenvalue	Standard Dev
1	1.2410	.0304
2	1.1913	.0218
3	1.1513	.0184
4	1.1121	.0165
5	1.0831	.0145
6	1.0497	.0127
7	1.0219	.0139
8	0.9955	.0140
9	0.9669	.0128
10	0.9395	.0132
11	0.9114	.0131
12	0.8847	.0142
13	0.8526	.0142
14	0.8198	.0159
15	0.7792	.0204

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Figure 5: Supplementary file 2 (Horn's parallel analysis)

Supplementary file 3: Pearson's correlation coefficients of POS items with EQ-5D index and items (N=783)

		EQ-5D items				
POS Items	EQ-5D index	Mobility	Self-care	Usual activities	Pain	Anxiety/depression
Pain	– 0.241	0.117	0.084	0.035	0.380	0.120
Other symptoms	– 0.111	0.004	0.056	– 0.055	0.170	0.101
Patient anxiety	– 0.155	0.032	0.072	0.101	0.091	0.303
Family anxiety	– 0.142	– 0.026	0.053	0.005	0.179	0.222
Information needs	– 0.044	0.028	0.026	0.149	– 0.044	0.001
Sharing feelings	– 0.139	0.050	0.132	0.086	0.098	0.165
Depression	– 0.214	0.047	0.080	0.124	0.121	0.414
Feeling good	– 0.196	0.048	0.142	0.128	0.143	0.324
Time wasted	– 0.102	0.030	0.094	0.038	0.089	0.051
Practical matters	– 0.072	0.047	0.102	0.058	0.063	0.060
Total POS score	– 0.252	0.067	0.152	0.142	0.239	0.342

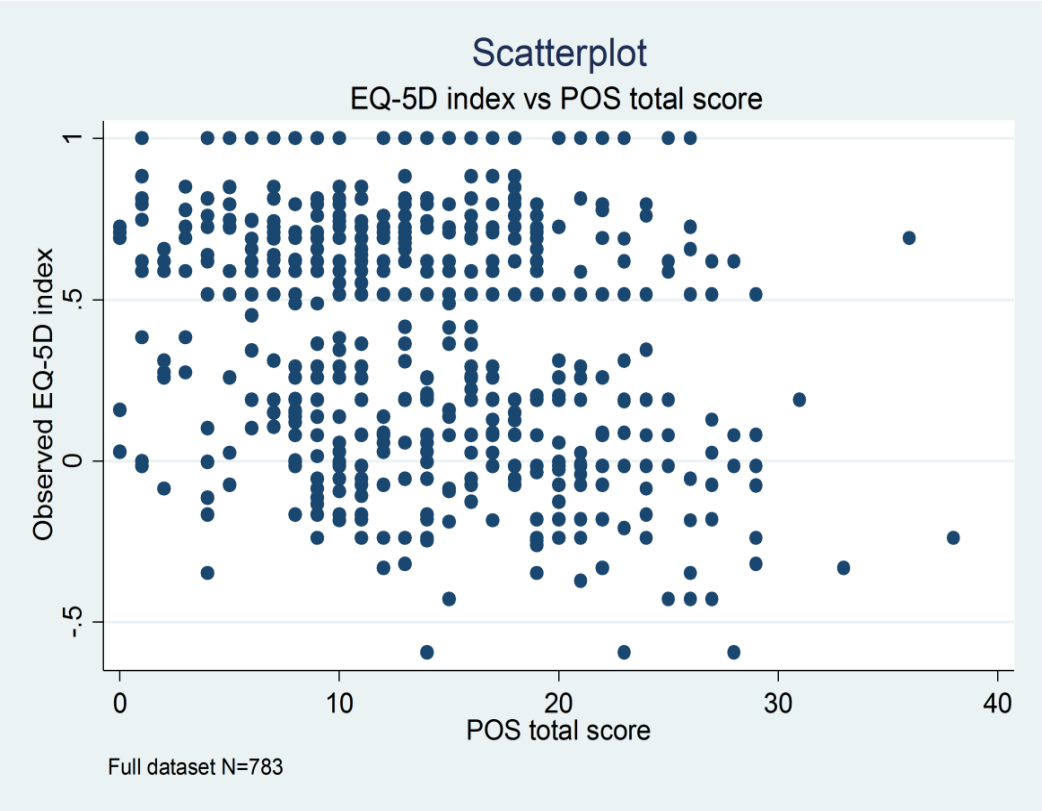


Figure 6: Supplementary file 4 (scatter plot of EQ-5D index vs POS total score)

Supplementary file 5: POS questionnaire

Development of a patient-reported palliative care-specific health classification system: the POS-E

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Journal: The Patient - Patient-Centered Outcomes Research

SAMPLE

Palliative care Outcome Scale
PATIENT QUESTIONNAIRE (version 2)

www.pos-pal.org

Patient name: ……..Assessment date: .....

Date of birth: ……..……...Assessment no: ……..

Care setting: ……

Please answer the following questions by ticking the box next to the answer that is most true for you. Your answers will help us to keep improving your care and the care of others.
Thank you.

1 Over the past 3 days, have you been affected by pain?

- ☐ 0 Not at all, no effect
- ☐ 1 Slightly - but not bothered to be rid of it
- ☐ 2 Moderately - pain limits some activity
- ☐ 3 Severely - activities or concentration markedly affected
- ☐ 4 Overwhelmingly - unable to think of anything else

2 Over the past 3 days, have other symptoms e.g. nausea, coughing or constipation seemed to be affecting how you feel?

- ☐ 0 No, not at all
- ☐ 1 Slightly
- ☐ 2 Moderately
- ☐ 3 Severely
- ☐ 4 Overwhelmingly

3 Over the past 3 days, have you been feeling anxious or worried about your illness or treatment?

- ☐ 0 No, not at all
- ☐ 1 Occasionally
- ☐ 2 Sometimes - affects my concentration now and then
- ☐ 3 Most of the time - often affects my concentration
- ☐ 4 Can't think of anything else - completely pre-occupied by worry and anxiety

4 Over the past 3 days, have any of your family or friends been anxious or worried about you?

- ☐ 0 No, not at all
- ☐ 1 Occasionally
- ☐ 2 Sometimes – it seems to affect their concentration
- ☐ 3 Most of the time
- ☐ 4 Yes, always preoccupied with worry about me

5 Over the past 3 days, how much information have you and your family or friends been given?

- ☐ 0 Full information or as much as wanted – always feel free to ask
- ☐ 1 Information given but hard to understand
- ☐ 2 Information given on request but would have liked more
- ☐ 3 Very little given and some questions were avoided
- ☐ 4 None at all – when we wanted information

6 Over the past 3 days, have you been able to share how you are feeling with your family or friends?

- ❑ 0 Yes, as much as I wanted to
- ❑ 1 Most of the time
- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all with anyone

7 Over the past 3 days, have you been feeling depressed?

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes
- ❑ 3 Most of the time
- ❑ 4 Yes, all the time

If you have placed a tick in boxes 3 or 4 for this question, please speak with your nurse or doctor at your next appointment.

8 Over the past 3 days, have you felt good about yourself as a person?

- ❑ 0 Yes, all the time
- ❑ 1 Most of the time
- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all

9 Over the past 3 days, how much time do you feel has been wasted on appointments relating to your healthcare, e.g. waiting around for transport or repeating tests?

- ❑ 0 None at all
- ❑ 2 Up to half a day wasted
- ❑ 4 More than half a day wasted

10 Over the past 3 days, have any practical matters resulting from your illness, either financial or personal, been addressed?

- ❑ 0 Practical problems have been addressed and my affairs are as up to date as I would wish
- ❑ 2 Practical problems are in the process of being addressed
- ❑ 4 Practical problems exist which were not addressed
- ❑ 0 I have had had no practical problems

7. Stages 2B and 2C: valuing POS-E health states [publication 4]

The following article reports the methods and results of stage 2B (valuation of a subs-sample of health states derived from stage 2A [publication3]) and stage 2C (modelling the results of stage 2B to predict the preference values of all other health states defined in stage 2A that were excluded from the valuation study in 2B). The valuation study reported in this article used a cross-sectional design. This article has been submitted to the Health Economics journal at the time of writing this thesis.

Because the POS has been used widely in research and clinical practice, developing a preference-based measure from the POS is expected to extend the scope of conducting economic evaluations of palliative care interventions using current and forthcoming POS data sets.

This chapter addresses objectives 3, 4, and 5 of this thesis as follows:

1. To conduct a valuation exercise to elicit health-state values for a sample of states
2. To model valuation results to produce utility values for all health states using regression / econometric models
3. To integrate results and produce an algorithm for estimating utilities for use in cost-utility analysis of palliative care interventions

Preference weights for a palliative care health classification system (POS-E): a valuation study

Short title: Preference weights for the POS-E measure

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Keywords

Preference-based measures, health-state utility, modelling, patient-reported outcomes, Palliative care Outcome Scale, time trade-off, palliative care

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College Hospital (London, UK); the Palliative Care teams across Guy's and St Thomas's Hospitals, St George's Hospital, and St Joseph's Hospice (London, UK); research nurses at Newcastle and Cumbria CCG; C Pannell, P Kaler, and J Ducker (research nurses) for their interviews with patients and volunteers; members of the PPI and the project advisory group for their advice during the course of the study; S Watson for entering and cleaning the data for this project. M.D., I.J.H, and P.M. conceived the idea of the study; and I.J.H, and P.M. secured funding. M.D., I.J.H, and F.E.M. set up the study. I.J.H, F.E.M., and M.D. oversaw the study. M.D. and P.M. analysed the data. M.D. produced the first draft of the paper. All authors commented on and contributed to the final draft. I.J.H. is the guarantor of the study. All authors had full access to all of the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of conflicting interests

All authors (MD, FEM, PM, and IJH) declare no conflicts of interest with respect to the research, authorship and/or publication of this article.

7.1 Background

The World Health Organization, defines palliative care as '*the active holistic care of patients with advanced progressive disease, aimed at achieving the best possible quality of life for patients and families, through the management of pain and other symptoms, as well as provision of spiritual, psychological and social support; which may be initiated early in the course of treatment along with other curative treatments*'' [15, 195]. Palliative care has to compete for limited health resources with other health services. Health policy makers seek to maximize 'value for money'. To justify funding palliative care, providers must show that interventions are good value for money and allocated resources are used efficiently.[196, 197]

Cost-utility analysis (CUA) is a means of assessing value for money of health care interventions[6, 9]. The Quality Adjusted Life Year (QALY), which combines length and quality of life into a single measure, is commonly used in CUA. The quality portion (or utility value) is based on a scale ranging from 1 (full health) to 0 (dead), and is derived from preference-based measures (PBM) of health. PBMs are instruments used to express the value of health states. PBMs comprise two components; a health state classification system, and a utility value set. The utility value set is generally elicited using choice-based techniques such as Time-Trade-Off (TTO),[25] or Standard Gamble,[2] to produce values to derive QALYs, often based on general population preferences. There is on-going debate about whose values (e.g. patients, general public, or health professionals) should be used in economic evaluations. Patients have experienced impaired health and may be better placed to understand and value health states.[73, 198] health professionals have a good understanding of health states [73], but in principle public resources should be allocated using population values. It remains unclear whether values from these different perspectives differ significantly. Generic PBMs are commonly used to calculate QALYs because they are developed for use across conditions. The EuroQol-5 Dimension (EQ-5D) [10] is recommended by the National Institute for Health and Care Excellence (NICE) [6] in England. However, generic measures may be insensitive to effects of some services such as palliative care, because they do not cover important domains. For example, a recent study found that EQ-5D misses important palliative-care-related domains such as practical matters and information needs [196]. Condition-specific measures may provide more

sensitive assessments of a service impact. The Palliative care Outcome Scale (POS) is a well-validated instrument, widely used to measure the domains that impact on the quality of life of palliative care patients [147]. Not being preference based, condition-specific measures cannot be used to estimate QALYs directly, but preference-based measures can be developed from existing measures to provide condition-specific utilities[89]. Using POS to derive a palliative care PBM would extend the scope for doing economic evaluations of palliative care interventions because POS has been used widely in palliative care clinical trials, including randomized controlled trials (RCTs) and observational studies; and for service evaluation.[111, 137, 149-156]

Deriving a PBM from an existing measure involves three stages: 1) developing a shorter health state classification system from the original instrument; 2) generating a utility value set for a subset of this new classification system using a preference elicitation method; and 3) deriving utility values for the rest of the new classification system using regression techniques [89]. The first stage, which produced a seven-item palliative-care-specific health classification (POS-E) has been previously reported [154]. This paper reports the second and third stages of developing a palliative-care specific preference-based measure (generating a utility value set for the POS-E). A secondary aim tested the hypothesis that patient values were not different from those of healthy volunteers.

7.2 Methods

Design

A cross-sectional valuation survey using a modified time-trade off method was applied to the previously derived POS-E health state classification system. The methodology was informed by Brazier et al. on deriving PBMs from condition-specific measures[89], and the checklist for conjoint analysis applications in health.[199] We used face-to-face interviews conducted by trained interviewers from King's College London.

Ethics approval

Protocol, procedures, information sheets, consent forms, and questionnaires were approved through the independent UK Integrated Research Approval System via the National Research Ethics Service (ref. 15/LO/1774). We were granted NHS Research and Development approval in all participating

sites.

The POS-E Health State Classification System

The POS-E health classification system, summarised below, was derived in a previous analysis [154]. POS-E health states are combinations of seven items (pain, other symptoms, family anxiety, depression, anxiety, practical matters, and feeling good about yourself); with two or three response categories for each item, [154] [appendix table 1], describing a total of 1,458 unique health states. The health states are coded as seven-digit numbers representing: family anxiety; other symptoms; pain; depression; anxiety; practical matters; and feeling good about one's self; where 0 represents the 'no' (not at all) response, 1 represents the 'mild/moderate' or 'present' option, and 2 represents the 'severely/overwhelmingly' option . The best state defined is '0000000' and the worst '2222212' [appendix table 1].

Selection of health states

We used the Rasch vignette method described by Brazier et al[89, 103] to select health states suitable for valuation from the 1,458 POS-E health states. Details on the selection of health states have been reported elsewhere[89, 154] and involved examining the Rasch threshold map to identify the most plausible combinations of item levels, based on the health states most frequently observed by palliative care patients, at various levels of severity. The map identified 14 health states (presented in order of severity) suitable for valuation [appendix table 2]. This approach also accounts for multiple interactions (and correlations) between items/dimensions.[103, 200] We preferred this method of selecting health states for valuation over statistical methods like factorial and orthogonal block designs because these treat items/domains as independent statements and so are inappropriate for measures with correlated items like the POS [154], and may result in selecting non sensible health states for valuation.[103] A recently published factor analysis of POS data,[196] showed it is unlikely that the problems seen in palliative care are unrelated. For example, a health state where someone feels 'good about him/herself always' and simultaneously feels 'depressed always' is implausible. The Rasch vignette method has been used in developing many PBMs including the SF-6D (SF-12)[92], the Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM)[200], the Stanford Health Assessment Questionnaire (HAQ)[201], the Audit of Diabetes-Dependent Quality-

of-Life (ADDQoL)[181], and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30)[42].

Participants

Patients

Eligibility criteria were patients: 18 years or older; with advanced disease (all patients being seen by specialist palliative care services); who could provide informed consent (i.e. neither too ill nor cognitively impaired); and who were English-literate and willing to participate. Patients were recruited from three NHS trusts and one hospice in London, and General Practitioner surgeries in Newcastle and Cumbria Clinical Commissioning Group. Patient were initially screened against the eligibility criteria by their clinical team. Eligible patients were approached about participating in the study by a member of their clinical team, or GP. Patients who expressed an interest in participating were then visited by a member of the research team who obtained informed written consent and subsequently conducted the interview.

Healthy volunteers

Eligibility criteria were healthy volunteers: 18 years or older; were English-literate; and were willing to participate. Healthy volunteers were recruited via the volunteer services of each of the study sites. Healthy volunteers were contacted about participating in the study via the leads of the respective volunteer departments through e-mails or directly in person.

Recruiting healthy volunteers this way was to obtain a convenience sample of relatively healthy people rather than a representative sample of the general population.

The valuation method

We used a modified version of the time-trade-off (TTO) developed by the Measurement and Valuation of Health group (MVH)[25] to elicit values for the health states. These modifications were to account for specific issues regarding TTO valuations. Modifications were based on feedback from the study's 'patient and public involvement' (PPI) group and the study advisory group regarding TTO in palliative care patients (who have a relatively short life expectancy), where it was deemed inappropriate to ask patients to trade-off years of life (10 to 20 years) which they know

they don't have. The PPI and study advisory group agreed that 10 months (rather than 10 years) was a reasonable estimate of life expectancy for this patient group. We therefore used 10 months instead of 10 years as per the MVH protocol. A previous study showed that it is feasible to elicit valid TTO values for durations as short as 10 weeks.[186, 187] See text box 1 in appendix for details of the

Valuation procedures

Sampling strategy

Sample size calculations are problematic for valuation studies and conjoint analysis generally, as indicated by the absence of a definitive statistical formula [202]. For our primary aim of deriving preference values for the POS-E, there is little guidance on the appropriate sample size. The sample size depends on the number of health states to be valued, the efficiency of the questionnaire design, the number of valuations per respondent, the availability of respondents, and the expected number of valuations per health states.[203] The number of valuations per health state reported in previous valuation studies vary widely. A review of studies developing condition-specific measures [89] found the average number of valuations per health state reported varied from 19, in the UK valuation study [40], to 615 in the US study [204]; almost half of the studies reported average valuations per health state of less than 30. The value sets for two commonly used generic PBMs, SF-6D (SF-12)[92] and SF-6D (SF-36)[26], were estimated on an average of 15 valuations per health state. Based on this and the limited pool of palliative care patients, we aimed for a minimum of 20 valuations per health state for aim 1 (deriving mean utility values for POS-E).

For our secondary aim of testing the null hypothesis that patient values are not different from those of healthy volunteers, using the formula; $\frac{2SD^2}{MID^2} \times (\delta(sig + power))^2$, assuming a power of 0.8, significance level of 0.05, and standard deviation of 0.2 (based on SD for EQ-5D utility of UK cancer patients [205]), 63 valuations per health state per group would be required to detect a difference of 0.1 (based on MID for EQ-5D of UK cancer patients) [205] between patients and healthy volunteers for each health state; and thus a total of 1,764 valuations for the 14 health states). [89, 90] However, the PPI group highlighted that some participants, particularly patients with advanced disease, might find it too burdensome to value 14 health states. Also, previous valuation exercises suggest that

respondents cannot value more than 13 health states at once,[3] and typically are asked to value between six and eight states[1, 3, 26, 40, 45]. Reducing the number of health states valued by each participant would necessitate increasing the number of interviews (and respondents) required to achieve 63 valuations per health state. To address this we split health states into two sets, with each set comprising eight health states. Health states 6 (2101100) and 13 (2222112) – appendix table 2 – were common to both sets so that we could assess any differences between patient and healthy volunteer TTO values using these two health states (i.e. six states unique to set 1; plus six states unique to set 2; plus two health states common to both sets = 14 health states). Each participant valued one set of cards comprising eight health states. Therefore, we aimed to conduct a total of 130 interviews (65 patients and 65 healthy volunteers; a total of 1,040 valuations). The two health states common to both sets would thus achieve the required 63 valuations each for our secondary aim, while the other health states would each have more than the required 20 valuations to achieve our primary aim. The sets of health state cards were assigned alternately to consecutive participants; with separate assignments for patients and for healthy volunteers. To limit order effects we altered The sequence in which the eight health states were displayed.

Analysis

To compare sociodemographic characteristics, Chi square / Fischer's Exact test were used for categorical and analysis of variance (ANOVA) for continuous variables (Bonferroni correction was applied to all *P* values to account for multiple comparisons). Mean TTO values were estimated for the 14 health states that were valued. Patient and health volunteer values were compared using simple t-tests. We used regression models to assess the relationship between mean TTO values for each of the 14 POS-E health states and their corresponding Rasch logit values derived from Rasch analysis of POS-E [154]. Prior to this the Rasch logit values were rescaled and anchored to the maximum and minimum values of observed TTO values obtained from the valuation survey, using the formula: $(\text{maxnew} - \text{minnew}) \div (\text{maxold} - \text{minold}) \times \text{v} - \text{minold}) + \text{minnew}$. The rescaled logit score was then used as the independent variable in the regression models to estimate health state values for the remaining 1,444 health states excluded from the valuation study. This method has been previously described by Young et al [89, 206]. We tested several regression models including simple linear, cubic, quadratic and quartic forms to account for possible non-linear

relationships [table 1]. We assessed model fit using the adjusted R^2 (co-efficient of determination) and the root mean squared error (RMSE). We selected the model with the best fit to predict mean TTO values of all other POS-E health states based on their corresponding Rasch logit value.

Table 1: Regression models used to estimate values for all POS-E health states omitted from the valuation survey

	Model	Specification
1	simple linear relationship	$y = \alpha + \beta_1 x$
2	quadratic relationship	$y = \alpha + \beta_2 x^2$
3	cubic relationship	$y = \alpha + \beta_3 x^3$
4	quartic relationship	$y = \alpha + \beta_4 x^4$
5	quadratic relationship	$y = \alpha + \beta_1 x + \beta_2 x^2$
6	cubic relationship	$y = \alpha + \beta_1 x + \beta_3 x^3$
7	quartic relationship	$y = \alpha + \beta_1 x + \beta_4 x^4$
8	cubic relationship	$y = \alpha + \beta_2 x^2 + \beta_3 x^3$
9	quartic relationship	$y = \alpha + \beta_2 x^2 + \beta_4 x^4$
10	cubic relationship	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_3 x^3$
11	quartic relationship	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_4 x^4$
12	quartic relationship	$y = \alpha + \beta_1 x + \beta_3 x^3 + \beta_4 x^4$
13	quartic relationship	$y = \alpha + \beta_3 x^3 + \beta_4 x^4$
14	quartic relationship	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_3 x^3 + \beta_4 x^4$
y: mean predicted TTO value, *x:* rescaled Rasch logit value; α: constant; β: regression coefficients		

7.3 Results

The valuation survey was conducted on 102 participants (52 patients and 50 healthy volunteers). We were unable to achieve 130 interviews as patients were often too ill to participate, but 102 interviews were sufficient to achieve our primary aim of estimating mean utility values. Palliative-care patients had various cancer and non-cancer diagnoses [appendix table 4]. Patients had a higher average age, a higher proportion of retired people, a higher proportion with degrees or professional qualifications and a lower proportion of women than healthy volunteers [Table 2]. Patients also had higher symptom burden and concerns than healthy volunteers, with many patients having severe problems [appendix table 3]. We achieved a 99% completion rate for all health states (only 1

missing value: participant was excluded because they assigned highest value to the worst). Most respondents (≥ 82%) found the TTO task easy to understand, while few (≤ 16%) found the number of months of life in TTO task too short to be meaningful. A few participants found the ranking (9.6% of patients; 6% of healthy volunteers) and TTO (11.5% of patients and 6% of healthy volunteers) tasks ‘very difficult’ or ‘rather difficult’. Interviewers reported that four patients may not have understood the ranking and TTO tasks. Only one participant (a patient) met the predefined exclusion criteria indicating a lack of understanding of the task.

Table 2: Characteristics of respondents

Personal characteristics	Patients (N=52)	Healthy volunteers (N=50)	P value
Mean age (SD)	63 (15.4)	43 (15.4)	<0.0001 †
Age distribution (%)			
18-40	4 (8)	30 (60)	
41-65	21 (40)	14 (29)	
>65	27 (52)	6 (12)	
Female, n (%)	27 (52)	32 (64)	NS
Married/partner (%)	34 (65)	38 (76)	NS
Employment (%)			
Employed or self-employed	4 (8)	36 (72)	<0.001§
Retired	36 (69)	5 (10)	
Student	1 (2)	4 (8)	
Other	1 (2)	2 (4)	
Degree or professional qualification (%)	18 (35)	41 (82)	<0.001 ‡
POS-E: Some or extreme problems (%)			
POS-E Pain	39 (75)	17 (34)	<0.001‡
POS-E Other symptoms	44 (85	11 (22)	<0.001‡
POS-E Depression	28 (54)	8 (16)	<0.001‡
POS-E Anxiety	34 (65)	21 (42)	NS
POS-E Feeling good	31 (60)	11 (22)	<0.001‡
POS-E Family anxiety	48 (92)	13 (26)	<0.001 ‡
POS-E Practical matters	22 (42)	12 (24)	NS
Time trade off (TTO) completion rate (%)	51 (98)	50 (100)	
Mean TTO completion time (minutes)	25	21	NS
Mean study completion time (minutes)	48	42	NS
Respondent found first rank valuation task very or rather difficult, n (%)	5 (10)	3 (4)	–
Respondent found first TTO valuation task very or rather difficult, n (%)	6 (12)	3 (6)	–
Interviewer doubted whether respondent understood first rank task, n (%)	4 (8)	0	–
Interviewer doubted whether respondent understood first TTO task, n (%)	4 (8)	0	–
†: t-test with Bonferroni correction; ‡: Chi square test; §: Fisher's Exact test; NS: not significant at α = 0.0036 following Bonferroni correction.			

TTO values obtained from the survey

The analysis was based on 408 valuations from 51 patients and 400 valuations from 50 healthy volunteers (808 valuations in total). Data were missing from one patient (did not complete the TTO task) and this was excluded from the analysis. Although we did not achieve 1,040 valuations required for assessing differences between the two groups, the data were sufficient for our primary aim of estimating mean utility values for the 14 health states. The two health states common to both

sets of health-state cards – health states 6 and 13 – had 101 and 99 valuations respectively [appendix table 5]. The number of valuations for the other health states ranged from 48 to 53. Mean TTO values ranged from 0.21 to 1 for patients, and 0.22 to 0.99 for healthy volunteers, for the worst and best health states respectively [appendix table 5].

Patient values and healthy volunteer values were very similar, with some areas of divergence [see figure 1]. These correspond to differences in ratings for pain, other symptoms, and practical matters. Practical matters had no impact on healthy volunteers' ratings, and there was a sharp decline in the TTO values for both groups when pain and other symptoms became severe/overwhelming. The mean difference between patient and healthy volunteer values was 0.0 (P = 0.96) for health state 6, and 0.03 (P = 0.77) for health state 13 (appendix table 5), although the study was underpowered for this analysis. Repeating the power calculations based on our achieved sample of 50 valuations health state (per group) showed that this analysis was powered to detect a difference of 0.112 (compared to MID of 0.10 in our original calculation). Nevertheless, it is clear from figure 1, and [appendix figure 3] that there is little variability between patient and healthy volunteer values. Also, values from both groups appear to have similar distributions [appendix figure 1; and appendix figure 2]. Given the apparent similarities between patient and healthy volunteer values, we combined the TTO values and used this for the remaining analysis [table 3]. The mean health state valuations for both groups combined ranged from 0.216 (SD = 0.429) to 0.991 (SD = 0.031) with corresponding median values of 0.2 to 1. The health states in table 3 are listed in descending order of severity. The TTO values all correspond logically with the order of severity of the health states. The least severe health state (0000000) had the highest value (0.991) and the most severe state (2222212) had the lowest (0.216). The mean values also correspond well with mean ranking scores [appendix figure 4].

Table 3: Time trade-off (TTO) values obtained from the valuation survey for each health state (pooled)

Health state profile	N (health states)	Observed Mean TTO	SD	Min	25th Percentile	Median	75th Percentile	Max	Mode
0000000	53	0.991	0.031	0.8	1	1	1	1	1
1000000	50	0.980	0.028	0.9	0.95	1	1	1	1
1100000	53	0.916	0.117	0.3	0.9	0.95	1	1	0.95
1100100	53	0.909	0.08	0.65	0.85	0.9	0.95	1	0.95
2100100	53	0.848	0.152	0.4	0.85	0.9	0.95	1	0.9
2101100	101	0.829	0.136	0.45	0.75	0.85	0.95	1	0.9
2111100	49	0.817	0.137	0.5	0.75	0.8	0.95	1	0.95
2111110	53	0.725	0.197	0.3	0.65	0.75	0.9	1	0.75
2111111	48	0.721	0.162	0.2	0.6	0.75	0.85	0.95	0.75
2121111	48	0.556	0.2	0	0.45	0.6	0.678	0.95	0.6
2221111	48	0.429	0.412	-1.86	0.4	0.45	0.6	0.9	0.45
2221112	52	0.381	0.259	0	0.2	0.3	0.5	0.95	0.3
2222112	99	0.305	0.429	-2.33	0.1	0.3	0.5	0.95	0.2
2222212	48	0.216	0.429	-2.33	0.1	0.2	0.4	0.85	0.1
Total	808								

SD: standard deviation; Min: minimum; Max: maximum

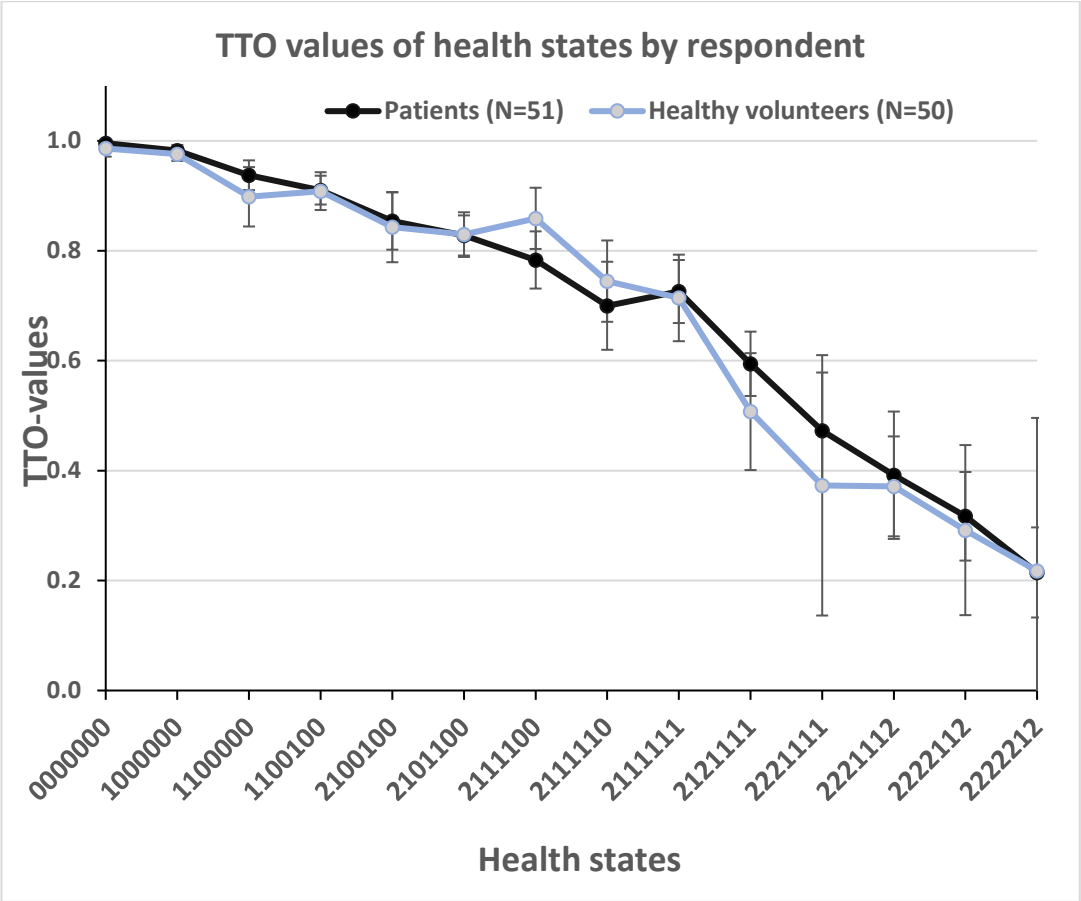


Figure 1: Time trade-off (TTO) values of health states by respondent group. Error bars indicate 95% confidence intervals.

Modelling POS-E health states values using Rasch model logit values

The Rasch logit values of the 14 POS-E states were rescaled and anchored at 0.991 and 0.216, which correspond to the observed mean values for the best health state (0000000) and the worst (2222212) respectively, from the valuation survey. The adjusted R^2 ranged from 0.536 (model 4) to 0.979 [model 14]. We selected model 14 – which included linear, quadratic, cubic, and quartic terms – to predict the mean TTO values of all other POS-E health because it had the highest adjusted R^2 value, the smallest RMSE (0.038), and regression coefficients that all had p-values less than 0.05 [table 4].

Table 4: Models 1–14 regression results and goodness of fit statistics for predicting mean health state values from Rasch (rescaled) logit values

	Model	α	p-value	β_1	p-value	β_2	p-value	β_3	p-value	β_4	p-value	Adj. R^2	RMSE
1	$y = \alpha + \beta_1 x$	0.01	0.911	1.13	<0.001							0.91	0.077
2	$y = \alpha + \beta_2 x^2$	0.33	<0.001			0.87	<0.001					0.80	0.118
3	$y = \alpha + \beta_3 x^3$	0.46	<0.001					0.77	<0.001			0.66	0.153
4	$y = \alpha + \beta_4 x^4$	0.52	<0.001							0.71	0.002	0.54	0.178
5	$y = \alpha + \beta_1 x + \beta_2 x^2$	-0.33	0.008	2.41	<0.001	-1.06	0.004					0.96	0.054
6	$y = \alpha + \beta_1 x + \beta_3 x^3$	-0.25	0.006	1.86	<0.001			-0.61	0.002			0.96	0.050
7	$y = \alpha + \beta_1 x + \beta_4 x^4$	-0.20	0.007	1.67	<0.001					-0.48	0.001	0.97	0.048
8	$y = \alpha + \beta_2 x^2 + \beta_3 x^3$	0.06	0.173			3.35	<0.001	-2.44	<0.001			0.97	0.044
9	$y = \alpha + \beta_2 x^2 + \beta_4 x^4$	0.11	0.011			2.20	<0.001			-1.37	<0.001	0.97	0.047
10	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_3 x^3$	0.08	0.697	-0.14	0.905	3.60	0.113	-2.57	0.047			0.97	0.046
11	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_4 x^4$	-0.03	0.868	0.74	0.423	1.25	0.308			-0.99	0.069	0.97	0.048
12	$y = \alpha + \beta_1 x + \beta_3 x^3 + \beta_4 x^4$	-0.10	0.456	1.26	0.029			1.20	0.408	-1.39	0.219	0.97	0.049
13	$y = \alpha + \beta_3 x^3 + \beta_4 x^4$	0.22	<0.001					4.60	<0.001	-3.90	<0.001	0.95	0.059
14	$y = \alpha + \beta_1 x + \beta_2 x^2 + \beta_3 x^3 + \beta_4 x^4$	1.03	0.041	-8.35	0.044	27.50	0.024	-30.94	0.029	11.77	0.041	0.98	0.038

RMSE: root mean square error; α: constant; Adj. R^2: adjusted r-squared; β: regression coefficients;

Given that POS-E health states with the same total (ordinal) score have the same Rasch logit value, it is possible to predict TTO values for all POS-E health states based on their total score. Figure 2 shows that the mean TTO values obtained from the valuation survey correspond well with the predicted TTO values for all potential POS-E health states based on regression model 14.

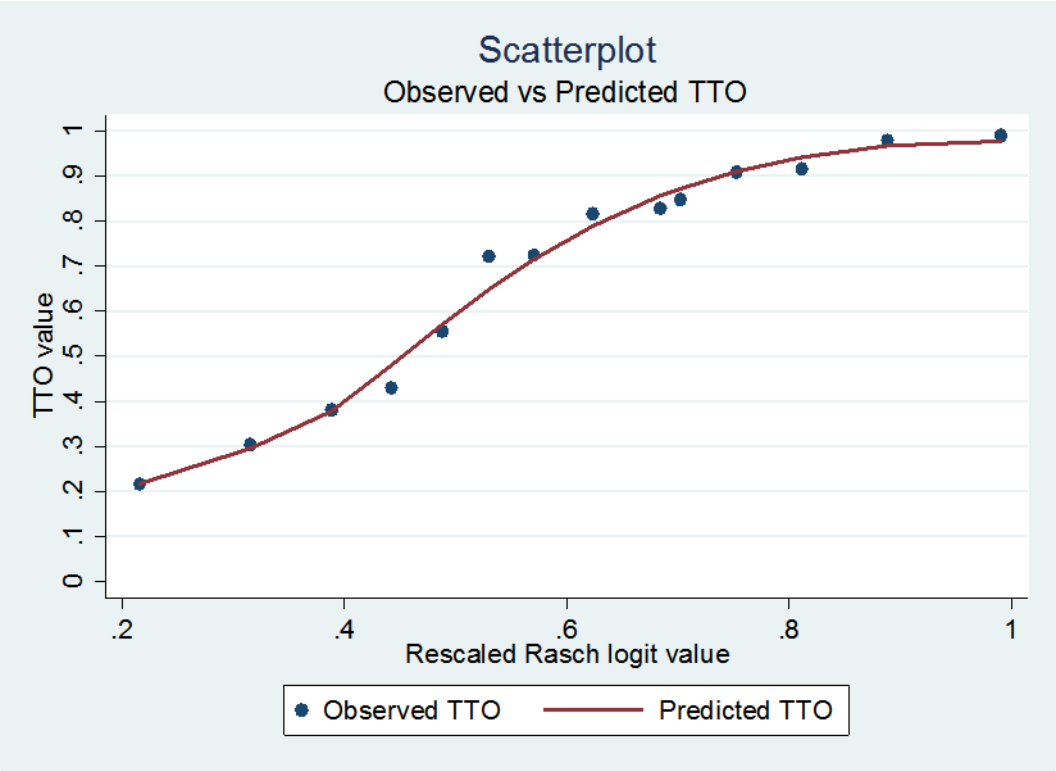


Figure 2: Mean observed (from the valuation survey) and modelled (based on regression model 14) time trade-off values by Rasch rescaled logit value. Modelled time trade-off (TTO) values are predicted using the Rasch rescaled logit value of the POS-E

The TTO value of each health state is estimated based on the total score of the health state [table 5].

Table 5: Modelled Mean Time Trade-off Values for all POS-E Health States, based on the total scores, using regression model 14

POS-E Total Score	Modelled Mean TTO
0	1.00
1	0.95
2	0.93
3	0.91
4	0.87
5	0.86
6	0.79
7	0.72
8	0.65
9	0.57
10	0.49
11	0.39
12	0.28
13	0.22

7.4 Discussion

We found that patients and healthy volunteers were able to make meaningful trade-offs of short time scales. The logical correspondence between the TTO values and the severity levels of the POS-E health state classification supports the internal validity of the POS-E value set. The mean utility values obtained from patients and healthy people were similar, with some areas of divergence around pain, other symptoms, and practical matters.

The POS-E is the first and only palliative-care-specific preference-based measure of health, although values have recently been generated for the ICECAP-Supportive Care Measure (ICECAP-SCM) [66, 207]. It is difficult to compare POS-E values to those of ICECAP-SCM as there are significant conceptual and methodological differences between the two measures. ICECAP-SCM is based on the concept of capability (i.e. measures the opportunity to achieve a good health/death) while the POS-E – like other PBMs of health – measures functioning (actual achievement of good health/death). This means the ICECAP-SCM is particularly suitable where health outcomes (or functioning) are not the focus of evaluation – e.g. social care interventions [208]. Another difference is that ICECAP-SCM values were derived using best-worst scaling [83] wherein death was assumed to be the absence of capabilities. On this philosophical basis, although negative values were obtained in the valuation study, the value set was recalibrated to constrain the minimum value to zero for no capability and one for maximum capability. This seems conceptually odd as not having "the opportunity to make any of the preparations I want to make" and being alive, is then regarded the same as 'not having it because I'm dead'. Although it is obvious that a dead person will have none of the seven capability domains included in the measure, a person might lack these capabilities and yet be alive. Furthermore, the ICECAP-SCM value set yielded implausible results for some capability states, possibly due to the method used. For example, in a person with no capability on any item (a tariff value of zero), an improvement from minimum to maximum on the support item does not result in any change in tariff value. This implies that providing support to patients with severe capability limitations is of no benefit. Despite these differences, "*the POS-E and ICECAP-SCM can be regarded as complementary rather than mutually exclusive, because palliative and*

end-of-life care include aspects of both health (e.g. pain) and wellbeing (e.g. availability of social support), among other things".[154]

This work has shown that it is possible to produce a preference-based health measure for economic evaluation of palliative care interventions. The mean utility values obtained from patients and healthy volunteers were similar which suggests that both could be used to inform resource allocation. There was a sharp decline in utility corresponding to severe/overwhelming pain and other symptoms, reflecting the importance of these domains and their potential impact on the quality of life of palliative care patients. No other study has compared patient values to those of healthy people in the context of palliative care. Studies in other patient groups show a mixed picture. Krabbe and colleagues [209] showed that patient derived VAS ratings (patients with cancer, and rheumatoid arthritis) were similar to those from healthy volunteers, while patient and healthy volunteer derived TTO valuations differed significantly. Schwalm et al. [210] compared valuations for 42 health states among musculoskeletal disease patients, healthy volunteers, and health care professionals, finding small but significant differences between the groups in only six of the 42 valued health states. Dolders and colleagues [211] conducted two meta-analyses of studies comparing general population valuations to those of patients with a variety of diagnoses including chronic kidney and liver disease, cancer, and COPD. They found no significant differences between patient and general population valuations. They concluded – as do we – that both valuations can be used to inform health resource allocation.

The POS-E values cover a smaller range (0.22 to 1) on the utility scale than the EQ-5D-3L tariff (–0.59 to 1). Values for the more severe POS-E health states (0.22 for the worst health state) are noticeably higher than those of the EQ-5D, suggesting that fewer people in our study selected immediate death over living with the varying durations of poor health described by the POS-E, possibly reflecting the shorter TTO duration used in our study. Previous studies have shown that preference values are a decreasing function of duration.[93, 212-214] Our study supports the hypothesis that impaired health states of shorter duration are more tolerable. It is possible that, regardless of the severity of a health state, patients nearing the end of life require a minimum time to prepare for death – e.g. to settle affairs and say goodbye to loved ones – and will be less inclined to accept

immediate death to avoid even the most severe health states – a notion referred to as 'Maximal Endurable Time' [213]. Nevertheless, the POS-E value set has a comparable range to those of the generic SF-6D (0.1 to 0.99) [92], and other condition-specific PBMs which have used longer durations including: Clinical Outcomes in Routine Evaluation-Outcome Measure (CORE-OM) [200] [0.23 – 0.96]; Flushing Symptoms Questionnaire (FSQ) [103] [0.42 – 0.98]; the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) [42], [0.13 – 0.95]; and atopic dermatitis[38], [0.365-0.81].

This study has limitations. First, the sample of healthy volunteers used is not fully representative of the general public. However, we included patients who have experienced palliative-care-specific health states, including older patients; and this could help inform preferences. Second, the sample size was too small to detect a 10% difference between the valuations in the two groups, but was sufficient to estimate mean preference weights for each health state. Third, POS-E is not an independent measure; its seven items are embedded in the 10-item POS. Extracting the seven POS-E items from the POS may affect the meaning, intensity and relative importance of the items, possibly influencing responses. But, besides differences in response levels, the seven items of an 'independent' POS-E should correlate with the corresponding seven items of the POS, because the POS-E items are derived exclusively from individual POS items. Nevertheless, caution should be applied in using POS-E as an independent instrument until further research demonstrates its appropriateness.

A strength of this study is the inclusion of preferences of patients with severe illness and a wide variety of diagnoses, therefore it can be considered a universal PBM for palliative care patients. The original scale, POS, was designed as a universal measure of palliative care problems in people with advanced life limiting illness including cancer and non-cancer. We also used a shorter time frame of 10 months of life (a realistic reflection of life expectancy of palliativecare patients) in the TTO exercise which respondents found neither too short nor too long to be meaningful, which may explain the logical consistency of the TTO values with the order of severity of the health state classification system.

7.5 Future research

We have developed a palliative care specific preference-based measure which, subject to further validation, can provide additional information for use in estimating QALYs. Subject to further validation, the POS-E can also be used to estimate QALYs in studies where only the POS has been used, provided the seven items used in the POS-E have been completed.

This valuation study needs to be repeated in a larger and more representative sample of the general population, and patients (including informal carers and health professionals) to further explore areas of divergence. Also, further research is needed to assess the appropriateness and validity of the POS-E against other generic PBMs like the EQ-5D in order to support the use of the POS-E to estimate QALYs by reimbursement agencies like NICE. Given the widespread use of the POS in assessing palliative care outcomes in the UK and internationally, the preference based POS-E is expected to facilitate broader economic evaluations of palliative care interventions using current and forthcoming POS data sets. Although this analysis is experimental, given the methodological deviations, there is cause for tentative optimism.

7.6 References

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7.7 Appendices

Tables

Appendix table 5: POS-E descriptive system

Item	Categories	Score
Your family or friends have been anxious or worried about you	No, not at all	0
	Occasionally/sometimes	1
	Most of the time/always	2
You have other symptoms e.g. nausea, coughing or constipation	No, not at all	0
	slightly/moderately	1
	severely/overwhelmingly	2
You have been affected by pain	No, not at all	0
	slightly/moderately	1
	severely/overwhelmingly	2
You have been feeling depressed	No, not at all	0
	Occasionally/sometimes	1
	Most of the time/always	2
You have been feeling anxious or worried about your illness or treatment	No, not at all	0
	slightly/moderately	1
	severely/overwhelming	2
Practical matters resulting from your illness, either financial or personal, have been addressed	Addressed	0
	Not addressed	1
Feeling good	Always/most of the time	0
	Occasionally/sometimes	1
	Not at all	2

Note: Adapted from previous analysis [154].

Appendix table 7: **Health states (and coverage) of the POS-E as identified by the threshold map**

Item no.	Health states (N=504)													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
4. Family anxiety	0	1	1	1	2	2	2	2	2	2	2	2	2	2
2. Other symptoms	0	0	1	1	1	1	1	1	1	1	2	2	2	2
1. Pain	0	0	0	0	0	0	1	1	1	2	2	2	2	2
7. Depression	0	0	0	0	0	1	1	1	1	1	1	1	2	2
3. Anxiety	0	0	0	1	1	1	1	1	1	1	1	1	1	2
10.Practical matters	0	0	0	0	0	0	0	1	1	1	1	1	1	1
8. Feeling good	0	0	0	0	0	0	0	0	1	1	1	2	2	2

Note: Adapted from previous analysis [154]

Appendix table 8: Participant symptom burden

	Patients N=52			Healthy volunteers N=50		
Yes I have a serious illness; N (%)	51 (98)			4 (8)		
	0	1	2	0	1	2
POS-E item	none	slight/ moderate	severe/ overwhelming	none	slight/ moderate	severe/ overwhelming
POS-E pain; N (%)	13 (25)	23 (44)	16 (31)	33 (66)	17 (34)	0 (0)
Other symptoms; N (%)	8 (15)	25 (48)	19 (37)	39 (78)	10 (20)	1 (2)
	no problem	occasionally/ sometimes	Always/ most of the time	no problem	occasionally/ sometimes	always/most of the time
Depression; N (%)	24 (46)	23 (44)	5 (10)	42 (84)	8 (16)	0 (0)
Anxiety; N (%)	18 (35)	25 (49)	9 (17)	29 (58)	20 (40)	1 (2)
Family anxiety; N (%)	4 (8)	28 (54)	20 (39)	37 (74)	12 (24)	1 (2)
	always/most of the time	occasionally/ sometimes	not at all	always/ most of the time	occasionally/ sometimes	not at all
Feeling good; N (%)	21 (40)	24 (47)	7 (15)	39 (78)	11 (22)	0 (0)
	none/ addressed	Not addressed		none/ addressed	not addressed	
Practical matters; N (%)	30 (58)	22 (42)	NA	38 (76)	12 (24)	NA

Appendix table 9: Patients' Diagnoses

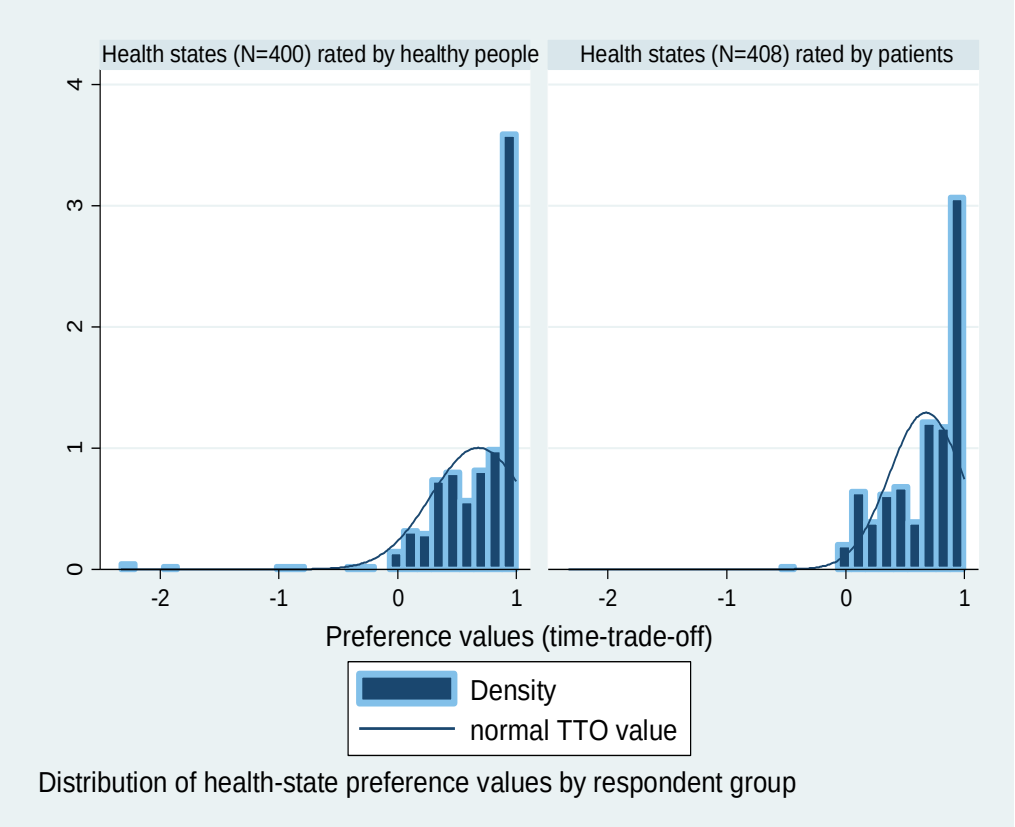
Primary Diagnosis	Patients (N=52)
Cancer	
Lymphoma	2
Leukaemia	2
Lung	5
GIT	5
Ovarian/prostate cancer	4
Breast	2
Other	9
Non-cancer	
Multiple Sclerosis	6
Heart failure	3
COPD	5
Parkinson's disease	1
Cystic fibrosis	3
Cerebral palsy	1
Kidney Failure	1
Missing†	3
Total	52
Patients with multiple co-morbidity‡	6
GIT: gastro-intestinal tract; COPD: chronic obstructive pulmonary disease †: did not provide information on diagnosis ‡: already counted as part of primary diagnosis above but have additional diagnoses.	

Appendix table 10: Time trade-off (TTO) values for each health state by respondent group

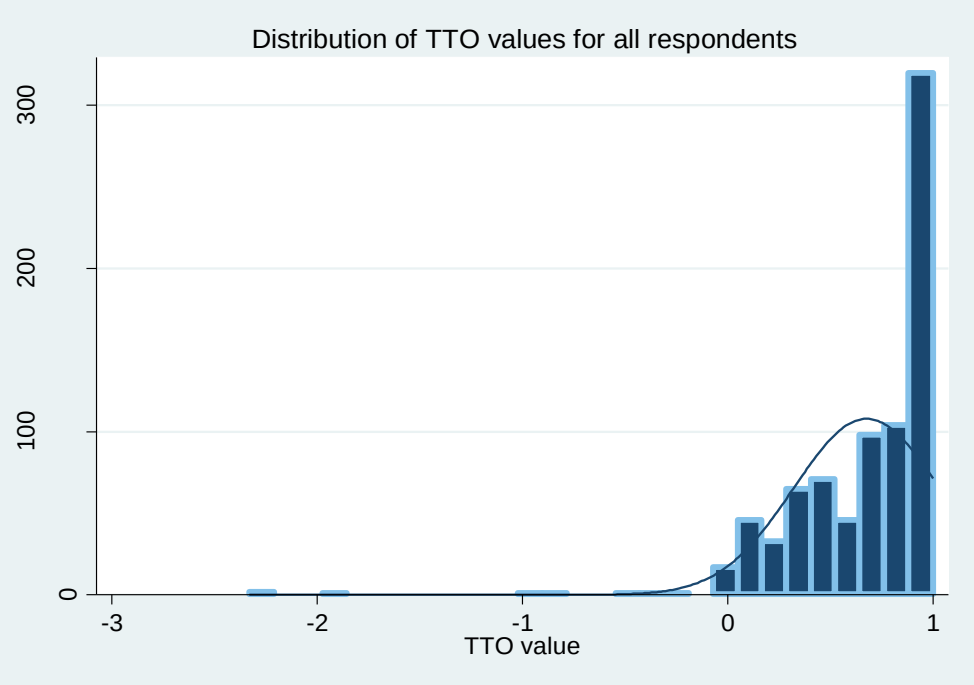
	Health state profile	Healthy volunteers (N=50)			Patients (N=51)				
No.		No. of valuations	Mean	SD	No. of valuations	Mean	SD	Difference	P-value
1	0000000	29	0.99	0.040	24	1.00	0.014	-0.01	0.266
2	1000000	22	0.98	0.029	28	0.98	0.028	0.00	0.464
3	1100000	29	0.90	0.145	24	0.94	0.066	-0.04	0.229
4	1100100	29	0.91	0.093	24	0.91	0.064	0.00	0.936
5	2100100	29	0.84	0.172	24	0.85	0.128	-0.01	0.795
6	2101100	50	0.83	0.144	51	0.83	0.130	0.00	0.955
7	2111100	22	0.86	0.131	27	0.78	0.135	0.08	0.054
8	2111110	29	0.74	0.199	24	0.70	0.196	0.04	0.416
9	2111111	21	0.71	0.180	27	0.73	0.149	-0.01	0.808
12	2121111	21	0.51	0.244	27	0.59	0.152	-0.09	0.136
11	2221111	21	0.37	0.543	27	0.47	0.275	-0.10	0.414
12	2221112	28	0.37	0.241	24	0.39	0.284	-0.02	0.782
13	2222112	49	0.29	0.542	50	0.32	0.285	-0.03	0.772
14	2222212	21	0.22	0.638	27	0.21	0.213	0.01	0.983
	Total number of valuations	400			408				

SD: standard deviation

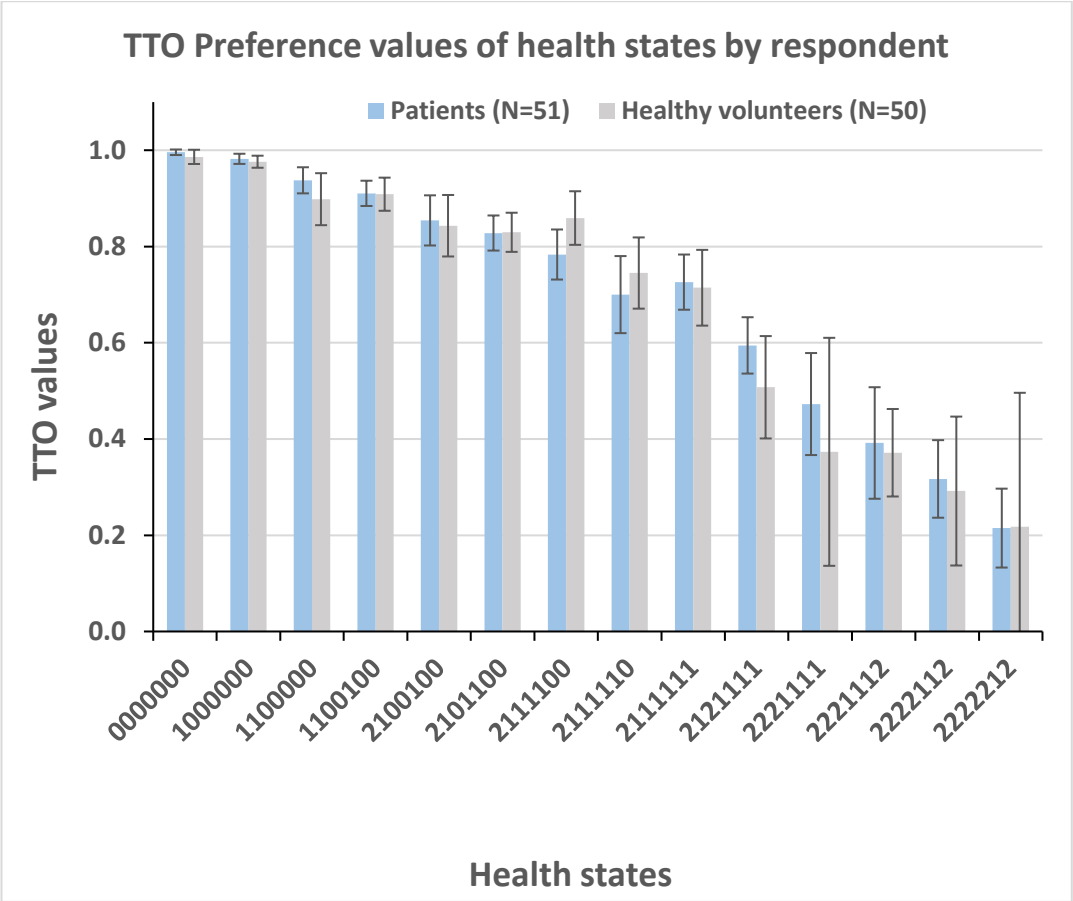
Figures



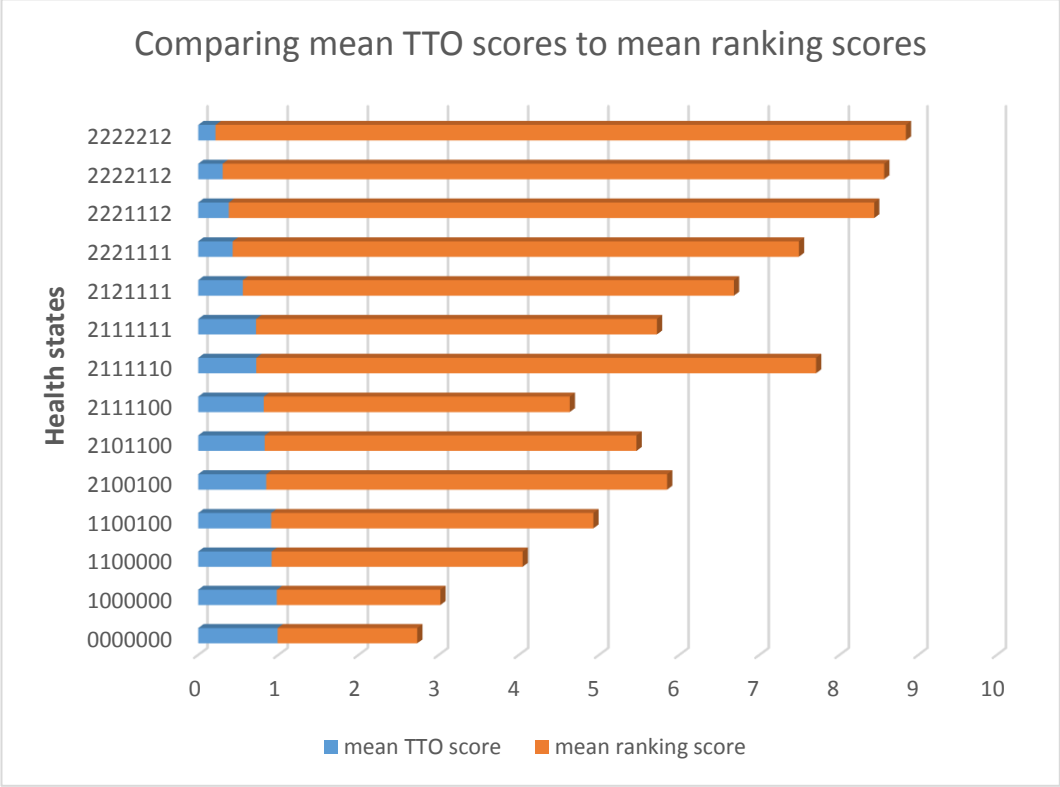
Appendix figure 3: Distribution of TTO values by respondent group



Appendix figure 4: Distribution of TTO values (pooled)



Appendix figure 5: Histogram of mean TTO values per health state by respondent group. Error bars indicate 95% confidence intervals.



Appendix figure 6: Bar chart comparing mean time-trade-off (TTO) scores to mean ranking scores for each health state (in descending order of severity from top to bottom)

Procedures for the valuation survey:

This survey used face-to-face interviews which were conducted by trained and experienced interviewers from King's College London. First, in order to familiarize participants with the POS-E, interviewers explained the aim of the study, and the POS-E classification system to respondents following which respondents were asked to classify their own health using the POS-E. The next section involved two warm up tasks to familiarize the respondents with the abstract concept of health states and the TTO procedure, and to identify respondents who were unable to understand the TTO task. As part of this warm up stage, participants were asked to embark on a ranking exercise of 10 health state cards comprising 8 POS-E health states from one of two card blocks; full health; and dead. Then prior to the formal valuation task, respondents were shown an example of the valuation task that they would be performing. Subsequently, respondents were asked to value the 8 POS-E health states (in the form of health state cards) which they previously ranked. Next, participants were asked to provide feedback on how easy/difficult they found the TTO questions. Finally, participants were asked basic socio-demographic questions including age, gender, and employment after. Where it was obvious that the participant did not understand the TTO task, the interview was terminated by the interviewer and the data excluded from the analysis.

For the formal valuation task, respondents were asked to choose between living for a period of t months in a specific health state (h_i) that is worse than full health, or to shorten their life expectancy to x months in full health, where $x < t$. The number of months in full health was varied until the point where the participant felt the two alternatives are equivalent. The utility value assigned to the state h_i is x/t.[2] The valuation procedure began with a question to indicate whether the participant regarded the state to be valued as better (or worse) than dead. Participants had to make a choice between a) living for 10 months in a palliative health state followed by death; or b) immediate death. The palliative health-state was deemed better than dead if the participant choses a), and worse than dead if b). Health states deemed better than dead were valued using the standard TTO technique previously described, with t=10 months. For health states deemed worse than dead, participants were asked to choose between two options A) living for m months in a palliative health-state h_i, followed by full health for x months and subsequently death (with $m + x = 10$); or B) immediate death. Months in full health (x) were varied simultaneously with months in the palliative health state (m) until the point where the participant felt the two alternatives were equivalent. TTO values for these health states were calculated using the formula $-x/10$ so that they had a lower limit of –1, in line with the method used to derive UK EQ-5D TTO values.[3]

Text box 1 (appendix): procedures for the valuation task

8. Integration of findings and discussion

8.1. Summary

The aim of this thesis was to develop a palliative-care-specific PBM for use in economic evaluations of palliative care. We first used secondary data to demonstrate for the first time that the most commonly used generic PBM – the EQ-5D – fails to capture some important palliative care concerns. It therefore would be inadequate for use in economic evaluations of palliative care interventions. We then proceeded to derive a simplified palliative-care-specific health classification system from a well validated and routinely used palliative-care instrument (POS) using Rasch and psychometric analyses. Finally, by conducting a valuation survey of both palliative-care patients and healthy volunteers, we were able to demonstrate that it is feasible to derive a meaningful PBM (POS-E) for use in economic evaluations of palliative-care interventions. Moreover, patient-derived preference values appear to be similar to those derived from healthy people. We propose that, subject to further psychometric validation, the POS-E can be used to provide palliative-care-specific utility values to complement generic utilities from more widely validated measures.

8.2. Main findings

Mapping the POS onto the EQ-5D (objective 1)

The first objective of this thesis was to assess the extent to which the EQ-5D captures palliative care concerns and the feasibility of mapping the POS onto the EQ-5D in order to derived utilities (second paper; chapter 5). This mapping analysis was crucial to this thesis as it provides the first evidence on the extent to which the EQ-5D – the most commonly used generic PBM – captures palliative care concerns, thereby substantiating (or refuting) some the criticisms discussed in section 2.4. This analysis was guided by the MAPS Reporting Statement for Studies Mapping onto Generic Preference-Based Outcome Measures[170].

The analysis found that the EQ-5D misses some important palliative-care concerns measured by the POS (including practical matters, impacts on family, and information needs), and that this is likely due to poor conceptual overlap between the two instruments. Palliative-care researchers have

long since raised concerns about the appropriateness of generic PBMs in palliative care particularly EQ-5D, which has been criticised for its focus on physical function, and the absence of important palliative-care domains. However, until now, the extent and significance of these concerns had not been demonstrated empirically. This analysis is the first to substantiate the anecdotal concerns about the relevance of the EQ-5D in palliative care as the results showed low correlations and low conceptual overlap between the two instruments. This suggests that the two instruments do not measure the same things. This analysis also showed that algorithms for mapping between the two instruments had unacceptably high errors – much higher than the published minimally important differences for the EQ-5D. This means that the mapping algorithms are likely to be insensitive to small but important changes. Therefore, the mapping approach is unlikely to provide an appropriate basis for estimating utilities for conducting CUAs in palliative care studies. Although we did not assess the relevance of other generic PBMs like the SF-6D and HUI3 in palliative care, it would be reasonable to expect similar conclusions because, like the EQ-5D, important palliative-care domains like practical matters and family concerns are missing. Because the preliminary factor analysis conducted in this analysis indicated a low conceptual correspondence between the POS and EQ-5D, the findings of the mapping analysis were not surprising, and so we proceeded to develop a new palliative-care-specific PBM from the POS. However, had the mapping analysis produced an acceptable algorithm, then we might have reconsidered the need for developing a palliative care preference-based measure. Nevertheless, it is noteworthy here that because the application of mapping increases the uncertainty and error around the resultant utility estimates, it is at best considered an inferior option to directly obtaining utility values [215]. However, where appropriate; it is a less burdensome option for patients and their family than creating a new measure.

Deriving a palliative-care-specific health classification system (objective 2)

Having determined that the EQ-5D misses important palliative care concerns and that it would be inappropriate to obtain utilities via the mapping approach, the second objective was to develop a palliative-care-specific PBM from the POS. In order to achieve this it was necessary to construct a simplified health state classification from the POS which would be amenable to valuation as the original 10-item POS describes a practically unmanageable 3,515,625 distinct health states.

Valuing such a large number of health states would impose unreasonable cognitive burden on respondents, particularly patients who are already burdened with illness.

This analysis was conducted according to the guide for developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome)[89]. Following Rasch and factor analyses on pooled data sets (which were split into two halves: one for development; and the other for validation) we derived a unidimensional health state classification which comprises seven items, each with 2-3 categories, and describes a total of 1,458 distinct health states. The health state classification was validated by repeating the above procedure on the validation data set. Of the 1,458 POS-E health states, the analysis identified 14 health states that were suitable for valuation as they span the severity spectrum of the scale.

Although this method of using Rasch to select health states for valuation has been criticised for generating a small number of health states – in this instance 14 out of a possible 1,458 – it addresses a serious and frequently encountered problem associated with more conventional methods (such as orthogonal[216], and factorial designs[217]) wherein implausible health states are selected for valuation. Selecting implausible health states for valuation is particularly problematic where the items/domains in a questionnaire are correlated – as is the case with the POS – because conventional designs assume that items are uncorrelated. Indeed, it is more likely than not for palliative care problems to be correlated. For example, it would seem implausible to define a health state where a person feels 'good about themselves always' and simultaneously feels 'depressed all the time' or; has 'overwhelming pain' and at the same time feels 'no anxiety' about their illness. The implication of including implausible health states in valuation studies is that it is likely to confuse participants and consequently may affect the validity of the preference weights. Indeed this was the case in the valuation study by Versteegh et al. [218] which used a fractional factorial design to select a sample of health states for valuation based on three condition-specific measures (Health Assessment Questionnaire for arthritis, Quality of Life Questionnaire for Cancer, and Multiple Sclerosis Impact Scale) [218]. Because the items were highly correlated, one of the health states selected for valuation consisted of the illogical combination of "able to get up from a chair" and "not able to get up from the toilet", which the authors admitted caused confusion among the participants.[218]

Eliciting values for a sample of POS-E health states (objective 3)

Having constructed a simplified health state classification consisting 1,458 distinct health states, and identified 14 plausible health states suitable for valuation, the third objective was to obtain value sets for the 14 health states directly via a valuation survey. This study was also conducted according the guide for developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome) [89]

The 14 POS-E health states identified via Rasch analysis were valued by both people receiving palliative-care and healthy people using a modified version of the time-trade-off (TTO) technique. The mean health state valuations ranged from 0.216 (for the worst health state) to 0.991 (for the best health state). The mean value for the best health state was slightly less than 1. This is because one of respondents felt that the best health state (0000000; equivalent to no palliative care problems) was not equivalent to full health and so affirmed ratings that were equivalent to a utility value of 0.8 in the TTO survey. Nevertheless, this did not significantly impact on the overall POS-E value set as the vast majority of respondents felt that the best health state was equivalent to full health and correspondingly affirmed TTO ratings that were equivalent to a utility value of 1. However, the preference value for the worst health state (2222212) was much higher than those of generic PBMs like the EQ-5D (minimum value of – 0.22 for the POS-E compared to – 0.59 for the EQ-5D UK value set). This is because considerably fewer POS-E health state values (8 out of 808) were judged to be 'worse than dead' compared to the EQ-5D value set (1% compared with over 30%). While seven out of the eight health states rated as 'worse than dead' were from healthy people, only one was from a patient. This means that participants, particularly patients, were averse to giving negative TTO values. In other words, participants were unwilling to choose immediate death over living with the varying durations of even the poorest health states described by the POS-E. Although we cannot fully explain the reason for this from our data, it is conceivable that the shorter TTO duration we used in the valuation study may have influenced the results in this way. Indeed, previous studies have shown that duration impacts significantly on preference values in that preference values are a decreasing function of duration.[93, 212-214] This suggests that impaired health states – particularly the more severe ones – are considered more intolerable as the time spent

in them increases. Our study supports the hypothesis that impaired health states are more tolerable the shorter they last. Within the context of palliative and end-of-life care, it is conceivable that, regardless of the severity of a health state, people (particularly patients nearing the end of life) require a minimum amount of time to prepare for death – e.g. to settle their affairs and say goodbye to loved ones – and therefore will be less inclined to accept immediate death in order to avoid even the most severe health states. Also, they may be more likely to have experienced these poor health states and see they can cope – more so than someone with no experience. This change in people's attitude towards quality of life improvements as time runs out has been documented elsewhere – the so called "indifference to health quality at short duration" [219]. Miyamoto et al. demonstrated this concept using the TTO in a sample of 64 patients aged between 20 and 50 years, with a variety of life limiting conditions (including cancer, heart disease, diabetes, arthritis), [219] where none of the patients with less than one year to live were willing give up any that time in exchange for better quality of life [219]. This 'indifference to health quality at short duration' was not observed in patients who had more than one year live [219].

Pain and other symptoms had the largest impact on the valuations for both groups, while practical matters did not seem to have any impact on healthy people. It is perhaps to be expected that the impact of practical matters would be less tangible to a much younger and healthier group, when compared with the older and much sicker patient group.

Noticeably, at an aggregate level, the agreement between respondents' valuations were higher for health states that were closer to full health, i.e. the variation (standard deviation) in TTO values seemed to increase with decreasing severity of health states. Nevertheless, from inspecting the valuation data at the individual participant level, there was no indication that the two groups of participants differed in their use of the scale, as their respective slopes (which indicate the relationships between utility values and health-state severity), and distribution of preference values were very similar. This could mean that fundamentally there is little heterogeneity of participants in their views about death.

Despite the severity of their illnesses, patients were willing and able to participate in the valuation survey, producing value sets that corresponded well with the severity levels of the health states. Although further psychometric evaluation is needed, this level of consistency is re-assuring as it supports the validity of the POS-E value set. Indeed, several valuation studies wherein the TTO method was used have raised concerns that some participants refuse to trade any lifetime in exchange for health improvements – the so-called "zero-traders".[220-223] For instance, in one study of 93 people with advanced cancer,[220] and another of 68 elderly people who had lost physical autonomy,[223] over 50% of the patients were zero traders. This resulted in a median preference weight of 1 (perfect health), thereby compromising the validity of the resultant value set. Some of the reasons cited by zero-traders for their unwillingness to trade include that they didn't understand the rational for the questions (especially among older participants),[224] the questions were too hypothetical, [222] and that questions were against religious or personal principles.[222] There were no zero-traders in the POS-E valuation study. The feedback from the POS-E PPI group likely contributed to this by highlighting issues and suggested improvements, including on the clarity of the study rational in the information leaflets, the questions in the questionnaire, the examples used in the TTO exercise, and the TTO training manual.

Are patient values different from those of healthy people?

In this study, patient-derived values were largely similar to those derived from healthy people, although there were some areas of divergence around pain, other symptoms, and practical matters. This similarity between the two groups was somewhat surprising as healthy people were significantly younger – by 20 years on average – and less educated than the patient group. Although this could be interpreted to mean that both general public- and patient-derived values could be used to inform resource allocation patients, it would be prudent to exercise caution here because we did not test for statistical significance, as the study was not powered for this exploration. Furthermore, the group of healthy people in this study were recruited as a convenience sample and so would not be considered representative of the general public. It is difficult to compare our findings with other studies in this regard because no other similar studies have been conducted in palliative care.

The evidence in other non-palliative-care disease groups is mixed. It appears there is a wide variation in the difference between patient and general population values, and this variation appears to be driven by several factors including the specific disease group/diagnosis of the patients, and the preference elicitation method used (e.g. VAS, TTO etc.). Krabbe and colleagues[209] found that while preferences derived from patients with cancer and patients with rheumatoid arthritis were similar to those of healthy people when the VAS was used, patient derived preferences differed significantly from those of healthy people when TTO was used. Regarding diagnosis, the study by Little and colleagues[225] found that while values obtained from patients with cancer and patients with stroke differed significantly from those of the general public, values from patients with diabetes and with myocardial infarction were similar to those of the general population. Schwalm and colleagues[210] found statistically significant (but small) differences between healthy volunteer valuations and valuations from patients with musculoskeletal disease in only 6 of the 42 health states examined. Arguably, however, the most robust evidence on the difference between patient and population valuations comes from Dolders and colleagues[211]. The authors conducted a systematic review and meta-analysis of 78 preference estimates from 33 articles comparing directly elicited patient and general population preferences. They found no significant differences between patient and general population valuations, and concluded that valuations from both can be used for resource allocation.

Although, the results of our study appear to support this conclusion, it is not possible to rule out alternative explanations for our findings. For example because the majority of the convenience sample of healthy volunteers were recruited from hospital and hospice volunteer services, they arguably would better understand the impact of advanced life-limiting illness on patients and their family than the general population. This could explain why patient-derived preference values were similar to those of healthy volunteers in this study. The fact that our results show little heterogeneity of participants in their views about death – as previously discussed – supports this notion. Clearly, further research will be required to further explore these areas.

Modelling valuation results to produce preference values for all other POS-E health states (objectives 4 and 5)

Having obtained value sets for the 14 POS-E health states directly via a valuation survey, the fourth and fifth objectives were to estimate preference values for the remaining 1,444 health states using regression modelling, and to produce an algorithm for estimating QALYs. This involved using regression models to estimate the relationship – in the form of a mathematical equation – between the preference values obtained from the valuation survey for of each of the 14 health states, and their corresponding Rasch logit score. We subsequently used this mathematical relationship between preference values and Rasch logit scores to estimate the preference values of other POS-E health states (which were excluded from the valuation survey) based on their respective Rasch logit scores. Having tested several models, the model chosen for estimating the mean preference values of all other POS-E health state was the one which included linear, quadratic, cubic, and quartic terms, as it had the least predictive error and best explained the variation in the preference values obtained from the valuation survey (as indicated by low RMSE and high R-squared values), and its coefficients were all statistically significant.

Taken together, the output of this thesis leads to POS-E, a unidimensional PBM, comprising 7-items, which was developed following Rasch analysis and psychometric assessment of POS data from palliative care patients with a variety of diagnoses in hospital, hospice, and community settings in the UK. Therefore, it is suitable for use in a wide range of services and settings, and can capture the full spectrum and range of symptom severity of palliative care concerns, as confirmed by the Rasch analysis used during its development. The POS-E value set has good internal consistency as indicated by the logical correspondence between POS-E values and the severity levels of the health state classification. Overall, although more work is required to validate the POS-E in a larger study, the results are encouraging.

8.3. How does POS-E compare with other palliative care preference-based measures?

The POS-E is the first palliative-care-specific PBM of health. Currently, the only condition-specific preference–based measure that is directly comparable to the POS-E is the ICECAP-Supportive Care

Measure (ICECAP-SCM)[66, 207] which measures capability rather than health (or functioning). Value sets for this measure have recently been published.[66] In what follows the similarities and differences between the POS-E and the ICECAP-SCM will be explored with a particular focus on their respective evaluative frameworks and overarching concepts.

Comparing the POS-E to ICECAP-SCM

The ICECAP-SCM was developed specifically for measuring capability for use in economic evaluations of end-of-life care.[207, 208] This measure was developed via in-depth interviews with older people: in the general population, in residential homes, and receiving palliative care. It comprises 7 items including choice, love and affection, physical suffering, emotional suffering, dignity, being supported, and preparation.

The concept of capability is based on the theory of assessing wellbeing, and was developed by Amartya Sen.[127, 226] Sen defined wellbeing as comprising "functionings" (a person's *achievements* i.e. observed outcomes including achieving good health / death), and capabilities (combinations of potentially achievable functionings that are available to a person e.g. the *opportunity* to achieve a good health / death).[119]

The developers of ICECAP-SCM argue that capabilities, rather than functioning, should be the focus of evaluation. The author's employ Sen's example of "*a person who is starving due to lack of food compared with a person for whom food is freely available but who chooses to fast, to illustrate why capability (ability to eat in this case), rather than functioning (having eaten), should be the important focus of evaluation*".[119, 226] They then attempt to consolidate this point by providing an example in the context of end of life care of "*two individuals, one living in an area where there is hospice provision and one where there is not. The former may not choose to use the hospice care available, preferring to receive care from family members; the latter, who may not have family and would have used hospice care if it had been available would look the same as the first individual in terms of functioning (i.e. no hospice care received), but in terms of capability (ability to access hospice care) is clearly worse off*".[119] The salient point in both examples is that the capability approach allows for choice; enabling people to decide how to manage the end of their life. However,

the latter example on access to hospice inadequately illustrates the intended message as the two individuals would be not be expected to have the same levels of function as indicated because the person who chose not to access hospice is still receiving care all be it from family members, while the second person is getting no care whatsoever. Nevertheless, these examples, as well as many others that have been used to argue for capabilities, clearly (and appropriately) relate to assessing wellbeing and subsequently the decision to intervene. In other words, intervening to provide food for a person who is starving due to lack of food might be more appropriate than intervening to provide food for a person fasting. Likewise, intervening to provide hospice care for a palliative care patient living in an area without hospice might be more appropriate than intervening to provide hospice care for a person living close to a hospice but chooses not to use this service because they receive the care they want from their family.

However, because the ICECAP-SCM has been designed as a tool for economic evaluation, it explicitly aims to assess the benefits of interventions. In addition, if the aim here is to evaluate the benefits of interventions, then the argument for assessing capabilities (the possible effects) rather than functionings (the actual effects or outcomes of an intervention) seems weaker. It is possible to argue against helping someone who has the capability to access hospice care, but chooses not to access it. It is much less convincing to argue that the effects of an intervention designed to improve the access to hospice / palliative care should be based on possible and not actual access. Furthermore, the argument for incorporating choice in this way becomes even weaker when health-seeking behaviour is considered. To justify the need for measuring capabilities based on the necessity to incorporate choice we will have to believe that there are people who seek health care but actually do not want it. In almost all instances, health care is offered to people who seek it – and not forced on people universally – therefore it would be reasonable to assume that a person seeking healthcare has chosen to do so because they want / need it. Using the same example above, a person who is asking to be fed is unlikely to be voluntarily fasting at same time.

Furthermore, several authors have viewed widening the evaluative space as one of the advantages of the capability approach. The evaluative space here refers to the domains included in the descriptive system i.e. the set of capabilities or functionings that are being evaluated, and also who

is included within the evaluation[119]. The QALY approach has been criticised for being too narrow because its evaluative space focuses solely on health/utility (e.g. pain, and mobility) and excludes non-health domains, while the capability approach includes higher order non-health domains (e.g. 'love and affection' in ICECAP-SCM) as well as impacts on people beyond the patient (e.g. family), and therefore is considered to have a wider evaluative space. Although there is a strong argument for broadening the evaluative space beyond just health in the context of palliative and end-of-life care, it is not obvious that the capability approach is needed to expand health-related measures to include non-health domains and impacts on family. The POS-E for example, incorporates non-health domains like practical matters, and also domains that capture impacts on family (e.g. family anxiety), and therefore could equally be considered to have a broad evaluative space. Yet the POS-E assesses functionings and can be used for evaluations within the QALY framework.

Another important distinction is the proposed valuation method. The best-worst scaling [83] method was used to derive value sets for the ICECAP versions for older people and has been proposed for the ICECAP-SCM.[64] In this method, death is assumed to be the absence of capabilities – on a philosophical basis – and so the instrument is anchored at 0 for no capability and 1 for maximum capability.[83] However, this seems conceptually odd, as it is not obvious that not having "the opportunity to make any of the preparations I want to make" and being alive is the same as not having it because I am dead. In other words, although it is obvious that a dead person will have none of the seven capability domains included in the measure, a person might be alive and yet lack same capabilities.

A final difference is in the definition and identification of the target patient group. While the POS is designed for evaluations in palliative-care patients (encompassing all people with advanced life-limiting conditions), the ICECAP-SCM is designed for evaluations in people at the end-of-life which developers define as people in the last year of life [208]. An obvious problem with this – as acknowledged by the developers – is that it is difficult to determine prospectively when a person is in the last year of life.[119]

Generally, the main differences between the ICECAP-SCM and instruments like POS-E are the constituents – rather than the breadth – of its evaluative space, and the shift from assessing functioning to capability. Clearly, expanding the evaluative space does not require the capability approach, and valuing capabilities presents conceptual challenges. Instruments like the POS-E, which evaluate functioning, are able to expand the evaluative space to include non-health attributes. Therefore, the conclusion here is not that one is superior to the other but that the two concepts (capability and functioning) are different with each being more appropriate in different circumstances. Emphasising the rational for the choice of constituents of the evaluative space rather than its breadth seems more important. This suggests the need to reflect, in each situation, on whether capabilities or functioning would be more appropriate. Doing so would illuminate the intrinsic value of capability measures including ICECAP-SCM as measures that are particularly suitable where health outcomes (or functioning) are not the focus of evaluation – e.g. social care interventions. Palliative and end-of-life care include aspects of both health (e.g. pain) and wellbeing (e.g. availability of social support), among other things, thus in the context of palliative care, the POS-E and ICECAP-SCM can be regarded as complementary rather than mutually exclusive. Dismissing one for the other would be akin to cutting off one's nose to spite one's face.

Comparing POS-E to other condition-specific preference-based measures for people with chronic life-limiting conditions

In what follows, the POS-E is compared against a selection of condition-specific preference-based measures for people with chronic life-limiting conditions (table 7). These measures were selected on the basis that some, though not all, of the patients at whom such measures are targeted would be expected to have palliative care needs. All but two measures were developed from pre-existing measures, like the POS-E. The TTO was the commonest valuation method used. Notably, the utility range of the value sets in table 7 are comparable to those of the POS-E, with the exception of ICECAP-SCM whose extreme values were fixed at zero and one respectively on theoretical grounds as discussed previously. Indeed besides ICECAP-SCM values, the upper and lower limits of the value sets were less than one and greater than zero respectively. Like the POS, Rasch analysis was employed in the initial stages of developing a simplified health state classification system prior

to valuation for the more recently developed measures including: the Asthma Quality of Life Questionnaire (AQLQ) [45]; the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire C-30 (EORTC QLQ-C30)[42]; and the Clinical Outcomes in Routine Evaluation–Outcome Measure (CORE-OM) [200]. Also like the POS-E, the rationale for developing these condition specific measures were based on the limitations of generic preference-based measures including: the insensitivity to small but important changes in the case of the EORTC QLQ-C30 [42]; the narrow focus on health and exclusion of impacts on family in the case of the ICECAP-SCM; the exclusion of important domains in the case of the CORE-OM [200]; and the opportunity to facilitate broader economic evaluations using existing datasets in the case of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [227].

The POS-E value set differs from these measures mainly in that: healthy volunteers were not representative of the general population; it includes patient preferences, albeit with a relatively small sample size, and the accompanying changes made to MVH protocol to account for specific palliative care concerns, including using a shorter TTO time frame. Altogether, although further evaluation is required, the methods used to derive the POS-E value set appears comparable to those used to derive value sets in majority of other condition-specific preference-based measures for people with chronic life-limiting conditions.

Table 7: Selection of condition-specific preference-based measures for people with chronic life-limiting conditions (adapted from Brazier and Rowen 2011 [228])

Condition	Measure derived from	Dimensions	Item categories	Health states	UK population values	Valuation technique	Evaluative space	Range of value set
Asthma [103, 229]	Asthma Quality of Life Questionnaire (AQLQ)	Concern, short of breath, weather and pollution, sleep, activities	5	3,125	Yes	TTO	functioning	0.39-0.94
Cancer [230]	EORTC QLQ-C30	Physical functioning, role functioning, pain, emotional functioning, social functioning, fatigue and sleep disturbance, nausea, constipation and diarrhoea 4-5 81920 Yes TTO Erectile (dys)functioning37 Index of Erectile Function (IIEF) Ability to attain an erection sufficient	4-5	81,920	Yes	TTO	functioning	0.13-0.95
Lung cancer [231]	FACT-L	Physical, social/family, emotional, functional, symptoms - general symptoms – specific	2	64	Yes	VAS	functioning	0.111-0.703
Parkinson's disease [232]	N/A	Disease severity, proportion of the day with 'off-time' (impact on quality of life due to condition covering domains: social function, ability to carry out daily activities, psychological function)	2-5	10	NO	VAS and SG	functioning	VAS: 0.17-0.83; SG: 0.49-0.85

Pulmonary hypertension [227]	Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)	Social activities, travelling, dependence, communication	2-3	36	Yes	TTO	functioning	0.136-0.962
Palliative and end-of-life care [154]	Palliative Care Outcome Scale (POS) [147]	Unidimensional (pain, other symptoms, anxiety, feeling good, family anxiety, depression, and practical matters	2-3	1,458	No	TTO	functioning	0.22-0.991
Mental disorders [200]	Clinical Outcomes in Routine Evaluation–Outcome Measure (CORE-OM) [233]	Emotional, and physical	3-5	729	Yes	TTO	functioning	0.23-0.96
End-of-life care (ICECAP-SCM)	N/A	Choice, love and affection, freedom from physical suffering, freedom from emotional suffering, dignity, support, and preparation	4	16,384	Yes	BSW and DCE	capability	0-1
TTO: time trade off; VAS: visual analogue scale; BSW: best worst scaling; DCE: discrete choice experiment; SG: standard gamble This table was adapted by including the POS-E and ICECAP-SCM to the original table.								

8.4. Strengths of this thesis

8.4.1 Addressing limitations of the QALY

An important strength of this thesis is that it addresses some (but not all) of the criticisms of the QALY described in chapter (2.4) as follows:

1) Imprecision of the QALY: the QALY has been criticised for excluding important palliative care domains. The POS-E addresses this by incorporating important palliative care concerns like 'feeling good about myself' into QALY calculations. The QALY has also been criticized for being too narrow by focussing solely on health gains. The POS-E addresses this issue by incorporating broader non-health domains like "practical matters" into QALY calculations. Furthermore, incorporating 'practical matters' into QALY calculations is in line with McNamee's plea for the inclusion of process factors into the QALY framework [114], although other important process factors like continuity and coordination of care are still missing. Likewise, the QALY has been criticized for its narrow focus on individual health benefits. The POS-E addressees this issues by incorporating impacts of family ("family anxiety") into QALY calculations.
2) The POS-E partially addresses the issue of non-additivity of time – due to instability of patient preferences – by using a time frame (10 months instead of 10 years) that represents the life expectancy of palliative-care patients in the valuation survey. However, the POS-E does not address the heightened value of time at the end of life. As discussed in section 2.4, this issue can be addressed by applying equity weights to reflect the additional value of time at the end of life. However, this is beyond the scope of this thesis. However, there are aspects of the non-additivity argument have not been addressed. For example, the QALY assumes that the value assigned to a given health states is not affected by the experiences (or outcomes) that precede or follow the health state. This suggests that a health state comprising say two months of severe depression followed by full recovery is valued the same as a health state comprising two months of severe depression followed by death. However, evidence suggests that this assumption, although reasonable for population values, is violated at the individual level [234], and perhaps more so for patients at the end-of-life. This suggests that, without accounting for contextual

factors, equal amounts of time are not additively separable at the individual level. It remains unknown whether the issue of non-additivity of time is significant at an aggregate level at the end-of-life.

8.4.2 Contribution to valuation methods

Another advantage of this thesis is that it contributes to the methodology for valuing health states. The POS-E study is the first valuation study to include palliative care patients and possibly patients at the end of life. This study demonstrates that it is feasible to obtain meaningful values from patients with severe and life-limiting illness. The standard protocols and questionnaires for valuation studies were not designed for use with patients, and so are neither directly applicable nor appropriate, particularly for patients with life limiting conditions. In designing the POS-E study a number of factors were taken into account including: ethical considerations of including severely ill patients in valuation studies; the need for the active involvement of clinicians in screening and identifying appropriate patients; and the phrasing of questions in the questionnaires to ensure that the questions were appropriate, particularly for patients with life limiting conditions.

By comparing patient and healthy volunteer values, it also contributes to the debate about whose values should be used. If, as indicated by the results of the POS-E study, patient values are similar to those of healthy people, then it would be appropriate for future valuation studies to use healthy population values – given that there are fewer ethical concerns with this approach. However, given the sample size limitations of the POS-E study, more research is needed.

8.4.3 Conducting economic evaluations of palliative care interventions

Conducting cost-utility analysis in palliative care has been challenging. Generic preference-based measures, which are used to calculate QALYs, are often excluded from palliative care studies, perhaps reflecting the unacceptability of such measures amongst researchers in palliative care. There are examples of economic evaluations of palliative care interventions where the ICER was expressed as cost per change in the score on a continuous scale, for example the multiple sclerosis study by Higginson et al[235]. The intervention in this study was more effective and cheaper than its comparator (a case of simple dominance), and so in this instance it was easy to judge the value for

money of the intervention. However, in the more commonly encountered situation where an intervention is more effective and more costly it would be near impossible to make value judgements based on scores of such non preference-based scales. Conversely, generic PBMs may miss important palliative care benefits as they do not incorporate palliative care domains [196]. The POS-E aims to address this issue as it can be used in cost-utility analysis of palliative care interventions. The results of such analyses will enable value judgements of interventions to be made more readily when compared with economic evaluations that use non preference-based scales.

Another strength of the POS-E is that it can be used as a universal PBM for all patients with advanced chronic illness. This is because the original scale, POS, was designed as a universal measure of palliative care problems in people with advanced life limiting illness including cancer and non-cancer cases.

8.5. Challenges and limitations

Limitations of stage 1: Mapping the POS onto the EQ-5D

An important limitation of this stage is that the analysis was based on data pooled from six, studies as the individual studies were based on relatively small samples. However, because the data were from patients with a variety of diagnosis including cancer and non-cancer, it is conceivably a reasonable reflection of the diverse diagnoses of palliative care patients and therefore more generalizable. This limitation also applies to the analysis in stage 2A. Furthermore, although the mapping analysis included the most commonly used generic preference-based measure (EQ-5D), other generic preference-based measures like the SF-12 were not included as the required data was not available. Therefore, the findings here apply to the EQ-5D only.

Finally, although three regression models were tested in this analysis, many others were not assessed e.g. Tobit models, Two-part models, and Generalized linear models [215]. However, the poor conceptual overlap between the POS and EQ-5D – as indicated by factor analysis – suggests other models would have likely yielded similar results.

Limitations of stages 2A, 2B and 2C: Developing a palliative care specific preference-based measure (POS-E)

The POS-E has a number of limitations. First, the POS-E is not an independent measure; its 7 items are embedded in the 10-item POS. Extracting the 7 POS-E items from the POS may affect the meaning, intensity and relative importance of each of the 7 items, which, consequently, affect the responses obtained. Although evidence suggests that the response rates and quality of responses to instruments extracted from longer questionnaires are unaffected by the length of the questionnaire [236], it is unclear whether and to what extent the context of the longer questionnaire affects responders, and whether extracting a small number of items (e.g. POS-E items) out of the context of a longer questionnaire (e.g. POS), affects the validity of responses. Although in practice it might seem tempting to use the POS-E as an independent measure in studies (in place of the POS) given its brevity and function as a utility measure, theoretically it might produce different responses from what would be obtained using the original POS.

A study comparing SF-6D preference values obtained directly as independent measure to those derived from responses of the SF-6D found significant differences between the two value sets, [237] and so concluded that the SF-6D should be used to derive preference weights for the original SF-36, and not as an independent instrument. However, it is noteworthy that two different versions of the SF-6D were used: the $SF\text{-}6D_{SF\text{-}36}$ (derived from the SF-36); and the $SF\text{-}6D_{SF\text{-}12}$ (the 'independent' SF-6D derived from the SF-12). Some of the dimensions of the $SF\text{-}6D_{SF\text{-}36}$ were derived by combining 2-3 items from the SF-36, whereas the dimensions of the 'independent' $SF\text{-}6D_{SF\text{-}12}$ were obtained directly from single SF-12 items[237]. This difference in the constituents of the dimensions of the two SF-6D versions might partly account for the discrepancy in the two value sets derived. Conversely, the POS-E items are derived exclusively from individual POS items, and hence, besides differences in response levels, the 7 items of an 'independent' POS-E should correlate with the corresponding 7 items of the POS. This suggests that compared to the SF-6D, the POS-E is perhaps more likely to be established as an independent measure. Nevertheless, the appropriate recommendation here would be to delay using the POS-E as an independent instrument until further research demonstrates its appropriateness as such.

Second, the healthy volunteers used in the valuation study are not fully representative of the general public, thereby limiting the generalisability of the findings and also making it difficult to compare POS-E values to those in other studies. For example, the EQ-5D was valued by 3,235 members of the general public [25]. The limited time and resources constraints of this PhD meant that it was not feasible to recruit a representative sample of the general public.

Third, the sample size was too small to detect a 10% difference between the valuations in the two groups, but was sufficient to estimate mean preference weights for each health state.

Limitations of the MVH TTO protocol

The MVH TTO protocol that was used in the POS-E valuation survey has a number of weaknesses, which are discussed in what follows.

The first weakness of the MVH TTO protocol is the effect of participants' age on valuations.[93, 238] It is conceivable that using a 10-year time horizon in the valuation exercise, as is the case with MVH protocol, may be too generous for older respondents (particularly palliative care patients) as discussed earlier but too brief for younger ones. However, the evidence around the impact of age on health state values suggests that differences in valuations between young and old respondents would have persisted if participants' life expectancy, rather than a fixed time horizon, had been used [239 240]. It is unlikely that this limitation of the MVH protocol had a substantial impact on the POS-E value sets, as patient derived values were similar to those from the significantly younger healthy volunteers. Moreover, we used a much shorter time frame (10 months), as discussed earlier, to reflect the life expectancy of palliative care patients.

The second weakness concerns the procedure for the valuing states that are worse than dead. One of the concerns with this procedure is that it includes the scenario of moving from poor health to full health, which might be deemed unrealistic, particularly in the context of palliative care. However, reversing the scenario so that full health precedes poor health risks the danger that participants may feel that they can commit suicide at the end of their time in full health[42]. Another concern is that this procedure for valuing states worse than dead is somewhat different from the procedure for valuing states better than dead. For states worse than dead the duration of the time

spent in full health is varied simultaneously with the time in the health state subject to valuation, while for states better than dead the duration in the health state to be valued is fixed and only the time spent in full health is varied. Often this can be confusing for responds, as it is obvious that the valuation procedure has changed and a new task is introduced. But a more serious consequence of using different valuation procedures for the two different scenarios is that it creates a 'gap effect' in the TTO values around death where "*the differences in TTO values for states either just above or below zero are at least twice as large compared with the differences between other adjacent states"* [241] [242]. This means states worse than dead are likely to be considerably worse than dead. Whilst this may reflect real respondent preferences, it is not possible to rule out effect of this particular feature of the MVH protocol. Although this gap effect for states worse than dead was observed in the POS-E study, we are inclined to believe that it does not have a serious impact on our results as only eight of the 808 POS-E health state valuations were rated as worse than dead.

The third weakness of the MVH protocol concerns the transformation of values for states considered worse than dead so that the minimum value possible is –1. Based on the TTO theory the standard formula for calculating the utility value of a health state considered worse than dead is $-x \div y$ where *y* is the initial time spent in the health state to be valued (also considered to be worse than dead), which is then followed by a given period of time in full health *x*. But, when using the TTO protocol where t = 10 (years) this yields utilities with a minimum possible value of −39 for any health state, where $x = 9.75$ and $y = 0.25$ implying that the participant is indifferent between the two scenarios (1) health state to be valued for 3 months (*y*), followed by full health for nine years and nine months (*x*); and (2) immediate death. This means TTO values for states worse than dead could potentially achieve a wider range (0 to –39) than values for states better than dead (0 to 1). This creates problems when using TTO values in the regression model used to estimate preference weights for all states defined by the classification system, because worse than dead responses have a larger impact on the model predictions than better than dead responses. One of the methods proposed to address this issue is to rescale the values to a minimum of –1 using either the formula proposed by Dolan $(-x/t)$[93], or the one by Shaw and colleagues $(\frac{-x/y}{z})$[243]. However, these transformed values can no longer be interpreted as utility values on the same utility scale as

states better than dead[244], because such transformation is based neither on empirical evidence nor on theory.

Two other approaches have been developed to address the problems with health states worse than dead. The first approach involves using a different modelling technique – the episodic random utility model (RUM)[245] – to estimate preference weights for all states defined by the classification system. This approach is based on the notion that in the aforementioned transformation by Dolan, the error constituents assigned for better-than-dead states are different from those of worse-than-dead states thereby producing unbalanced estimates, whereas the episodic RUM approach assigns the same error constituents therefore producing balanced estimates. In other words, when estimating preference weights for all states defined by the classification system, the episodic RUM model treats all TTO responses equally. However, this alternative method only addresses the approach to modelling existing TTO data, but the aforementioned issue of different TTO tasks for better than dead and worse than dead states still exists. This led to the development of the second approach which uses the same TTO task to value all states. This second approach developed by Devlin and colleagues, [187] incorporates a period in full health – the "lead time" – to the beginning of the normal TTO task, thus valuing states worse than dead by decreasing the lead time, and using the same method for states better than dead. This method has the advantage that it does not draw attention to the fact that participants are valuing a state as worse than dead, however the risk here is that respondents may not be fully aware of the implication of their responses. Furthermore, this approach substantially assumes 'additive separability', where it is assumed that the value of a health state remains unchanged whether or not it is proceeded by a period of full health. Also, the long overall time period of this approach (up to 20 years) may be unrealistic for older respondents and palliative care patients in particular, and in the pilot study for this approach some participants used up all of the lead-time. The EuroQol group are conducting further research into this new approach.

Admittedly, the POS-E study suffers from this third weakness of the MVH protocol. Also, the deviations of the methods of the POS-E study from the norm makes it difficult to compare the POS-E value sets with those of the EQ-5D, which is necessary if the POS-E is to be considered in decision making contexts by bodies such as NICE. However, the most recent NICE methods

guidance no longer requires the same valuation method with that adopted for EQ-5D when alternative PBMs are used for the estimation of QALYs.[130]

8.6. Research implications

Because of the widespread use of the POS in assessing palliative care outcomes in the UK, the preference based POS-E, subject to further validation, is expected to facilitate broader assessments of value-for-money of palliative care interventions. The POS-E can be used in palliative care studies in the future e.g. to conduct economic evaluations alongside clinical trials. Given its brevity, it is unlikely to cause significant burden to patients especially if people are already using POS.

Further, in instances where studies have included the original POS but no other generic preference-base measures, POS scores can easily be mapped onto the POS-E to calculate QALYs. The ability to map the POS onto the POS-E also means that cost effectiveness analysis can be done retrospectively using POS data from previous studies.

Beyond the UK, POS is routinely used in 126 other countries, as validated translations are now available in about 14 other languages, including Dutch, French, German, Italian, Japanese, Spanish, Norwegian, Portuguese, and Chinese. It is possible to use the POS-E in regions that use translated versions of the POS although further research will be required to enable this.

Beyond academia, the POS-E may be relevant to industry. New oncology treatments are progressively targeting advanced disease and people at the end-of-life. For example, Methylnaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care [246]. The POS-E will be useful in evaluating interventions in other life limiting conditions. New treatments targeting patients with life limiting conditions are expected to yield only small gains in quality (and length) of life, thus these patients are like to differ from patients without life limiting conditions whose expected health gains are considerably larger.

8.7. Policy implications – can the POS-E be considered in NICE's decision making context?

Although the EQ-5D is NICEs preferred instrument for estimating QALYs when assessing the cost-effectiveness of different competing interventions, NICE's methods guide states that alternative preference-based measures to the EQ-5D will be considered in instances where EQ-5D is inappropriate or EQ-5D data is not available [228]. In the absence EQ-5D data, NICE's methods guide further expresses a preference for using mapping techniques to derive EQ-5D values rather using an alternative preference-based measure [169]. In instances where the EQ-5D is thought to be inappropriate for assessing benefits in a specific patient group, such assertions must to be substantiated by evidence in order to justify using an alternative to the EQ-5D [228]. Alternatives to the EQ-5D include other generic preference-based measures, condition-specific preference-based measures, health state vignettes, or the direct valuation of patients own health (e.g. via the TTO method). Alternative condition-specific preference-based measures developed from validated patient-reported outcome measures can be used [228]. The values should be based on UK general public values obtained using a choice-based method, ideally the TTO with the same protocol as the UK EQ-5D valuation. The processes involved in deriving the alternative measure need to be described in detail including how the health state classification system was developed and from the original instrument and how its value set was derived; and also how this compares with those used for EQ-5D. Robust empirical evidence should outline the measurement properties of the alternative instrument including validity and reliability. Finally, where EQ-5D data is available, the difference in QALYs gained from using a condition-specific preference-based method instead of EQ-5D.

NICE's criteria[228] can be summarised as follows:

1. supporting arguments and evidence for the choice of alternative preference-based measure;
2. The health state classification system being valued should be based on a validated patient reported outcome measure;
3. The method used to value the health states defined the alternative preference-based measure must be comparable to those used to value the EQ-5D;

4. The effect of using the alternative preference-based measure on the results of economic evaluations should be provided and compared to EQ-5D (where EQ-5D data is available)

So to what extent does the POS-E fulfil NICE's criteria in the above guidance? In this thesis, chapter two provides supporting arguments about the inappropriateness of the EQ-5D in palliative care, while the results of mapping analysis in chapter five provides the evidence demonstrating this, thereby fulfilling criteria 1. The analyses presented in chapter six describes the development of a health state classification system (POS-E) from the POS – a validated patient-reported measure widely used in palliative care – thereby fulfilling criteria 2. As presented in chapter seven, POS-E values were obtained from palliative care patients and a (non-representative) sample of healthy volunteers in the UK using a modified TTO – but nevertheless a choice-based method. Furthermore, although the POS-E exhibited good internal validity (as indicated by the logical consistency of the TTO values with the severity levels of the health state classification), other psychometric properties – e.g. practicality and reliability – have not yet been tested. Therefore, the POS-E, in its current state, only partially satisfies criteria 3. The POS-E currently does not satisfy criteria 4 as it is still in early stages of development and has not yet been used in any studies, although it is currently being considered for inclusion in forthcoming work.

Given the time and resource constraints of undertaking a PhD it was not feasible to assess the psychometric properties of the POS-E in this thesis. However, this is a clear signal for the direction of further research. Overall, the prospect of POS-E being considered by NICE in evaluating palliative care interventions is encouraging. Subject to further validation and large scale valuation using a more representative sample, the POS-E can be used in NICE's decision making context, particularly when assessing palliative care interventions in studies that have not included the EQ-5D. An example of where a palliative-care preference based measure like the POS-E would have been useful was in the NICE clinical guideline on Care of dying adults in the last days of life which was published in 2015 [247]. This guideline encompassed the clinical care of adults (18 years and over) who are dying during the last 2 to 3 days of life and covering a variety of aspects including the management of pain, breathlessness, and nausea vomiting. One of the recommendations was for clinicians to "*seek specialist palliative care advice if the dying person's symptoms do not*

improve promptly with treatment or if there are undesirable side effects, such as unwanted sedation" [247]. However economic evaluation was not conducted for this guideline because the guideline development group identified that there were "*uncertainties around the quantification of health benefit, particularly QALYs*" in this patient group [247]. NICE is currently developing a national guideline – due to be completed in July 2018 – on "End of life care for adults in the last year of life: service delivery" (an update of the 2014 with the same title and scope) [248]. As part of this, I was invited by NICE in 2016 to present evidence on the challenges of conducting economic evaluations in palliative care on the bases of the papers that were published as part of this PhD. Unfortunately, the POS-E has 'missed the boat' for this guideline, given that further evaluation is required. Nevertheless, there is cause for tentative optimism.

8.8. Future research

8.8.1 Validating POS-E in a larger valuation study

The preference-based POS-E was developed with a small number of participants thereby limiting its generalisability. Therefore, POS-E study needs to be repeated in a larger and more representative sample of the general population, and patients (including informal carers and health professionals) to further explore areas of divergence. The psychometric properties of the POS-E also need further evaluation. However, Brazier and Deverill have highlighted that conventional psychometric approaches are only partially aligned with the aims of preference-based measures designed for economic evaluations [73]. They argue that because conventional psychometrics and economic evaluations aim to measure different concepts, both approaches differ with regard to validity [73]. In other words, while psychometric approaches aim to quantify patient-reported change in health status (health outcome), preference-based measures aim to quantify the value or strength of preference for the health outcome. On this basis, they developed a checklist for assessing the measurement properties of preference-based measures of health comprising three concepts adapted from conventional psychometrics of practicality, reliability and validity. Validity was further categorised into three sub-groups as follows: validity of the descriptive system, validity of the valuation method, and empirical validity [73]. The POS-E has already demonstrated good descriptive

validity as indicated by the results in section 6 [publication 3]. The consistency of POS-E values as described in the results section 7.3 [publication 4] demonstrate the internal validity of the valuation method. However, further research is needed to demonstrate practicality, reliability and other psychometric properties of the POS-E value sets.

8.8.2 Deriving preference values for the IPOS

The POS-E was derived from the Palliative care Outcome Scale [147] (POS), which in the near future will be superseded by the broader and more comprehensive Integrated Palliative care Outcome Scale (IPOS) which is currently undergoing psychometric validation. The IPOS incorporates the most important items from POS, POS-S and the APCA African POS. IPOS is a brief tool for global measurement of palliative care concerns, suitable for completion by patients, carers, and health care staff in various care settings. It incorporates the most important palliative care symptoms and includes new broad domains like '*feeling at peace*' while retaining others like '*practical concerns*', '*information needs'*; and impacts on family e.g. '*family anxiety*'.

Therefore, once the IPOS has been fully validated, the logical next step would be to derive and validate a preference-based measure from the IPOS, using in a larger and more representative sample and also incorporate a psychometric validation component.

8.8.2 Other research recommendations

Further research recommendations relating to the outputs of this thesis include mapping the POS onto the POS-E and producing an algorithm for translating POS scores onto the POS-E; translating the POS-E into different languages; and developing POS-E tariffs for other countries.

8.9. Survey recruitment issues

Given the number of study sites involved in the valuation study and the distances between them (one of the study site was based in Newcastle) it was necessary to involve research nurses in recruiting and interviewing participants for this study. However, these interviewers needed adequate training and retraining. This was an area that required a lot of attention and development for several reasons. First, it was necessary for interviewers to learn about specific health economics

principles relevant to the study, which were somewhat abstract and complex. Second, because some of the questions involved contemplating dying (or living for a short period of time) there was a risk that patients, particularly those at the end of life, would become distressed. This required interviewers to be sensitive to patients' emotions and to be able to recognise and manage distress promptly. The ethics committee also raised this issue. Although all interviewers had attended 'good clinical practice' training as well as a 5-hour training session for this specific study was required. It was difficult to agree an ideal time to deliver the training as group, which meant I had to repeat the training numerous times at each site some of which were located quite fare away (e.g. in Newcastle).

Another challenge we encountered during recruitment was that other studies with similar eligibility criteria as the POS-E were running at the same time thereby competing for the same patients. Some sites had two other palliative-care studies running concurrently with the POS-E study. This meant that it took longer than expected to recruit the required number of patients, and so it became necessary to apply to the ethics committee for a study extension. It was also necessary to meet with the leads of the other studies together with the clinical teams to discuss a recruitment strategy that would benefit all parties. We also used other strategies to encourage clinical staff to continue screening including: progress reports on recruitment from all sites so that each site could see how others were performing; staff training; and thank you cards during holidays.

Furthermore, it became apparent that completing interviews with patients would require more than one attempt and in some cases up to four attempts. This was mainly because patients were receiving care from many specialists including therapists, oncologists, and radiologists, and so interviews were often interrupted to accommodate visits from the clinical team. On a few occasions, interviews were interrupted due to illness related fatigue.

8.10. Personal development and learning

This PhD was my second research job. Prior to starting my PhD, I worked as a health economist at the National Institute for Health and Care Excellence NICE (NICE). It was while at NICE that I became interested in cost and health economics issues in palliative care. This was mainly because

there was considerable debate among health economists about the relevance of traditional economic evaluation methods (particularly the relevance of QALYs and cost-utility analysis) in palliative care. This often meant that palliative care guidelines contained as many recommendations for research as there were for best clinical practice. As a result, I was driven to know more about palliative and to better understand the challenges of conducting economic evaluations in palliative care. While embarking on this PhD I developed several academic as well as inter-personal skills. These are detailed in what follows.

Learning academic skills through working with co-authors and supervisors: Having input from co-authors from divers disciplines ensures that research outputs incorporate multiple perspectives; however, one of the disadvantages I experienced with this approach was that sometimes there were conflicting opinions and perspectives. I learnt that in such instances tact, tolerance, and objectivity are key to making progress. Through working with supervisors, I learnt the importance of recognising and acknowledging research limitations as well as the magnitude and direction of the impact of such limitations on the overall findings. Through supervision, I also learnt to the importance of aligning research conclusions with research findings. Embarking on this PhD enabled me to gain a more in-depth understanding of health economics and cost issues in palliative care particularly around the different theories and methods underpinning economic evaluations in palliative care. I also learnt how write academically, and how to develop research ideas including, articulating arguments to justify the need for research, developing study protocols, designing questionnaires, and piloting studies.

Engaging patients and clinicians in research: the benefits of participating in research may not always be obvious to patients and clinicians, particularly with methods research, as was the case with the POS-E study. The patient and public involvement (PPI) group highlighted that the information in the patient information sheet (PIS) for the POS-E was too technical and contained a lot of health economic jargon. The PPI group warned that participants (particularly patients) would find it difficult to understand and as a result might be dissuaded from participating. The clinicians in the advisory group for the POS-E study also echoed this observation. In order to address this, a draft version of the questionnaires and information leaflets were reviewed with three PPI members

and three clinicians who made suggestions to improve clarity. The ethics committee commended the final version of the document for its clarity and conciseness. The study participants also reported that they had no difficulty in understanding the information provided. Furthermore, it became obvious at the start of the POS-E study that although clinicians at NHS Trusts had agreed in principle to screen for eligible patients during clinical team meetings, it was necessary for me to be present at such meetings to remind them to do so, as they were often overwhelmed due to staff shortage. I was unable to attend all the clinical team meetings as we were recruiting from several Trusts, which were far apart with teams meetings often happening at the same time. In order address this; we invited research nurses where available to attend clinical team meetings to remind clinicians to screen patients for the study. Through this I gained a better understanding of how clinical services in the UK operate and UK and the different ways in which the various services interaction with each other and with other sectors e.g. with social care and with policy.

Navigating research ethics and governance procedures: The POS-E study made me appreciate, first hand, the complexity of navigating research ethics and governance procedures in the UK. I learnt the different research governance processes and categories available for different study designs and different participant groups. It became clear that there were a myriad of issues to consider e.g. participants capacity to consent, whether participants were patients or not, and in the case of patients, whether they were recruited via the NHS or via the voluntary / charity sector. It was even more challenging in the POS-E study as we recruited both healthy volunteers and patients from NHS sites (including primary, secondary and tertiary care centres) and also from the charity sector. In addition to obtaining ethical approval, we also had to navigate the research governance procedures for individual research sites, each requiring numerous face-to-face meetings and phone calls, exchanging documents, and signing contracts and letter letters of access. As part of this process, I also learnt how create site-specific documents (e.g. each site had to have their organisational logo on each of the research documents including PIS, consent forms, and study questionnaires). This was further complicated by the fact that midway through 'adopting' sites for the POS-E study, the centralised research ethics and governance procedures across the country changed from the Integrated Research Application System (IRAS) to the new and more streamlined

system run by the Health Research Authority (HRA). Because some but not all POS-E research sites had been approved via the old IRAS system, we had to apply for approval for the latter sites through the HRA system. This meant that some of the processes were duplicated. Through this process, I learnt the art of recruiting participants into research studies, managing research studies and ensuring that recruitment is on track, and working with the various governance bodies involved, including the Clinical Research Network (CRN).

Other skills that I learnt include: academic writing and writing for publication; coordinating research across several sites and managing different personalities; collaborating with external researchers, experts, and stakeholders including the PPI group; disseminating research findings to different audiences such as clinicians, students, researchers, policy makers, and lay groups; and time management. These transferrable skills have helped me develop as a researcher and have helped me in planning future research, but most of all they have helped me improve as a person.

8.11. Contribution to the science of economic evaluations in palliative care and beyond

In recent years, there has been a rapid increase in the use of economic evaluation in the assessment of health care. It is important for palliative care interventions to be routinely subjected to economic evaluation for at least two reasons. Firstly, economic evaluations allow comparisons between palliative care interventions to determine the most efficient use of allocated resources. Interventions that can be demonstrated to be relatively ineffective and costly can be replaced by those that accomplish more for less. Secondly, failure to demonstrate the cost-effectiveness of interventions will result in weak arguments in the competition for scarce resources. Therefore, to enable health policy makers to provide the resources required to meet the needs of palliative care patients, it is necessary for the palliative care community to provide information on the 'value for money' of palliative care services. However, palliative care research has too often failed to evaluate the 'value for money' of interventions that have been shown to be beneficial to patients, mainly because traditional health economic tools miss important palliative care benefits like practical matters.

This thesis contributes to the science of economic evaluations in palliative care in the following ways:

1. Developing a palliative care preference-based measure from an existing palliative care measure – POS – rather than developing a new one was crucial to this. Using a measure that was well validated and widely used in research and clinical practise meant that I could build upon existing knowledge. This also considerably extends the scope for conducting economic evaluations in palliative care by using existing POS data sets. The output of this thesis is a palliative-care-specific preference-based measure (with good internal validity) that can be used in economic evaluations of palliative care interventions.
2. This thesis also addresses some of the theoretical and methodological criticisms of using the QALY framework in palliative care including: the issue of imprecision of the QALY by incorporating important palliative care concerns; the issue of the narrow focus of the QALY on health domains; the issue of the narrow focus of the QALY on individual health; and (partially) the issue of non-additive of time due to instability of patient preferences.
3. This thesis also contributes to the science of economic evaluations more broadly. The issue of whose values (e.g. patients, general public, or health professionals) should be used in economic evaluations has been debated considerably. Patients have experienced impaired health and may be better placed to understand and value health states, health professionals have a good understanding of health states, and on the principle of public resources the values of the general public have been argued to be more appropriate. We demonstrated that it is feasible to derive meaningful values from patients with advanced chronic illness. We also showed that patient values are similar to healthy volunteer values meaning that both can be used in economic evaluations. This is important and possibly has implications beyond palliative care to all people with advanced illness.

8.12. Next steps

There are three particular areas of research I would like to progress after completing this doctorate degree.

The first will aim to further develop the outputs of this thesis, with a focus on addressing some of the limitations therein. As previously discussed in section 8.5, this would involve repeating the

study in a larger and more representative sample – based on the IPOS – and incorporating a psychometric validation component. Such a project would be an ideal fit for the Department of Health's National Institute for Health Research (NIHR) 'Post-Doctoral Fellowship' programme, which is targeted at early post-doctoral researchers. This project would also be a good fit for the "Sir Henry Wellcome Postdoctoral Fellowship Programme" which also targets applicants in the final year of their PhD studies or early post-doctoral stage.

Related to the above, I would also like to explore methods for incorporating costs and outcomes of informal carers into formal economic evaluations of palliative care interventions. Costs and outcomes of informal carers are often omitted in traditional economic evaluations, which means the benefits of interventions are undervalued. This issue is even more pertinent in palliative care where interventions are targeted not only at patients but also at family members. The analysis reported in Publication 5 (appendix 7) study on the cost of managing refractory breathlessness in patients with advanced disease which found that informal care accounted for over 70% of the total cost of care. It therefore seems inappropriate that these significant contributions of informal carers are often ignored in full economic evaluations. Such a project fits the remit of the co-funded MRC/NIHR Methodology Research Programme (MRP), which covers methodology research in several health disciplines including Health economics and decision science.

The third research area will aim to evaluate the optimal model(s) of palliative care (in terms of outcomes and cost) for different levels of need and complexity. A systematic review by Brereton and colleagues found numerous models of palliative care, each showing benefits for patients and their carers, with no evidence for negative effects; with some models appearing to be cost saving [249]. However, due to heterogeneity, poor reporting, and methodological weakness, it was impossible to predict which models of provision are most appropriate for specific contexts or for specific patient groups. The authors recommend further research to assess models of palliative care to enable decision makers to determine which models are likely to be most effective in different settings and for different patient groups[249]. Such a project would fit the remit of the "Grants for academic or clinical research" scheme run by the Dunhill Medical Trust, in partnership with the NIHR which supports research identifying and developing new and effective ways to improve the

lives of older people or research into treating diseases and conditions which disproportionately affect older people but are less well-funded.

8.13. Conclusion

The POS-E is a palliative care specific preference-based measure that can be used to calculate QALYs for cost-utility analysis of palliative care interventions. It has addresses most of the theoretical and methodological concerns of cost-utility analysis in palliative care. This thesis demonstrates that it is feasible to obtain meaningful preference values from patients with advanced chronic illness, and also that patient values are similar to similar to those of healthy people. It also demonstrates that the QALY is still a useful vehicle for quantifying joint mortality and morbidity impacts of palliative care at individual and population level. Given the widespread use of the POS in assessing palliative care outcomes in the UK and internationally, the POS-E is expected to facilitate broader economic evaluations of palliative care interventions using current and forthcoming POS data sets. Although further research and testing is needed, there is cause for cautious optimism.

9. References

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10. Appendices

10.1. Appendix 1: Description of datasets and data merging procedure for secondary data analyses

10.1.1 Description of datasets

Secondary analysis was performed on six different datasets collected in several studies of palliative care patients (N=1011) as follows:

1. a cross-sectional study on symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer in Germany(N109);[189]
2. a study of Parkinson's disease (longitudinal community study of predictive factors N=82);[190]
3. a randomised phase II trial of dignity therapy (N=45, UK);[191]
4. a longitudinal study on trajectories of illness of stage 5 chronic renal disease (N=74, UK)[113];
5. a cancer mortality follow-back survey (N=596) from 2009 to 2010 in London (The QUALYCARE study);[194]
6. a randomised controlled trial on the effectiveness of an integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness in the UK (N=105), 2014;[250]

Data sets were selected based on availability. All datasets contained longitudinal collected assessment data using different measurement tools but for the purposes of the thesis's objectives only baseline estimates were used. Data sets 1, 3, and 4 contained only POS data, whereas, datasets 2, 5, and 6 contained both POS and EQ-5D data. Datasets that contained both POS and EQ-5D (2, 5, and 6; N=783) were used for mapping analysis, while all six datasets were used for the development of a health classification (factor and Rasch analyses).

For factor and Rasch analyses, a random subsample of 400 respondents (estimation data) was used, as there is evidence that some Rasch fit statistics for polytomous scales such as the POS are sensitive to sample size and larger samples can have a higher chance of type 1 errors.[193] The results were validated on an additional random subsample of 400 respondents (validation data). Similarly, for the mapping analysis, the three data sets containing both POS and EQ-5D data were pooled into a single data set (N=783) which subsequently was randomly split into development (N=392) and validation (N=391) datasets .

More information on the background of each dataset can be found in the already published papers on the datasets[251-256]. The following

Table 8 presents the characteristics of the datasets, summarizing the patients samples, their personal characteristics (i.e. age, gender and ethnicity), and the number of patients in each dataset.

Table 8: Summary of characteristics of POS and EQ-5D datasets

	Dataset 1 (POS)		**Dataset 2** (POS & EQ5-D)	**Dataset 3** (POS)	**Dataset 4** (POS)	**Dataset 5** (POS & EQ5-D)	**Dataset 6** (POS & EQ5-D)
Diagnosis:	COPD:	Lung cancer	Parkinson	Cancer	Chronic Kidney Disease stage 5 (CKD5)	Cancer	Cancer, COPD, CHF, ILD, Other
Number (N) of patients:	60	49	82	45	74	596	105
Demographics:							
Mean Age(SD)	64.7 (9.56)	63 (8.99)	67 (8.82)	67 (16.73)	80 (6.74)	74 (12.8)	67 (9.87)
Sex (% female)	51.7	49.0	37	51.1	48.6	48.5	41.9
Ethnicity (frequencies in valid percentages)	Not provided.		78.0 % White (English, Welsh, Scottish)/ 2.4% White (Irish)/ 3.7% Black (Caribbean)/ 2.4%Pakistani; 1.2% Chinese; 2.4% Anglo Indian; 6.1% Any Other Group	80% White/ 2.2% Black/ 4.4% White-Italian/ 2.2% Asian-Sri Lanken/ 4.4% Black-Carribean/ 4.4% Black African/ 2.2% Black British	68.9% White/ 16.2% Black/ 8.1% South Asian/ 6.8% Other Ethnicities	92.% white/ 2.8% Black/ 1.7% south Asian/	77.1% white/ 14.3% Black/ 1.7% south Asian/

					0.5% Chinese/ 2.6% other	0.0% Chinese/ 5.7% other
Total number of cases with missing data = 162 (16%) Total number of cases with complete data = 849 (16%)						

10.1.2 Data cleaning and merging

Before merging the data, we examined the response labels and the codes of variables in each dataset and the version of the POS questionnaire that was used to collect the data. These characteristics were then compared and adjustments (e.g. recoding of variables into different variables) were made in order to obtain standardize the variables. For the purposes of the planned analysis the following variables were selected for further analysis: diagnosis; age; gender; ethnicity, EQ-5D scores and POS scores. Upon completion of data standardisation, the six datasets were merged into a single dataset. The merged dataset was further examined for missing data and for inconsistencies such as unexpected large or small counts for variables or implausible values.

The statistical software SPSS version 21.0 was used to perform the analyses.

The results of the preparation of the datasets (i.e. recoding of the variables) are presented in Table 10 and 11.

Table 9: Median scores of self-reported 10-itme POS assessments (on Likert-scale from 0-4; 0= best score and 4=worst score)

POS-items:	**Dataset 1 COPD N= 60**	**Dataset 1 Lung-cancer N= 49**	**Dataset 2 Parkinson's N= 82**	**Dataset 3 Cancer N= 45**	**Dataset 4 CKD5 N= 74**	**Dataset 5 Cancer N=596**	**Dataset 6 Cancer/non-cancer N=105**	**All patients N= 1011**
	Median	**Median**	**Median**	**Median**	**Median**	**Median**	**Median**	**Median**
POS-item 1: pain	0	1	2	2	1	1	1	1
POS-item 2: other symptoms	0	1	2	2	1	1	1	1
POS-item 3: patient anxiety	0.5	1	1	1	1	1	2	1
POS-item 4: family anxiety	2	3	2	2	1	3	2	3
POS-item 5: information	0	0	0	0	0	0	3	0
POS-item 6: share feelings	0	0	1	0	1	2	1	1
POS-item 7: depression	1	0	1	1	0	1	1	1

POS-item 8: feeling good	0	1	2	1	1	1	2	1
POS-item 9: wasted time	0	0	0	0	0	0	0	0
POS-item 10: practical problems	0	0	0	0	0	0	2	0

10.1.4 Description of preparation activities for secondary data-analyses on 6 POS-datasets

Merging POS-datasets

Introduction

1. Dataset 1(Excel file): end-stage renal failure patients ; N : 74
2. Dataset 2 (Excel file): COPD-patients with N: 60 and lung cancer patients N: 49
3. Dataset 3 (SPSS file): Parkinson patients; N: 82
4. Dataset 4 (SPSS file): cancer patients (general); N: 45
5. Dataset 5 (SPSS file): cancer; N: 596
6. Dataset 6 (SPSS file): cancer & non-cancer; N: 105

Total = **1011 patients**.

2. Comparison of the included variables and <u>their values</u> as presented in their dataset and the recoded variables

The values of the variables that needed recoding are marked in red in this table.

Table 10: Data Cleaning and merging

POS-dataset 1	**POS-dataset 2**	**POS-dataset 3**		**POS-dataset 4**	**FINAL values used in merged dataset**
Extra variable for merged datasets: 'diagnosis': **0= stage 5 Chronic Kidney Disease** **1= COPD (stage III and IV)**					

2= lung-cancer **3= Parkinson** **4= cancer patients**					
Age:					
string; no defining of missing values (age at data entry)	string; no defining of missing values	age in years; discrete missing values (DMV): 999, 988, 977		age can be calculated via 'date of birth' DMV: 999-888-777	
Gender/ sex:					
1= female => **1= male** 0= male => **2 = female** no defining of missing values	1= male 2= female no defining of missing values	1= male 2= female DMV: 999, 888, 977		1= male 2= female DMV: 999-888-777	**1= male** **2= female**
Ethnicity:					
1= White 2= Black 3= South Asian 4= Chinese 5= other	**This variable was not in the dataset.**	1= White (English, Scottish, Welsh) 2= White (Irish) => **= 1, White** 3= White (European) => **= 1, White**		1= White 2= Black 3= Asian	**1= White** **2= Black** **3= South Asian** **4= Chinese** **5= other**

		11= White (Americans) => = **1, White** 4= Black (African) 5= Black (Caribbean) => **2, Black** 6= Black (Other) => **2, Black** 7= Indian => **=3, South Asian** 8= Pakistani => **=3, South Asian** 9= Bangladeshi => **=3, South Asian** 12= Anglo Indian => **=3, South Asian** 13= Asian => **=3, South Asian**		4= Chinese 5= Mixed => **=5, Other** 6= All ethnic => **N/A** 7= White other – Italian => **=1, White** 8= Asian Other, Sri Lankan => **=3, South Asian** 9= Black Other, Caribbean=> **=2, Black** 10= Black Other, African => **=2, Black** 11= Black Other, British => **=2, Black** DMV: 999-888-777	

		10= Chinese => = **4, Chinese** 88= Any other group; DMV: 999, 988, 977 => **=5, Other**			
POS-items:					
POS- 1: pain 0= not at all, no effect 1= slightly-but no bothered to be rid of it 2= moderately-pain limits some activity 3= severely-activities or concentration markedly affected 4= overwhelmingly-unable to think of anything else *DMV: 997,998,999*	*POS- 1: pain* 0= not at all, no effect 1= slightly-but no bothered to be rid of it 2= moderately-pain limits some activity 3= severely-activities or concentration markedly affected 4= overwhelmingly-unable to think of anything else DMV: a, b *POS-2: other symptoms*	*POS- 1: pain* 0= not at all 1= slightly 2= moderately 3= severely 4= overwhelmingly DMV: 999, 988, 977 *POS-2: other symptoms*		*POS- 1: pain* 0= not at all 1= slightly 2= moderately 3= severely 4= overwhelmingly DMV: 999-888-777 *POS-2: other symptoms*	**POS- 1: pain** **0= not at all, no effect** **1= slightly-but not bothered to be rid of it** **2= moderately-pain limits some activity** **3= severely-activities or concentration markedly affected** **4= overwhelmingly-unable to think of anything else** **POS-2: other symptoms** **0= no, not at all**

POS-2: other symptoms 0= not at all 1= slightly 2= moderately 3= severely 4= overwhelmingly *DMV: 997,998,999* *POS-3: worry/ anxiety by the patient* 0= not at all 1= occasionally 2= sometimes-affects my concentration now and then 3= most of the time-often affects my concentration	0= not at all, no effect 1= slightly 2= moderately 3= severely-activities or concentration markedly affected 4= overwhelmingly-unable to think of anything else DMV: a, b *POS-3: worry/ anxiety by the patient* 0= no, not at all 1= occasionally 2= sometimes-affects my concentration now and then 3= most of the time-often affects my concentration	0= not at all 1= slightly 2= moderately 3= severely 4= overwhelmingly DMV: 999, 988, 977 *POS-3: worry/ anxiety by the patient* 0= not at all 1= occasionally 2= sometimes 3= most of the time 4= can't think of anything else		0= not at all 1= slightly 2= moderately 3= severely 4= overwhelmingly DMV: 999-888-777 *POS-3: worry/ anxiety by the patient* 0= no 1= occasionally 2= sometimes 3= most of the time 4= pre-occupied DMV: 999-888-777	**1= slightly** **2= moderately** **3= severely** **4= overwhelmingly** **POS-3: worry/ anxiety by the patient** **0= no, not all** **1= occasionally** **2= sometimes-affects my concentration now and then** **3= most of the time-often affects my concentration** **4= can't think of anything else-completely preoccupied by worry and anxiety**

4= can't think of anything else-completely pre-occupied by worry and anxiety *DMV: 997,998,999* *POS-4: family/ friends worry/ anxiety* 0= no, not at all 1= occasionally 2= sometimes-it seems to affect their concentration 3= most of the time 4= yes, always pre-occupied with worry about me *DMV: 997,998,999*	4= can't think of anything else-completely pre-occupied by worry and anxiety DMV: a, b *POS-4: family/ friends worry/ anxiety* 0= no, not at all 1= occasionally 2= sometimes-it seems to affect their concentration 3= most of the time 4= yes, always pre-occupied with worry about me DMV: a, b	DMV: 999, 988, 977 *POS-4: family/ friends worry/ anxiety* 0= no, not at all 1= occasionally 2= sometimes 3= most of the time 4= yes, always DMV: 999, 988, 977		*POS-4: family/ friends worry/ anxiety* 0= no 1= occasionally 2= sometimes 3= most of the time 4= pre-occupied DMV: 999-888-777 *POS-5: information given*	**POS-4: family/ friends worry/ anxiety** **0= no, not at all** **1= occasionally** **2= sometimes-it seems to affect their concentration** **3= most of the time** **4= yes, always pre-occupied with worry about me** **POS-5: information given** **0= full information-always free to ask what I want** **1= information given but hard to understand** **2= information given on request but would have liked more**

POS-5: information given 0= full information or as much as wanted-always feel free to ask what I want 1= information given but hard to understand 2= information given on request but would have liked more 3= very little given an some questions were avoided 4= none at all *DMV: 997,998,999*	*POS-5: information given* 0= full information or as much as wanted-always feel free to ask 1= information given but hard to understand 2= information given on request but would have liked more 3= very little given and some questions were avoided 4= none at all-when we wanted information DMV: a, b	*POS-5: information given* 0= full information 1= info given but hard to understand 2= info given on request but would have liked more 3= very little given and questions avoided 4= none at all DMV: 999, 988, 977		0= full information 1= info given – hard to understand 2= info given on request 3= very little given 4= none at all DMV: 999-888-777	**3= very little given and some questions were avoided** **4= none at all** **POS-6: emotional support/ share feeling** **0= yes, as much as I wanted to** **1= most of the time** **2= sometimes** **3= occasionally** **4= no, not at all with anyone**

POS-6: emotional support/ share feeling 0= yes, as much as I wanted to 1= most of the time 2= sometimes 3= occasionally 4= not at all with anyone *DMV: 997,998,999* *POS-7: depressed*	*POS-6: emotional support/ share feeling* 0= yes, as much as I wanted to 1= most of the time 2= sometimes 3= occasionally 4= not at all with anyone DMV: a, b	*POS-6: emotional support/ share feeling* 0= yes, as much as I wanted 1= most of the time 2= sometimes 3= occasionally 4= no, not at all with anyone DMV: 999, 988, 977 *POS-7: depressed*		*POS-6: emotional support/ share feeling* 0= as much as I wanted to 1= most of the time 2= sometimes 3= occasionally 4= not at all DMV: 999-888-777 *POS-7: depressed*	**POS-7: depressed** **0= yes, all the time** **1= most of the time** **2= sometimes** **3= occasionally** **4= no, not at all**

0= no, not at all 1= occasionally 2= sometimes 3= most of the time 4= yes. definitely *DMV: 997,998,999* *POS-8: feeling good about themselves (self-esteem)* 0= yes, all of the time 1= most of the time 2= sometimes 3= occasionally 4= no, not at all *DMV: 997,998,999*	*POS-7: depressed => **other name for it: 'have you felt that life was worthwhile?'*** **0= yes, all the time** **1= most of the time** **2= sometimes** **3= occasionally** **4= no, not at all** DMV: a, b *POS-8: feeling good about themselves (self-esteem)* 0= yes, all the time 1= most of the time 2= sometimes 3= occasionally 4= no, not at all	0= no, not at all 1= occasionally 2= sometimes 3= most of the time 4= yes, definitely DMV: 999, 988, 977 *POS-8: feeling good about themselves (self-esteem)* 0= yes, all the time 1= most of the time 2= sometimes 3= occasionally 4= not at all DMV: 999, 988, 977		0= not at all 1= occasionally 2= sometimes 3= most of the time 4= definitely DMV: 999-888-777 *POS-8: feeling good about themselves (self-esteem)* 0= yes, all of the time 1= most of the time 2= sometimes 3= occasionally 4= not at all DMV: 999-888-777	**POS-8: feeling good about themselves (self-esteem)** **0= yes, all the time** **1= most of the time** **2= sometimes** **3= occasionally** **4= no, not at all** **POS-9: wasted time** **0= none at all** **2= up to half a day wasted** **4= more than half a day wasted** **POS-10: practical problems (= personal affairs)**

POS-9: wasted time 0= none at all 2= up to half ad day wasted 4= more than half a day wasted *DMV: 997,998,999* *POS-10: practical problems (= personal affairs)* 0= practical problems have been addressed and my affairs are as up to date as I would wish	DMV: a, b *POS-9: wasted time* 0= none at all 2= up to half a day wasted 4= more than half a day wasted DMV: a, b *POS-10: practical problems (= personal affairs)* 0= practical problems have been addressed and my affairs are as up to date as I would wish	*POS-9: wasted time* 0= none at all 2= up to half a day wasted 4= more than half a day wasted DMV: 999, 988, 977 *POS-10: practical problems (= personal affairs)* 0= practical problems addressed 2= practical problems in process of being addressed		*POS-9: wasted time* =>'appointments': 0= none 2= up to half a day 4= more than half a day *POS-10: practical problems (= personal affairs)* 0= up to date **1= no practical probs => recode and give this value '0'** 2= being addressed 4= practical probs not addressed DMV: 999-888-777	**0= I have had no practical problems/ problems have been addressed and my affairs are as up to date as I would wish** **2= practical problems are in the process of being addressed** **4= practical problems exist which were not addressed**

2= practical problems are in the process of being addressed 4= practical problems exist which were not addressed **0= I have had no practical problems** *DMV: 997,998,999*	2= practical problems are in the process of being addressed 4= practical problems exist which were not addressed **0= I have had no practical problems** DMV: a, b	4= practical problems exist which were not addressed DMV: 999, 988, 977			

Table 11: Descriptive statistical measures of included variables

POS-dataset 1	**POS-dataset 2**	**POS-dataset 3**	**POS-dataset 4**	**Merged datasets-results/ all respondents of the 4 datasets together:**
Age: mean : 80	***For COPD:*** ***Age:***	***Age:*** mean: 67	***Age:*** mean: 67	***Age:*** mean: 69.2

SD: 6.738 Min.-Max.: 51-95 ***Gender: frequencies in valid percentages:*** 31.4 male and 48.6 female (38 male and 36 female) ***Ethnicity: frequencies in valid percentages:*** 68.9 White/ 16.2 Black/ 8.1 South Asian/ 6.8 Other Ethnicities ***POS-items: frequencies in valid percentages:***	mean : 64.7 SD: 9.564 Min.-Max.: 38-81 ***Gender: frequencies in valid percentages:*** 48.3 male and 51.7 female (29 male and 31 female) ***Ethnicity: frequencies in valid percentages:*** ***Not provided*** ***POS-items: frequencies in valid percentages:*** *POS-item 1:*	SD: 8.817 Min.-Max.: 38-86 ***Gender: frequencies in valid percentages:*** 54.9 male and 37 female (45 male and 37 female) ***Ethnicity: frequencies in valid percentages:*** 78.0 White (English, Welsh, Scottish)/ 2.4 White (Irish)/ 3.7 Black (Caribbean)/ 2.4 Pakistani; 1.2 Chinese; 2.4 Anglo Indian; 6.1 Any Other Group ***POS-items: frequencies in valid percentages:***	SD: 16.731 Min.-Max.: 24-99 ***Gender: frequencies in valid percentages:*** 48.9 male and 51.1 female (22 male and 23 female) ***Ethnicity: frequencies in valid percentages:*** 80 White/ 2.2 Black/ 4.4 White-Italian/ 2.2 Asian-Sri Lanken/ 4.4 Black-Carribean/ 4.4 Black African/ 2.2 Black British	SD: 11.887 Min.-Max.: 24-99 ***Gender: frequencies in valid percentages:*** 51.3 male and 48.7 female (159 male and 151 female) ***Ethnicity: frequencies in valid percentages:*** 77.1 White/ 10.4 Black/ 7.0 South Asian/ 0.5 Chinese/ 5.0 other ***POS-items: frequencies in valid percentages:***

POS-item 1: 0= 37.8 1= 13.5 2= 36.5 3= 12.2 Median (M)= 1 *POS-item 2:* 0= 24.3 1= 29.7 2= 37.8 3= 6.8	0= 68.3 1= 3.3 2= 13.3 3= 11.7 4= 1.7 1 missing value while .b= 1.7 M= 0 *POS-item 2:* 0= 70.0 1= 15.0 2= 5.0 3= 6.7 4= 3.3 M= 0	*POS-item 1:* 0= 17.1 1= 9.8 2= 43.9 3= 28.0 4= 1.2 M= 2 *POS-item 2:* 0= 15.9 1= 9.8 2= 29.3 3= 37.8 4= 7.3	***POS-items: frequencies in valid percentages:*** *POS-item 1:* 0= 31.1 1= 11.1 2= 20.0 3= 28.9 4= 8.9 M= 2 *POS-item 2:* 0= 24.4 1= 20.0 2= 28.9	*POS-item 1:* 0= 37.5 1= 10.4 2= 28.2 3= 21.0 4= 2.9 1 missing value M= 2 *POS-item 2:* 0= 34.8 1= 17.1 2= 24.8 3= 17.4 4= 5.8

4= 1.4 M= 1 *POS-item 3:* 0= 45.9 1= 29.7 2= 20.3 3= 4.1 M= 1 *POS-item 4:* 0= 23.0 1= 27.0 2= 13.5	*POS-item 3:* 0= 50.0 1= 21.7 2= 10.0 3= 10.0 4= 8.3 M= 0.5 *POS-item 4:* 0= 36.7 1= 10.0 2= 10.0 3= 13.3	M= 2 *POS-item 3:* 0= 29.3 1= 25.6 2= 19.5 3= 23.2 4= 2.4 M= 1 *POS-item 4:* 0= 14.6 1= 24.4	3= 13.3 4= 13.3 M= 2 *POS-item 3:* 0= 42.2 1= 24.4 2= 22.2 3= 8.9 4= 2.2 M= 1 *POS-item 4:* 0= 17.8	M= 1 *POS-item 3:* 0= 38.7 1= 25.5 2= 18.7 3= 11.9 4= 5.2 M= 1 *POS-item 4:* 0= 20.9 1= 22.9 2= 17.6

3= 27.0 4= 6.8 2 missing values while 998= 2.7 M= 1 *POS-item 5:* 0= 77.0 1= 9.5 2= 6.8 3= 4.1 4= 2.7 M= 0 *POS-item 6:*	4= 26.7 2 missing values while .b= 33 M= 2 *POS-item 5:* 0= 66.7 2= 11.7 4= 20.0 1 missing value while .b= 1.7 M= 0 *POS-item 6:* 0= 68.3	2= 25.6 3= 24.4 4= 11.0 M= 2 *POS-item 5:* 0= 62.2 1= 9.8 2= 19.5 3= 6.1 4= 2.4 M= 0	1= 22.2 2= 26.7 3= 24.4 4= 8.9 M= 2 *POS-item 5:* 0= 68.9 1= 15.6 2= 11.1 3= 4.4 M= 0	3= 23.9 4= 14.7 4 missing values M= 2 *POS-item 5:* 0= 71.1 1= 7.1 2= 12.0 3= 3.9 4= 5.8 2 missing values M= 0

0= 47.3 1= 21.6 2= 27.0 3= 1.4 4= 2.7 M= 1 *POS-item 7:* 0= 58.1 1= 24.3 2= 10.8 3= 5.4	1= 10.0 2= 1.7 3= 1.7 4= 16.7 1 missing value while .b= 1.7 M= 0 *POS-item 7: <u>life worthwhile</u>* 0= 46.7 1= 21.7 2= 13.3 3= 3.3 4= 13.3 1 missing value while .b= 1.7	 *POS-item 6:* 0= 34.1 1= 23.2 2= 19.5 3= 3.7 4= 19.5 M= 1 *POS-item 7:* 0= 37.8 1= 23.2	 *POS-item 6:* 0= 60.0 1= 22.2 2= 13.3 3= 2.2 4= 2.2 M= 0 *POS-item 7:* 0= 35.6	*POS-item 6:* 0= 52.8 1= 18.4 2= 16.5 3= 2.3 4= 10.0 1 missing value M= 0 *POS-item 7:* 0= 46.4 1= 22.7 2= 16.2 3= 6.2

4= 1.4 M= 0 *POS-item 8:* 0= 24.3 1= 55.4 2= 9.5 3= 9.5 4= 1.4 M= 1 *POS-item 9:*	M= 1 *POS-item 8:* 0= 56.7 1= 26.7 2= 5.0 3= 5.0 4= 6.7 M= 0 *POS-item 9:* 0= 93.3 2= 5.0	2= 23.2 3= 7.3 4= 8.5 M= 1 *POS-item 8:* 0= 19.5 1= 24.4 2= 34.1 3= 9.8 4= 12.2 M= 2	1= 20.0 2= 26.7 3= 2.2 4= 15.6 M= 1 *POS-item 8:* 0= 26.7 1= 33.3 2= 15.6 3= 6.7 4= 17.8 M= 1	4= 8.4 2 missing values M= 1 *POS-item 8:* 0= 32.5 1= 33.1 2= 16.6 3= 7.8 4= 10.1 2 missing values M= 1 *POS-item 9:*

0= 59.5 2= 29.7 4= 10.8 M= 0 *POS-item 10:* 0= 78.4 2= 10.8 4= 10.8 M= 0	4= 1.7 M= 0 *POS-item 10:* 0= 76.7 2= 15.0 4= 8.3 M= 0 ***For lung cancer:*** ***Age:*** mean: 63 SD: 8.985	*POS-item 9:* 0= 81.7 2= 14.6 4= 3.7 M= 0 *POS-item 10:* 0= 58.5 2= 32.9 4= 8.5 M= 0	*POS-item 9:* 0= 51.1 2= 28.9 4= 20.0 M= 0 *POS-item 10:* 0= 55.6 2= 31.1 4= 13.3 M= 0	0= 71.9 2= 19.0 4= 9.0 M= 0 *POS-item 10:* 0= 70.0 2= 21.0 4= 9.0 M= 0

	Min.-Max.: 40-80 ***Gender: frequencies in valid percentages:*** 51.0 male and 49.0 female (25 male and 24 female) ***Ethnicity: frequencies in valid percentages:*** ***Not provided*** ***POS-items: frequencies in valid percentages:*** *POS-item 1:* 0= 38.5 1= 14.3 2= 14.3 3= 26.5			

	4= 6.1 M= 1 *POS-item 2:* 0= 49.0 1= 10.2 2= 18.4 3= 16.3 4= 6.1 M= 1 *POS-item 3:* 0= 26.5 1= 24.5			

	2= 22.4 3= 10.2 4= 16.3 M= 1 *POS-item 4:* 0= 10.2 1= 28.6 2= 10.2 3= 28.6 4= 22.4 M= 3 *POS-item 5:*			

	0= 81.6 2= 8.2 3= 4.1 4= 4.1 1 missing value while .b= 2.0 M= 0 *POS-item 6:* 0= 65.3 1= 12.2 2= 16.3 3= 2.0 4= 4.1 M= 0			

	POS-item 7: 0= 51.0 1= 22.4 2= 6.1 3= 12.2 4= 6.1 1 missing value while .b= 2.0 M= 0 *POS-item 8:* 0= 40.8 1= 20.4 2= 12.2			

	3= 6.1 4= 16.3 2 missing values while .b= 4.1 M= 1 *POS-item 9:* 0= 67.3 2= 18.4 4= 14.3 M= 0 *POS-item 10:* 0= 81.6 2= 14.3			

	4= 4.1 M= 0			

10.2. Appendix 2: Instruments used in mapping study

Table 12: The structure of the 3-level response version of EQ-5D (available from www.euroqol.org [Accessed 12 May 2014])

Dimension	Level	Statement
Mobility	1	I have no problems in walking about
	2	I have some problems in walking about
	3	I am confined to bed
Self-care	1	I have no problems with self-care
	2	I have some problems washing or dressing myself
	3	I am unable to wash or dress myself
Usual activities *(e.g. work, study, housework, family or leisure activities)*	1	I have no problems with performing my usual activities
	2	I have some problems with performing my usual activities
	3	I am unable to perform my usual activities
Pain/Discomfort	1	I have no pain or discomfort
	2	I have moderate pain or discomfort
	3	I have extreme pain or discomfort
Anxiety/Depression	1	I am not anxious or depressed
	2	I am moderately anxious or depressed
	3	I am extremely anxious or depressed

Structure of the 10 item POS questionnaire (patient version)

1 **Over the past 3 days, have you been affected by pain?**

- ❑ 0 Not at all, no effect
- ❑ 1 Slightly - but not bothered to be rid of it
- ❑ 2 Moderately - pain limits some activity
- ❑ 3 Severely - activities or concentration markedly affected
- ❑ 4 Overwhelmingly - unable to think of anything else

2 **Over the past 3 days, have other symptoms e.g. nausea, coughing or constipation seemed to be affecting how you feel?**

- ❑ 0 No, not at all
- ❑ 1 Slightly
- ❑ 2 Moderately
- ❑ 3 Severely
- ❑ 4 Overwhelmingly

3 Over the past 3 days, have you been feeling anxious or worried about your illness or treatment?

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes - affects my concentration now and then
- ❑ 3 Most of the time - often affects my concentration
- ❑ 4 Can't think of anything else - completely pre-occupied by worry and anxiety

4 Over the past 3 days, have any of your family or friends been anxious or worried about you?

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes – it seems to affect their concentration
- ❑ 3 Most of the time
- ❑ 4 Yes, always preoccupied with worry about me

5 Over the past 3 days, how much information have you and your family or friends been given?

- ❑ 0 Full information or as much as wanted – always feel free to ask
- ❑ 1 Information given but hard to understand
- ❑ 2 Information given on request but would have liked more
- ❑ 3 Very little given and some questions were avoided
- ❑ 4 None at all – when we wanted information

6 Over the past 3 days, have you been able to share how you are feeling with your family or friends?

- ❑ 0 Yes, as much as I wanted to
- ❑ 1 Most of the time

- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all with anyone

7 Over the past 3 days, have you been feeling depressed?

- ❑ 0 No, not at all
- ❑ 1 Occasionally
- ❑ 2 Sometimes
- ❑ 3 Most of the time
- ❑ 4 Yes, all the time

If you have placed a tick in boxes 3 or 4 for this question, please speak with your nurse or doctor at your next appointment.

8 Over the past 3 days, have you felt good about yourself as a person?

- ❑ 0 Yes, all the time
- ❑ 1 Most of the time
- ❑ 2 Sometimes
- ❑ 3 Occasionally
- ❑ 4 No, not at all

9 Over the past 3 days, how much time do you feel has been wasted on appointments relating to your healthcare, e.g. waiting around for transport or repeating tests?

- ❑ 0 None at all
- ❑ 2 Up to half a day wasted
- ❑ 4 More than half a day wasted

10 Over the past 3 days, have any practical matters resulting from your illness, either financial or personal, been addressed?

- ❑ 0 Practical problems have been addressed and my affairs are as up to date as I would wish
- ❑ 2 Practical problems are in the process of being addressed
- ❑ 4 Practical problems exist which were not addressed
- ❑ 0 I have had had no practical problems

10.3. Appendix 3: Instruments used in the valuation study

10.3.1 Participant information sheet

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of study

Development of a preference based outcome measure for use in economic evaluations of palliative care

We would like to invite you to participate in this original postgraduate research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

Aims of the research and possible benefits

- Primary aim: To develop a self-report questionnaire from an existing measure used in clinical practice (POS – Palliative Care Outcome Scale). The new self-report questionnaire can then be used to value a patient health state e.g. before and after a palliative care intervention or treatment.
- Secondary aim: to investigate the mathematical relationship between the POS and another measure called the EQ-5D which is regularly used in valuing health states across all health areas.
- The key benefit will be the development of a measure that is more applicable or suitable for use in the discipline of palliative care.

Who funds the project?

The project forms part of a large programme of palliative care research called BuildCARE for which funding has been secured.

Recruitment

The aim is to recruit patients from King's College Hospital, Guy's and St. Thomas' Hospital, and South London and Maudsley NHS Trust, who are able to give informed consent for their participation. Because this research has limited funding in support of a PhD the following exclusion criteria has been chosen

- People deemed unable to give informed consent by clinical staff

- People with a diagnosis of dementia and therefore will not be able to participate in the evaluation exercise
- People under 18 years of age
- People who are unable to communicate verbally in English

What will happen if the participant agrees to take part (when, where, how long etc.)

If you agree to take part in this study you will be asked to:

- Give consent to participate in a two part study (Part A & Part B) where you can choose to participate in A or B or Both
- Part A-Complete a short self-assessment questionnaire called the EQ-5D which aims to measure your own health state. (5min exercise)
- Part B- At a later stage, if you agree you will be approached to participate in the valuation of a new tool developed from a pre-existing tool which is regularly used in palliative care to value health. This will involve answering around 10 questions (45 min exercise)
- Details such as your age, gender and ethnicity will be used alongside your answers from part A of the study in an analysis of the data collected

- Although the data accessed will be confidential and made anonymous before use, any information disclosed during the proceedings which the principal investigator believes are potential risks to the participants health or others, or a disclosure of serious criminal offences may need to be disclosed to a third party e.g. include possibility for distress, potential adverse reactions, violence)

Possible benefits

If wanted, patients will have be allowed access to a copy of the report from this study

Arrangements for ensuring anonymity and confidentiality.

No information that can be used to identify patients will be used in this study. This study will be in compliance with the UK Data Protection Act 1998. Only the information contained on the EQ-5D questionnaire and information on the valuation exercise will be retained. As mentioned previously this data will be anonymous. This data will be held and stored securely by the chief investigator. Information stored on any portable devices or on university computers will be password encrypted. All written documentation will be kept in a locked room and locked drawer at the Institute, King's College London.

Anticipated plans for dissemination/publication.

Data will be presented at Kings College possibly Cicely Saunders at the Institute and to clinical/academic staff at the participating hospitals.

- The aim is to publish findings at the end of the study in an appropriate journal.
- A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive
- If you agree to take part you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not to be re-contacted
- If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form
- If you are completing a questionnaire on line then submission of a completed questionnaire implies consent to participate
- If you are completing a questionnaire on line then submission of a partially completed questionnaire implies consent (by pressing the 'store', 'next' or 'continue' buttons) to participate, and for data entered up to this point to be included in the study. Submission of a completed questionnaire (by pressing the 'submit' or 'finish' buttons) implies consent to participate, and for all data collected to be used. (For studies using online survey tools, where data from partially completed questionnaires is to be used)
- As participation is anonymous it will not be possible for us to withdraw your data once you have returned your questionnaire

It is up to you to decide whether to take part or not. If you decide to take part you are still free to withdraw from the study at any time and without giving a reason.

If you have any concerns or require more information about this study, please contact the researcher using the following contact details:

Name: Mendwas Dzingina

Telephone: 020 7848 5572

Email: Mendwas.dzingina@kcl.ac.uk

If you remain unhappy and wish to make a formal complaint, you can do so by contacting the research team on 020 7848 5565. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

10.3.2 Study Protocol

Development of a preference-based outcome measure for use in economic evaluations of palliative care services

Investigators/ Researchers
Dr Mendwas Dzingina, Cicely Saunders International PhD Training Fellow, Department of Palliative Care, Policy and Rehabilitation, King's College London
Professor Irene J Higginson, Professor of Palliative Care and Policy, King's College London
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1. Background

At the 67th World Health Assembly (23rd MAY 2014), the World Health Organisation (WHO) passed the first ever resolution on palliative care; recommending National health systems to provide palliative care in conjunction with potentially curative treatment, and not just as an "*optional extra*".[1] The resolution also urges member states to develop and implement policies which support the integration of cost-effective and equitable palliative care services in the continuum of care, across all levels.[2]

Palliative care is currently being incorporated into main stream health service provision in the UK. It is important for palliative care interventions to be routinely subjected to economic evaluation for at least two reasons. Firstly, economic evaluation can enable comparisons between palliative care services to determine the most efficient use of currently allocated resources. "*Services that can be shown to be relatively ineffective and costly can be replaced by those that achieve more for less*". [3]

Secondly, and most importantly, palliative care will always compete with other health care services for the same funds. It is the responsibility of health policy makers to consider 'value for money' when deciding what services to fund. Arguing for special consideration based on an intrinsic value of a service is no longer sufficient. Failure to demonstrate the cost-effectiveness of interventions will result in weak arguments in the competition for scarce resources.[3] Therefore, to enable health policy makers to provide the resources required to meet the needs of dying patients, it is necessary for the palliative care community to provide information on the 'value for money' of palliative care. Economic evaluation using cost-utility analysis (CUA) is the recommended means of providing such information.[4]

However, economic evaluations of palliative care are relatively rare. This is partly due to the complexities of estimating costs and benefits. *"Economic evaluation of palliative interventions poses some challenges, both for palliative medicine and for economics"*.[3, 5]

CUAs compare interventions in terms of their cost per quality adjusted life years (QALYs) gained. QALYs combine life expectancy (in years) and quality of life (expressed in the form of "health state values") into a single metric, based on peoples' preferences. The quality of life (QOL) portion is estimated by assigning a numerical value to each health state experienced by a patient on a scale from one for full health, to zero for states regarded equivalent to being dead (and negative values for states worse than being dead).[6] In other words, a utility is a quality of life score that has been converted into a standardized scale ranging from zero to one. They are cardinal values that represent the strength of an individual's preferences for specific health-related outcomes.

Measuring health utilities involves two main steps: defining a set of health states of interest, and valuing those health states. There are direct or indirect methods of utility valuation.
A common way of measuring health utilities is to use a ''generic'' preference-based measure (PBM) such as the EQ-5D, SF-6D and HUI.[7] All PBMs have a preference-based algorithm for assigning utility values to each health state. In other words, a PBM could be regarded as a

quality-of-life tool whose item-levels have been assigned 'preference weights' which reflect the desirability (or importance) of each item-level relative to the others. These preference weights are usually obtained by asking members of the general public preference-elicitation questions using methods such as the 'time-trade-off' approach, the 'standard gamble' approach or the 'visual analogue scale' approach.[8] Generic PBMs were developed on the basis that they can be used in all patients, irrespective of their medical condition because they concentrate on core aspects of health-related quality of life (HRQoL). This claim has been supported in many interventions and disease groups, for example Marra et al. (2005) demonstrated the discriminative ability of four generic measures across severity levels for patients with rheumatoid arthritis.[9]

However, for certain medical conditions, generic PBMs have been found to be inappropriate or insensitive to "small but important changes". In the discipline of palliative care, there are concerns that generic PBMs are heavily focused on physical function (e.g. 4 of the 5 dimensions of the EQ-5D measure physical aspects of HRQoL), and so do not incorporate many aspects of HRQoL important to palliative-care patients.[10, 11] This has led to proposals for the development of a palliative-care-specific PBM that would be appropriate for palliative-care patients with a variety of conditions.[10, 12] Presently, no such measure exists. The Palliative Care Outcome Scale (POS) has been suggested as suitable for this purpose.[10]
This study aims to develop a preference based outcome measure, specific to palliative care, for use in economic evaluations of palliative care. This involves exploring the importance (or value) of different aspects of health (such as pain, anxiety, depression etc.) relative to each other. For example, is treating moderate pain more important than treating severe anxiety, and if so, how much more important is getting treatment for moderate pain over treatment for severe anxiety?

2. Study aim and objectives

AIM

To develop a preference based outcome measure, specific to palliative care problems, for use in economic evaluations of palliative care.

Objectives

1. To assess the feasibility of mapping the Palliative Care Outcome Scale (POS) unto the EQ-5D
2. To derive and validate a simplified health-state classification from the POS
3. To conduct a valuation exercise to elicit health-state values for a sample of states
4. To model valuation results to produce utility values for all health states using regression / econometric models
5. To compare utility values obtained from patients to those obtained from healthy volunteers using simple t-tests
6. To integrate results and produce an algorithm for, and a guide to, estimating QALYs for cost-utility analysis of palliative care interventions

Objectives 1 to 4 involve secondary data analysis and have now been completed.
Objectives 5, 6 and 7 require primary data collection.

3. Overview of methods

The overall design for this study is secondary-data analysis followed by a cross-sectional survey.

The study consists of two main stages.

Stage 1: Mapping POS onto the EQ-5D (secondary-data analysis)

The first stage of this study explores the feasibility of mapping the Palliative Care Outcome Scale (POS) onto the 3-level EQ-5D, using pre-existing data. This stage has now been completed using pre-existing data. The EQ-5D was chosen because it is the most commonly used generic PBM and has been recommend by the National Institute for Health and Clinical Excellence (NICE) as the reference measure for cost-utility analyses of health care in the United Kingdom.[13] Likewise, NICE endorses the use of mapping to obtain utility values. [14]

Stage 2: Deriving a preference based measure from the POS

The second stage involves deriving preference weights for the POS. The approach here consists of six steps which broadly fall into 3 phases (see **Error! Reference source not found.**):

- Stage 2A (secondary-data analysis): the aim here is to construct a simplified health state classification containing a subset of items that are most representative of the POS. This involves conducting secondary analysis of POS datasets using factor analysis, Rasch

analysis, and other standard psychometric techniques. This stage has now been completed.

- Stage 2B: this stage involves primary data collection in a cross sectional survey and is the focus of this protocol. The aim here is to elicit health-state utility values/weights for a **sub-sample** of health states derived from stage 2A. These health states will be valued by asking patients and healthy volunteers, 'Time-Trade-Off' (TTO) questions in a 'valuation' survey.

- Stage 2C: the aim here is to derive utility values for **all** other health states that were not included in stage 2B using regression analysis

- Stage 2A has been completed using pre-existing data, while stages 2B will involve primary data collection and is the focus. Stage 2C will involve further analysis of the data from 2B.

The methods used for stage 2 are based on recommendations in the Health Technology Assessment (HTA) guidance document on "developing and testing methods for deriving

preference based measures of health from condition-specific measures (and other patient based measures of outcome)".[15]

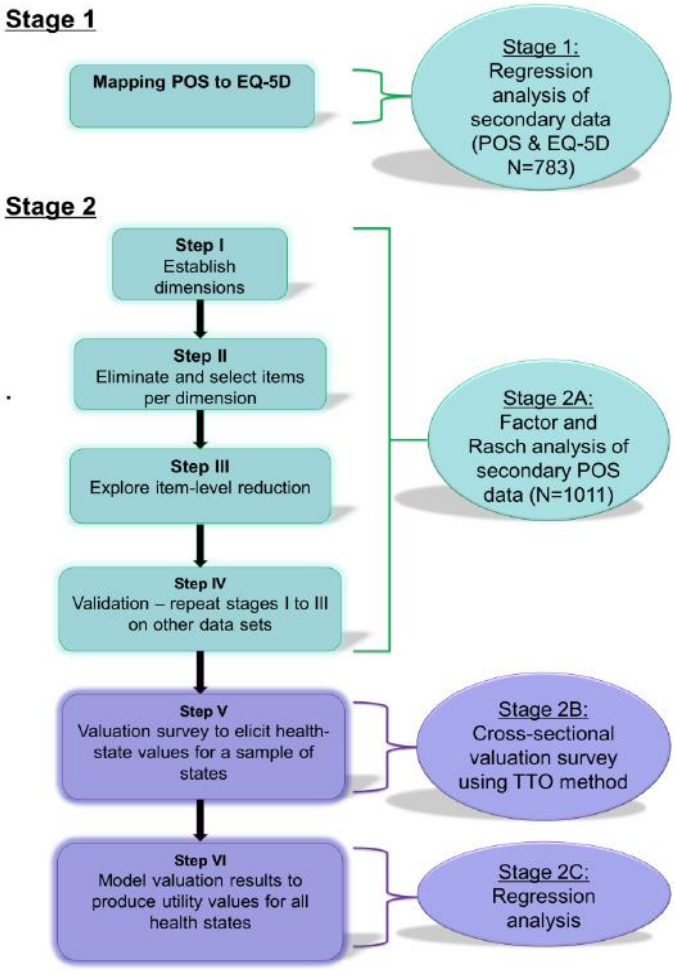


Figure 1: Overview of methods (Green coloured areas have been completed using pre-existing data, while purple sections involve primary data collection)

4. Methods for stages 2B and 2C

Study Design

This study is a cross sectional valuation survey in which patients with advanced disease and healthy volunteers will be asked to complete a one-off interviewer-administered questionnaire.

Study funding

This study is partly funded by the Cicely Saunders International, and partly by the C-Change project, a project aimed at developing an activity based funding system for palliative care in the UK. The study will receive sponsorship from King's College London. Ethical and governance approvals for the study will be sought through the Integrated Research Application System (IRAS) and approval from each site will be sought from the Research and Development departments in the participating organisations. At present, we propose to recruit from 5 sites – King's College Hospital NHS Trust; Guy's and St Thomas' NHS Hospital Trust; St. Joseph's Hospice; and St Christopher's Hospice – in London. We also plan to open the study to more sites in England.

Study setting

The study will be run from the department of Palliative Care, Policy and Rehabilitation at King's College London Cicely Saunders Institute. At present, we propose to recruit from 5 sites – King's College Hospital NHS Trust; Guy's and St Thomas' NHS Hospital Trust; St. Joseph's Hospice; and St Christopher's Hospice – in London. We also plan to open the study to more sites in England.

Study Participants

Two groups of study participants will be recruited into this study:

a) Patients with advanced disease (i.e. patients being seen by specialist palliative care services): all patients seen by specialist palliative care services have, by definition, advanced disease.
b) Healthy volunteers

Inclusion criteria

Patients:

1. 18 years or older;
2. with advanced disease (all patients being seen by specialist palliative care services): such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease;
3. able to provide informed consent;
4. who are English-literate; and
5. who are willing to participate

Healthy volunteers:

1. 18 years or older;
2. able to provide informed consent;
3. who are English-literate; and
4. who are willing to participate

Exclusion criteria:

Patients:

1. unable to provide informed consent;
2. who are too unwell , symptomatic , or distressed to participate – as judged by their clinical team,
3. who do not speak or cannot read English; and
4. who do not have advanced disease

Study organisation and management

An advisory group is being formed for this study, the study research team and wider steering group includes patient representatives and experts in psychological research, patient reported outcomes, health economics, palliative care, data management, research nurses, statistics and epidemiology, and psychometrics and measurement development. The conduct and progress of the study will be discussed and reviewed in regular meetings of the core research team and chief investigator, and also in regular meetings of the steering group. The study will be submitted for inclusion in the UK National Institute for Health Research (NIHR) Clinical Research Network Portfolio (CRN). Monthly, anonymised reports on the study accrual will be sent to the CRN office. Six-monthly reports will be provided to the funders of the study.

The questionnaire used in this study will be piloted with patients and healthy volunteers in order to: determine whether the questions work as intended; explore the acceptability of the questions; determine the completion time of the questionnaire; and assess the overall research burden.

Sampling

We will use consecutive sampling and include all patients that have been screened as eligible and are willing to participate. All members of the available population will be considered for participation in the study.

Identification and consent

Patients

Potential patient participants will be screened against the inclusion and exclusion criteria in the first instance by a member of their clinical team (specialist palliative care team), at the participating NHS Trusts or hospices. If screened as appropriate and eligible by the clinical team, potential participants will be given the information sheet by a clinician and have a

further discussion about the study, with the opportunity to ask questions. A member of the research team will then visit patients who have expressed an interest in taking part at least 24 hours after initial identification. If they are still willing to take part, full informed written consent will be obtained. Patients will be allowed to participate in a way comfortable to them, and be offered flexibility around the time and place of interviewing completion.

Healthy volunteers

Healthy volunteers will be recruited via the Volunteer services of each of the study sites. Volunteers will be contacted about participation in the study via the leads of the respective volunteer departments through e-mail or directly in person. Volunteers who express interest in participating in the study will be contacted by a member of the research team who will explain that participation is entirely voluntary, and provide more details about the study.

Steps to prevent harm to participants

Participants will be advised that they are under no obligation to participate. The purpose of the project will be explained. Participants will be given the choice not to answer any question. They may skip the question and move on, return to the question later, omit the question altogether, or discontinue the questionnaire. Patients will be made aware that they can withdraw from the study at any time, and this will have no impact on their clinical care.

Distress protocol

It is possible that participants may become distressed or raise issues during the study which may be of concern or warrant a change in their medical management. Should this be the case, then a member of the research team will team will seek consent from the participant to discuss matters with the relevant member(s) of the multi-disciplinary clinical care team, as appropriate. All members of the research team will have completed Good Clinical Practice training and training on how to handle distress in research. The study includes a system for handling patients reporting abnormal results or indicating a clinically significant problem. The clinical team of such participants will be notified of the results.

Regarding patients, we anticipate distress to be infrequent and likely to reflect advanced disease. All questionnaires will be screened immediately following completion to check their content for any areas of clinical concern. This screening will be done at the site where the participant has been recruited. Screening will be conducted by a member of the clinical team nominated by the principal investigator (PI) at each site. If participants disclose any ideations of self-harm or other risks to themselves or others, this will be dealt with as urgent matter for discussion with the PI and a senior member of the treating medical team. Provision will be made to ensure that the researchers have PI or senior back-up available by phone during collecting data.

Mode of administration and data collection

Participants will be asked to fill in a time-trade-off (TTO) questionnaire once. The valuation survey will be via interviewer-administered questionnaires. The questionnaire booklet will

include items on socio-demographic information, an assessment of the respondent's own health (based on the revised POS scale), and the valuation tasks. The valuation task involves deriving utility values for health states directly by asking patients and healthy volunteers 'Time-Trade-Off' (TTO) questions. At the beginning of a session, an explanation will be given on the purpose of the exercise and how to undertake each task using a set of prepared notes.

An example the valuation time-trade-off (TTO) valuation task

"Figure 2 below presents a choice between being in LIFE A (full health) for a certain length of time, or LIFE B for 10 Months. I am going to ask you about the state at the top which is LIFE A (figure 2) and the state at the bottom which is LIFE B (figure 2). The state in LIFE A will stay the same but the time for which you will be in this state will change. The state in LIFE B will change but the length of time of time will always be the same at 10 Months."

LIFE "A"

FULL HEALTH

LIFE "B"

I HAVE BEEN AFFECTED BY PAIN **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN AFFECTED BY OTHER SYMPTOMS **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN FEELING DEPRESSED **OCCASIONALLY** OR **SOMETIMES**

I HAVE BEEN FEELING ANXIOUS **OCCASIONALLY** OR **SOMETIMES**

I HAVE FELT GOOD ABOUT MYSELF **OCCASIONALLY** OR **SOMETIMES**

MY FAMILY AND FRIENDS HAVE BEEN ANXIOUS ABOUT ME **OCCASIONALLY** OR **SOMETIMES**

I HAVE **UNRESOLVED** PRACTICAL MATTERS

Figure 2: time-trade-off show cards depicting two different health states

"Table 1 shows an answer sheet with an example of how we would like you to make your choice. Here there are two columns which represent the two possibilities, LIFE A and Life B (table 1). The left hand column depicts different lengths of time that you could be in LIFE A for. The right hand column shows the length of time that you could be in LIFE B for. This time is always the same at 10 months."

"You would look at each row on this answer sheet, and then decide whether you would prefer to have either Life A or Life B. You would place a tick in the box if you would prefer Life A, and a cross if you would prefer Life B. You would place an equal's sign if you feel Life A and Life B are equivalent (i.e. you could not choose between Life A and Life B)."

"In this example, being in Life A for 9 months and 2 weeks is seen as the same as being in Life B for 10 months."

LIFE "A"(full health)		**LIFE "B"**
10 Months	✓	10 Months
9 Months 2 Weeks	=	10 Months
9 Months	X	10 Months
8 Months 2 Weeks	X	10 Months
8 Months	X	10 Months
7 Months 2 Weeks	X	10 Months
7 Months	X	10 Months
6 Months 2 Weeks	X	10 Months
6 Months	X	10 Months
5 Months 2 Weeks	X	10 Months
5 Months	X	10 Months
4 Months 2 Weeks	X	10 Months
4 Months	X	10 Months
3 Months 2 Weeks	X	10 Months
3 Months	X	10 Months
2 Months 2 Weeks	X	10 Months
2Months	X	10 Months
1 Month 2 Weeks	X	10 Months
1 Month	X	10 Months
0 Months 2 Weeks	X	10 Months
0 Months	X	10 Months

Table 1: TTO example answer sheet

Place a "✓" if you prefer Life "A"
Place an "X" if you prefer Life "B"
Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

In the example above, the utility value for health state B (Life B) will be calculated as:

$9.5 \div 10 = 0.95$

Sample size

Valuation of the 14 states has two aims: (1) to produce mean values for each health state; and (2) to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests.

Assuming a power of 0.8, significance level of 0.05, SD of 0.3 and an expected difference of 0.1, 73 valuations are required for each health state (37 from patients and 37 from healthy volunteers) and thus a total of 1,022 valuations for the 14 health states.[15] If we assume that participants are able to value 14 health states each, then a total sample size of 73 would be sufficient to achieve 73 valuations per health state. However, consultations with clinicians and patient representatives revealed that some participants, particularly patients with advanced disease, might find it too burdensome to value 14 health states. Also, previous valuation exercises have shown that respondents cannot value more than 13 health states at a time (Dolan et al., 1996),[16] and typically they are asked to value between 6 and 8 health states (Brazier et al., 2002, 2005b & 2008; Dolan et al., 1996; Yang et al., 2011).[16-19 20] Conversely, reducing the number of health states to be valued by each participant will necessitate an increase in the sample size (of participants) required to achieve 73 valuations per health state.

In order to address this issue, health states will be divided into two blocks, with each block comprising of 8 health states. In each of the two blocks there will be two health states that will be common to both blocks and 6 unique health states (i.e. 6 states unique to block 1; + 6 unique to block 2; + 2 common states = 14 states). Each participant will value only one block comprising of 8 health states. Based on this, a total of 130 participants will be required (65 patients and 65 healthy volunteers). The two health states common to both blocks will thus have 73 values each and so will be used to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests (aim 2). The other health states will be used to calculate mean values for each health state (aim 1) as a much smaller number of valuations per health is required for this. This method has been used in previous valuation studies.[15]

Data analysis

The TTO is a technique used in health economics to help determine the quality of life of an individual (or patient) or a group. In the original version an individual will be presented with a set of directions for example:

"Imagine that you are told that you have 10 years left to live. In connection with this you are also told that you can choose to live these 10 years in your current health state or that you can choose to give up some years-of-life to live for a shorter period in full health. Indicate with a cross on the line, the number of months in full health that you think is of equal value to 10 years in your current health state".

The line usually ranges from 0 to 10 and the person's score is calculated by dividing the number corresponding to their cross by 10. For example, if someone marks a cross at 6 on the TTO line, they would be given a TTO score of 0.60. This number is often used in turn to calculate quality-adjusted life years (QALYs). In our example, if this person were to live for 2 years at their current health-state (of 0.6) this would be equal to 1.2 QALYs (2 × 0.6). QALYs enable health care decision makers to combine mortality and morbidity into a single interval scale, thereby enabling the comparison of interventions between different diseases and across a variety of disciplines.

However, for this study, we propose to use a modified version of the TTO which uses a time interval of 0 to 10 months (instead of 0 to 10 years). The rationale behind this is based on the fact that on average, patients with advanced disease usually have a life expectancy much shorter than 10 years, and so it may be inappropriate to ask them to trade-off lengths of time they know they don't have.

Mean TTO values will be estimated for each of the 14 health states that will be valued. The mean values between the two common-states that were valued by both patients and healthy volunteers will be compared sing simple t-tests.

Data management and security

All personal data will be managed according to the principles established in the Data Protection Act 1998. All researchers will undertake and update the Good Clinical Practice Training, and current research governance processes will be followed. Completed questionnaires, demographics forms and interview scripts will be anonymised using a unique study identification number and contain no patient identifiable data. The only place that the study identification number will be linked to the participants' name will be on the consent form. Questionnaires and demographics forms will be stored separately from the consent forms, each in a separate locked cabinet.

Dissemination

Findings will be disseminated through the Cicely Saunders Institute's organised training days for healthcare professionals and researchers about the use of preference-based outcome measures in economic evaluations of palliative care interventions/services, where the newly developed preference-based outcome measure will be discussed. Results will also be published through scientific journals (and conferences) as they emerge through the project.

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10.3.3 Distress Protocol

Distress Protocol

The proposed study is expected to have minimal risk for participants. Nonetheless, interviewer administered questionnaires may uncover physical complaints, psycho-social concerns, and/ or other problems being experienced by the patient and/ or their caregiver participants.

In order to help prevent undue concerns, the following steps will be taken:

1. Before each questionnaire is administered, it will be emphasised that:
    - Participation is entirely voluntary and that the participant can withdraw from the study at any time.
    - Participants do not have to answer any question(s) that they do not feel comfortable with.
    - Participants can withdraw from the study at any time, and for any reason.
2. After completing the questionnaire, time will be set aside to ensure that all respondents are comfortable with the process of the interview.
3. All participants will be provided with the contact details for the Macmillan Information & Support Centre, based at the Cicely Saunders Institute, King's College Hospital. The purpose of the Macmillan centre is to provide information, support and a welcoming relaxed environment for patients, carers or family and friends of people with cancer or other long term conditions.

If a participant withdraws from and/or experiences distress during the study, the following additional steps will be taken:

1. The research team member will encourage the participant to seek help from their GP, especially if the issue raised is one regarding the participants own physical or mental wellbeing.

2. If a participant withdraws from the study:

    - The researcher will offer any required support and ensure that the participant is comfortable before leaving, if there is a family member or friend present.

    - If no-one else is present, participants will be encouraged by the research team member to contact a friend or family member. The researcher will remain with the participant (if they are agreeable to this) until this additional support is available.

    - Should the participant be unable or unwilling to identify someone to contact, the researcher will offer any required support and ensure that the participant is comfortable before leaving. The research team member will then make contact with the participant, within 24 hours, to further ensure that the participant is not unduly distressed, and ascertain whether any further support is required.

3. Should a researcher have serious concerns regarding the physical and/ or mental wellbeing of a participant, this will be discussed as a matter of urgency with one of the research study supervisors and appropriate action will then be taken.

10.3.4 Participant consent form

King's College London
University of London

King's College Hospital NHS
NHS Foundation Trust

Participant consent form

Development of a preference based outcome measure for use in economic evaluations of palliative care

Initials

1 I confirm that I have read and understood the information leaflet dated ..... for the above research study and I have received an explanation of the nature, purpose, and duration of the research study and what my involvement will be. ☐

2 I have had time to consider whether to take part in this research study. My questions have been answered satisfactorily and I have received a copy of the Participant Information Leaflet. ☐

3 I confirm that the information collected about me can be used for teaching and educational purposes as well as future research projects if it is anonymised before use. ☐

4 I agree to be contacted during the time of the study; for example to clarify information you provided during the survey ☐

5 I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications ☐

7 I agree to take part in the above research study. ☐

…….	……	.....
Name of Participant (block letters)	Date	Signature

Tick here if participant has given consent but is physically unable to enter signature and has requested an impartial witness. ☐

I witness that _____ has agreed to participate in this research study. I confirm that I have initialled the consent statements as per their wishes.

…….	……	…….
Name of witness (block letters)	**Date**	**Signature**

…….	……	…….
Name of person taking consent (block letters)	**Date**	**Signature**

King's College London, Cicely Saunders Institute,
Department of Palliative Care, Policy and Rehabilitation,
6 Bessemer Road, Denmark Hill, London SE5 9PJ;
Telephone: +44 (0)20 7848 5565; Fax: +44 (0)20 7848 5517
www.csi.kcl.ac.uk

Thank you

10.3.5 Questionnaire

POS-E study 2015

Answer Booklet (interviewer administered)

Thank you very much for agreeing to take part in this survey. As we explained in the information leaflet, this is a survey for King's College London about the different ways in which people feel about health and illness.
All your responses will be treated as confidential, and when we write our report all participants will be anonymous.
If at any stage you feel uncomfortable about any of the questions, you can end the interview.
We are interested in people's views, and there are no right or wrong answers.
Please tell us what you think.

Participant ID _____

Interviewer ID _____

Card block _____

Start time _____

End time _____

[A]

Instructions for the interviewer are shown using CAPITALISED TEXT.
These should not be read to the participant.

Instructions for the participant are shown using blue text.
These should be read aloud to the participant.

Before starting:

- Make sure that the participant has read the information sheet and signed the consent form.
- Check that you have the correct set of health state cards ready.

FILL IN RESPONDENT ID, INTERVIEWER ID, CARD BLOCK AND START TIME ON FRONT PAGE OF THE INTERVIEWER BOOKLET.

READ ALOUD THE INTRODUCTION ON THE FRONT PAGE.

To start off, I would like you to answer a few questions about your own health.

HAND RESPONDENT SELF-COMPLETION BOOKLET OPENED AT PAGE 3
Please answer the questions in section A1 and then return the booklet to me

MAKE SURE RESPONDENT HAS ONLY TICKED ONE BOX IN EACH GROUP

AFTER SECTION A1 HAS BEEN COMPLETED TAKE THE SELF-COMPLETION BOOKLET FROM RESPONDENT.

GO TO **[A1]**.

[A1] Your own health

The following questions ask about your health. There are seven groups of statements. Please read each statement and think how often you felt that way over the last three days. Please tick one statement in each group to show the statement which best describes your specific health concerns DURING THE PAST THREE DAYS.

Pain

I have **not** been affected by pain ❑ 0

I have been affected by pain **slightly** or **moderately** ❑ 1

I have been affected by pain **severely** or **overwhelmingly** ❑ 2

Other symptoms *(e.g. nausea, coughing or constipation)*

I have **not** been affected by other symptoms ❑ 0

I have been affected by other symptoms **slightly** or **moderately** ❑ 1

I have been affected by other symptoms **severely** or **overwhelmingly** ❑ 2

Depression

I have **not** been feeling depressed ❑ 0

I have been feeling depressed **occasionally** or **sometimes** ❑ 1

I have been feeling depressed **most of the time** or **always** ❑ 2

Anxiety

I have **not** been feeling anxious ❑ 0

I have been feeling anxious **occasionally** or **sometimes** ❑ 1

I have been feeling anxious **most of the time** or **always** ❑ 2

Feeling good

I have felt good about myself **most of the time** or **always** ❑ 0

I have felt good about myself **occasionally** or **sometimes** ❑ 1

I have **not** felt good about myself **at all** ❑ 2

Family Anxiety

My family and friends have **not** been anxious about me ❑ 0

My family and friends have been anxious about me **occasionally** or **sometimes** ❑ 1

My family and friends have been anxious about me **most of the time** or **always** ❑ 2

Practical matters *(e.g. financial or personal)*

I **do not** have unresolved practical matters ❑ 0

I **have** unresolved practical matters ❑ 1

GO TO SECTION [B] RANKING EXERCISE

Section [B] Ranking Exercise

CARD BLOCK 1: SHUFFLE ALL 8 GREEN CARDS AND THE PINK AND PURPLE CARDS

PLEASE SHUFFLE THE ALL 8 GREEN (OR BLUE) CARDS AND THE PINK (FULL HEALTH) AND PURPLE (DEAD) CARDS.

DO NOT INCLUDE THE WHITE SHOW CARDS OR THE BLACK EXAMPLE CARD.

THERE ARE 10 CARDS TO BE RANKED IN TOTAL.

SHOW PACK OF CARDS TO RESPONDENT

"The previous sections that you have just completed had questions made up from statements about health for you to choose from. I now have some cards which describe different states that you might find yourself in, and each of these is made up by combining the statements that you have just seen."

"For example here is a card which has a description of a state written on it."

GIVE THE BLACK CARD (Health state X – example) TO THE RESPONDENT TO LOOK AT.

"If you were living in this state you would"… **READ CARD ALOUD**

FOR EXAMPLE, for the card pictured below:

- I have been affected by pain slightly or moderately
- I have I have been affected slightly or moderately by other symptoms e.g. nausea, cough or constipation
- I have been feeling depressed occasionally or sometimes
- I have been feeling anxious occasionally or sometimes
- I have felt good about myself occasionally or sometimes
- My family and friends have been anxious about me occasionally or sometimes
- I have unresolved practical matters

YOU WOULD SAY ALOUD: "if you were living in this health state you would be affected by pain slightly or moderately; be affected slightly or moderately by other symptoms like nausea, cough, or constipation; feel depressed occasionally or sometimes; feel anxious occasionally or sometimes; feel good about yourself only occasionally or sometimes; your family and friends will be anxious about you occasionally or sometimes; and you would have unresolved practical matters"

"We are now going to use a technique called ranking to find out how good or bad you think living in some of the states would be. The states that we will show you have nothing to do with the answers you have just provided about your own health."

"Now, here is a set of 10 cards. Each of them has a description of a state written on it. Each card has a different state description on it."

"I would like you to place the cards in order of how good or bad you think they are. I would like you to imagine that you yourself are actually in each state and that you would live in that state for 10 months. You should assume that you have only 10 months to live. Please read each card carefully to see exactly what the state is and how it differs from the others. When you have finished reading through, please place the cards in order of how good or bad you think they are. Put the one you think is best at the top **(POINT TO TOP END)**, and the one that you think is worst at the bottom (**POINT TO THE BOTTOM END**)."

PASS CARDS TO RESPONDENT

"If you think two states are equal, put them side by side. You will notice that there is a card which says "dead". Please also put this with the other cards in order where you think it belongs. You can change your ordering at any time."

RECORD THE RESULTS OF THE RANKING EXERCISE IN THE TABLE BELOW. IF MORE THAN TWO CARDS ARE RANKED EQUALLY, CROSS OUT THE NUMBER IN THE RANK COLUMN AND WRITE THE CORRECT RANK.

INTERVIEWER: PLEASE RECORD HERE THE RANK ORDER OF THE 10 HEALTH STATE CARDS.

Rank	Health state card e.g. 10
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

SECTION [C] VALUATION EXERCISE

INTERVIEWER SCRIPT FOR TTO

HAVE THE RESPONSE SHEET FOR TTO (PAGE TTO1) READY

HAVE SHOWCARDS 1- 3 READY.

NOTE START TIME OF THE TIME TRADE-OFF ON PAGE TTO1

1. **REMOVE THE PINK CARD AND PURPLE CARD FROM THE PACK OF RANKED CARDS.**
PLEASE SHUFFLE ALL 8 GREEN (OR BLUE) CARDS THAT HAVE JUST BEEN RANKED.

"Now we are going to use a technique called the time trade off to find out how good or bad you think living in some of the health states would be. The time trade off asks you to compare living in two health states for a maximum period of 10 months. You should assume that you have only 10 months to live."

2. **PLACE TTO SHOWCARD 1 ON THE TABLE AND SAY TO RESPONDENT:**
"First, let's go through an example together. Here is a choice between being in LIFE A for a certain length of time, or LIFE B for 10 Months."

"I am going to ask you about the state at the top which is LIFE A (POINT TO LIFE A) and the state at the bottom which is LIFE B (POINT TO LIFE B). The state in LIFE A will stay the same but the time for which you will be in this state will change. The state in LIFE B will change but the length of time of time will always be the same at 10 Months."

3. **PLACE TTO SHOWCARD 2 ON THE TABLE NEXT TO TTO SHOWCARD 1:**
"This is an example of how I would like you to make your choice. Here are the two possibilities, LIFE A and Life B (POINT TO THE TWO COLUMNS). In the left hand column, is shown the different lengths of time that you could be in LIFE A for. In the right hand column is shown the number of years that you could be in LIFE B for. This time is always the same at 10 months."

You would look at each row on this answer sheet, and then decide whether you would prefer to have either Life A or Life B. You would place a tick in the box if you would prefer Life A and a cross if you would prefer Life B. You would place an equal's sign if you feel Life A and Life B are equivalent (i.e. you could not choose between Life A and Life B)."

"In this example, being in Life A for nine months is seen as the same as being in Life B for 10 months."

4. **TAKE TTO SHOWCARD 2 AWAY AND PLACE TTO SHOWCARD 3 ON THE TABLE NEXT TO TTO SHOWCARD 1.**

"This is another example. This one shows that being in Life A for 5 months is the same as being in Life B for 10 months.

You will notice that in this example not all the boxes have been filled in. This is because it is sometimes hard to say whether you would definitely choose Life A or definitely choose life B. When this happens you will have a number of boxes where you find it difficult to choose between the two choices. In these cases, please place an equals sign in the one box which shows your 'best guess', for example at 5 months in Life A being the same as 10 months in Life B as shown here."

"This is the kind of choice I will ask you to make. Do you understand what I would like you to do?"

IF YES: CIRCLE ANSWER ON PAGE TTO1, TAKE BACK SHOWCARDS 3 AND 1, GO TO 5

IF NO: CIRCLE ANSWER ON PAGE TTO1, TAKE BACK SHOWCARDS 1 AND 3, and GO BACK TO 1 AND SAY: "Let's go through this again."

5. **PUT TTO SHOWCARDS 1 TO 3 AWAY**

a. "Now we are ready to begin. From now on I would like you to imagine that you yourself are in these states without any change and that you had only 10 months to live."

INTERVIEWER CHECK:

b. PICK UP PACK OF 8 GREEN (or BLUE) HEALTH STATE CARDS (SHUFFLED) THAT WERE JUST RANKED

c. TAKE OUT <u>FIRST</u> GREEN (or BLUE) CARD TO BE VALUED. ENTER THE CARD'S HEALTH STATE NUMBER: _____

d. HAND THE RESPONDENT THE ANSWER BOOKLET FOR STATE 'X' OPENED AT FIRST DOUBLE PAGE (i.e. pages 2 and 3):

PLACE CARD TO BE VALUED (BLUE or GREEN) OVER THE BOX MARKED LIFE B

"This is the first choice that I would like you to make. Please read through carefully the states for Life A and Life B. These are both states that you have seen before. Please tell me when you have finished reading."

WHEN RESPONDENT HAS FINISHED READING, SAY:

"Now please mark your answer on this sheet. Remember that you would place a tick in the box if you would prefer Life A, and a cross if you would prefer Life B. You would place an equal's sign if you feel Life A and Life B are equivalent (i.e. you could not choose between Life A and Life B)."

"You may change your answer at any time by using the rubber provided. Please return the booklet to me when you have finished."

WHEN THE RESPONDENT HAS COMPLETED FILLING THE BOOKLET, TAKE BACK THE BOOKLET AND PROCEED AS FOLLOWS:

- **IF RESPONDENT HAS PLACED AN '=' WHICH IS NOT IN THE BOTTOM LINE, CIRCLE APPROPRIATE SCORE. THEN GO TO 6**

- **IF AN '=' IS PLACED ON THE BOTTOM LINE, SAY TO RESPONDENT**: "I see that you have placed an equal sign on the bottom line. Do you think that being in Life B for 10 months is equal to immediate death or do you think or do you think it is worse than immediate death?"

- **IF EQUAL: LEAVE ANSWER AS IT IS, CIRCLE '0.00', AND GO TO 6**

- **IF WORSE: WRITE BESIDE THE BOTTOM LINE: 'WORSE THAN DEATH' Then GO TO TTO PROTOCOL FOR STATES WORSE THAN DEATH.**

- **IF BETTER: ASK RESPONDENT TO THINK AGAIN ABOUT THE CHOICES IN THE BOTTOM FEW ROWS.**

- **IF RESPONDENT HAS PLACED TICKS FOR ALL CHOICES, GO TO TTO PROTOCOL FOR STATES WORSE THAN DEATH.**

- **IF RESPONDENT HAS PLACED CROSSES FOR ALL CHOICES, SAY**: "I see that you have put a cross for all the choices. Do you think that 10 months in Life B is better, worse, or the same as 10 months in Life A"?

- **IF BETTER: ASK** "why", **AND RECORD THE ANSWER VERBATIM ON THE LAST PAGE OF THE BOOKLET. CIRCLE "+97.00" ON PAGE 3 IN THE BOOKLET.**

- **IF WORSE: ASK RESPONDENT TO THINK AGAIN ABOUT THE CHOICES IN THE TOP FEW ROWS**
- **IF SAME: ASK** "why", **AND RECORD THE ANSWER VERBATIM ON THE LAST PAGE OF THE BOOKLET. CIRCLE '1.00' ON PAGE 3 IN THE BOOKLET.**

6. **TAKE BACK COMPLETED BOOKLET FOR STATE X**

a. REMOVE GREEN (or BLUE) CARD FROM COMPLETED BOOKLET FOR STATE X

b. GIVE THE RFSPONDENT THE BOOKLET FOR THE NEXT STATE

c. TAKE OUT <u>SECOND</u> – GREEN OR BLUE – CARD TO BE VALUED.

d. ENTER THE CARD'S HEALTH STATE NUMBER: _____

e. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 7]

7. **TAKE OUT <u>THIRD</u> – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 8]

8. **TAKE OUT <u>FOURTH</u> – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 9]

9. **TAKE OUT <u>FIFTH</u> – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 10]

10. **TAKE OUT <u>SIXTH</u> – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 11]

11. **TAKE OUT <u>SEVENTH</u> – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 12]

12. **TAKE OUT EIGHTH – GREEN OR BLUE – CARD TO BE VALUED.**

a. ENTER THE CARD'S HEALTH STATE NUMBER: _____

b. [REPEAT PROCESS AS IN SECTION 5d – WHERE 'GO TO 6' REPLACE BY 'GO TO 13]

13. **WHEN RESPONDENT HAS FINISHED ALL HEALTH STATES: NOTE FINISH TIME OF TTO ON PAGE TTO1.**

14. **GO TO SECTION D**

TIME TRADE-OFF PROTOCOL FOR STATES RATED AS WORSE THAN DEATH: SELF COMPLETEION METHOD

1. "I need to ask you another question about this state."

TURN TO THE SECOND DOUBLE PAGE OF THE BOOKLET (i.e. PAGES 4 AND 5), AND THEN GIVE THE BOOKLET BACK TO THE RESPONDENT. SAY:

"As you can see, Life A and Life B are now different to the first page. Life B involves dying immediately (**POINT TO LIFE B**)."

"Life A now involves experiencing two health states. First is the health state that you rated as worse than death (**POINT TO HEALTH STATE ON LEFT HAND SIDE OF LIFE A**) which is then followed by this health state (**POINT TO HEALTH STATE ON RIGHT HAND SIDE OF LIFE A**)."

"The number of months that you will be in each of these health states is shown on your answer sheet here (**POINT TO THE COLUMNS**)."

"I would still like you to imagine that you yourself are in these states, and that they would last up to a maximum of 10 months. You should assume that you have only 10 months to live."

"Please fill in your answer sheet in the same as before and when you have finished hand the booklet back to me and we will move on to the next question".

WHEN RESPONDENT HAS FINISHED GO TO NEXT STATE.

<u>NOTE FOR CODING RESPONSES (STATES WORSE THAN DEATH)</u>

IF AN '=' IS PLACED ON THE BOTTOM LINE, CIRCLE '0.00' ON PAGE 5 OF THE BOOKLET

IF THE RESPONDENT HAS PLACED TICKS FOR ALL CHOICES, CIRCLE '+97.00' ON PAGE 3 OF THE BOOKLET

IF THE RESPONDENT HAS PLACED CROSSES FOR ALL CHOICES, CIRCLE '+97.00' ON· PAGE 3 OF THE BOOKLET

Respondent Serial Number | | | | | | |

TIME RECORD SHEET FOR THE TIME TRADE-OFF: SELF COMPLETION METHOD

1. Time at start of trade-off exercise

24 hour clock

2. Time at end of trade-off exercise

24 hour clock

3. Time taken for the time trade-off exercise

Minutes

4. Did the respondent understand the exercise the first time?

Yes	1: continue exercise
No	2: repeat script

5. Did the respondent understand the exercise the second time?

Yes	1: continue exercise
No	2: continue exercise

PAGE TTO1

[D] PARTICIPANT FEEDBACK QUESTIONS

"Now we would like to know how easy or difficult you found the questions, and also to ask you a few background questions"

HAND RESPONDENT THE BOOKLET OPEN AT SECTION [D]
ASK PARTICIPANT TO FILL SECTIONS D AND E

1	I found it **easy to understand** the tasks I was faced with today	Agree 1 2 3 4 5 Disagree
2	I found it **easy to tell the difference** between the health states I was asked to think about	Agree 1 2 3 4 5 Disagree
3	When completing a task, I **tried to be consistent** with how I had answered the previous questions	Agree 1 2 3 4 5 Disagree
4	I found it **difficult to decide** on the exact point at which I thought Options A and B were the same	Agree 1 2 3 4 5 Disagree
5	The number of months of life in the tasks was **too long** for it to be meaningful to me	Agree 1 2 3 4 5 Disagree
6	It is not as bad to become ill **in the future** as it is to become ill **now**	Agree 1 2 3 4 5 Disagree
7	When you live in a very poorly state for a long time, it can get more and **more difficult to cope with**	Agree 1 2 3 4 5 Disagree
8	When I thought about living in the very poorly health states, I took into account the possibility that some **treatment or relief would be provided**	Agree 1 2 3 4 5 Disagree
9	The number of months of life in the tasks was **too short** for it to be meaningful to me	Agree 1 2 3 4 5 Disagree
10	I think going from **good health to poor health** is **more realistic** than going from **poor health to good health**.	Agree 1 2 3 4 5 Disagree

[E] BACKGROUND QUESTIONS

1. Are you currently experiencing serious illness?

☐ Yes ☐ No

If yes, please state diagnosis _____

2. Which of the following statements best describes you:

I am a current smoker ☐

I am an ex-smoker ☐

I have never been a smoker ☐

3. Which of the following best describes your main activity?

In employment or self-employment ☐

Retired ☐

Housework ☐

Student ☐

Seeking work ☐

Other (please specify) ☐ _____

4. Did your education continue after the minimum school leaving age?

Yes ☐

No ☐

5. Do you have a Degree or equivalent professional qualification?

Yes ☐

No ☐

6. Does your household:

Own your home outright, or with a mortgage; ☐

Rent from a local authority; ☐

Rent from the private sector. ☐

7. How old are you? _____years

8. Are you male or female?

Male ☐

Female ☐

9. How many people are there in your household? _____

10. How many of these are under the age of 18? _____

Thank you for taking part in this survey

[K] INTERVIEWER FEEDBACK TO BE COMPLETED AFTER THE INTERVIEW

1. How well do you think the respondent understood and carried out the ranking exercise during the interview?

Understood and performed exercises easily…….…….....☐

Some problems but seemed to understand the exercises in the end.....☐

Doubtful whether the respondent understood the exercises…….……..☐

2. In terms of effort and concentration, which one of the following statements best describes the way the respondent undertook the ranking exercise?

Concentrated very hard and put a great deal of effort into it…..…☐

Concentrated fairly hard and put some effort into it…….……...☐

Didn't concentrate very hard and put little effort into it…….…….☐

Concentrated at the beginning but lost interest/concentration before reaching the end…..……..……..☐

3. How well do you think the respondent understood and carried out the time trade off exercises during the interview?

Understood and performed exercises easily…….…….....☐

Some problems but seemed to understand the exercises in the end.....☐

Doubtful whether the respondent understood the exercises…….……..☐

4. In terms of effort and concentration, which one of the following statements best describes the way the respondent undertook the first set of time trade off exercises?

Concentrated very hard and put a great deal of effort into it……☐

Concentrated fairly hard and put some effort into it…….……..☐

Didn't concentrate very hard and put little effort into it…….…….☐

Concentrated at the beginning but lost interest/concentration before reaching the end…..……..……..☐

10.3.6 TTO show cards and example cards

TTO SHOWCARD 1: EXAMPLE

LIFE "A"

FULL HEALTH

LIFE "B"

I HAVE BEEN AFFECTED BY PAIN **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN AFFECTED BY OTHER SYMPTOMS **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN FEELING DEPRESSED **OCCASIONALLY** OR **SOMETIMES**

I HAVE BEEN FEELING ANXIOUS **OCCASIONALLY** OR **SOMETIMES**

I HAVE FELT GOOD ABOUT MYSELF **OCCASIONALLY** OR **SOMETIMES**

MY FAMILY AND FRIENDS HAVE BEEN ANXIOUS ABOUT ME **OCCASIONALLY** OR **SOMETIMES**

I HAVE **UNRESOLVED** PRACTICAL MATTERS

TTO SHOWCARD 2: EXAMPLE ANSWER SHEET (1)

LIFE "A"(full health)		**LIFE "B"**
10 Months	✓	10 Months
9 Months 2 Weeks	=	10 Months
9 Months	**X**	10 Months
8 Months 2 Weeks	**X**	10 Months
8 Months	**X**	10 Months
7 Months 2 Weeks	**X**	10 Months
7 Months	**X**	10 Months
6 Months 2 Weeks	**X**	10 Months
6 Months	**X**	10 Months
5 Months 2 Weeks	**X**	10 Months
5 Months	**X**	10 Months
4 Months 2 Weeks	**X**	10 Months
4 Months	**X**	10 Months
3 Months 2 Weeks	**X**	10 Months
3 Months	**X**	10 Months
2 Months 2 Weeks	**X**	10 Months
2Months	**X**	10 Months
1 Month 2 Weeks	**X**	10 Months
1 Month	**X**	10 Months
0 Months 2 Weeks	**X**	10 Months
0 Months	**X**	10 Months

Place a "✓" if you prefer Life "A"

Place an "X" if you prefer Life "B"

Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

TTO SHOWCARD 3: EXAMPLE ANSWER SHEET (2)

LIFE "A"(perfect health)		**LIFE "B"**
10 Months	✓	10 Months
9 Months 2 Weeks	✓	10 Months
9 Months	✓	10 Months
8 Months 2 Weeks	✓	10 Months
8 Months	✓	10 Months
7 Months 2 Weeks	✓	10 Months
7 Months	✓	10 Months
6 Months 2 Weeks		10 Months
6 Months		10 Months
5 Months 2 Weeks		10 Months
5 Months	=	10 Months
4 Months 2 Weeks		10 Months
4 Months		10 Months
3 Months 2 Weeks	**X**	10 Months
3 Months	**X**	10 Months
2 Months 2 Weeks	**X**	10 Months
2 Months	**X**	10 Months
1 Month 2 Weeks	**X**	10 Months
1 Month	**X**	10 Months
0 Months 2 Weeks	**X**	10 Months
0 Months	**X**	10 Months

Place a "✓" if you prefer Life "A"
Place an "X" if you prefer Life "B"
Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

10.3.7 Response Booklet for health states

Respondent Serial Number | | | | | | |

Health state No.:

Card block:

TIME TRADE-OFF: SELF-COMPLETION METHOD

RESPONSE BOOKLET FOR STATE

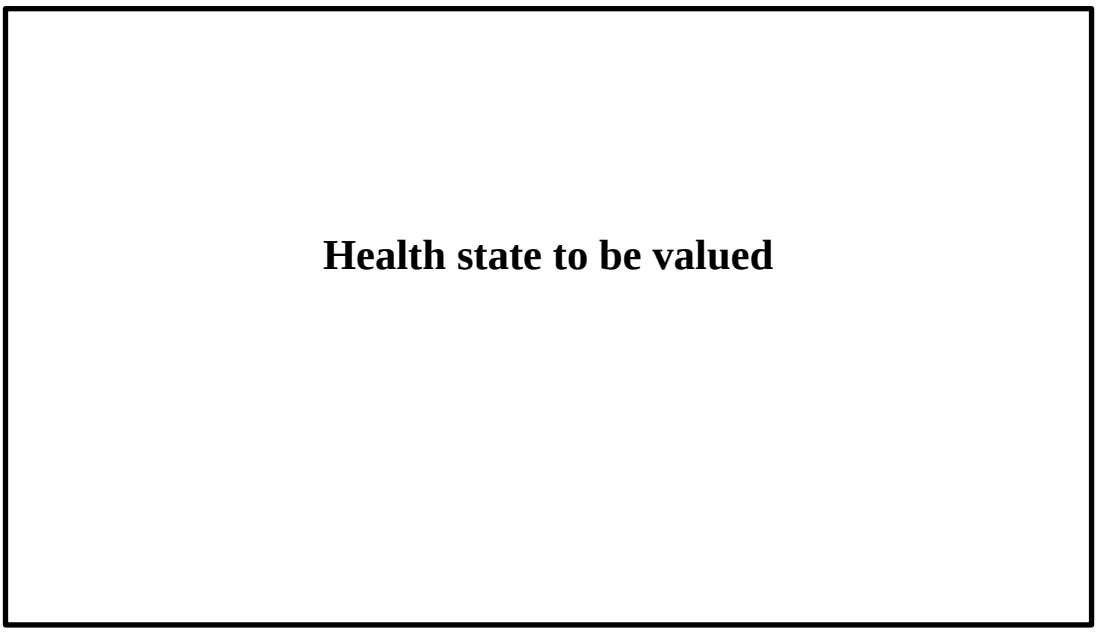
X

HEALTH STATE RATED BETTER THAN DEATH

LIFE "A"



LIFE "B"



HEALTH STATE RATED BETTER THAN DEATH

LIFE "A" (full health)		LIFE "B"	FOR INTER VIEWER USE
10 Months		10 Months	+01.00
9 Months 2 Weeks		10 Months	+00.95
9 Months		10 Months	+00.90
8 Months 2 Weeks		10 Months	+00.85
8 Months		10 Months	+00.80
7 Months 2 Weeks		10 Months	+00.75
7 Months		10 Months	+00.70
6 Months 2 Weeks		10 Months	+00.65
6 Months		10 Months	+00.60
5 Months 2 Weeks		10 Months	+00.55
5 Months		10 Months	+00.50
4 Months 2 Weeks		10 Months	+00.45
4 Months		10 Months	+00.40
3 Months 2 Weeks		10 Months	+00.35
3 Months		10 Months	+00.30
2 Months 2 Weeks		10 Months	+00.25
2 Months		10 Months	+00.20
1 Month 2 Weeks		10 Months	+00.15
1 Month		10 Months	+00.10
0 Months 2 Weeks		10 Months	+00.05
0 Months		10 Months	+00.00
			+97.00

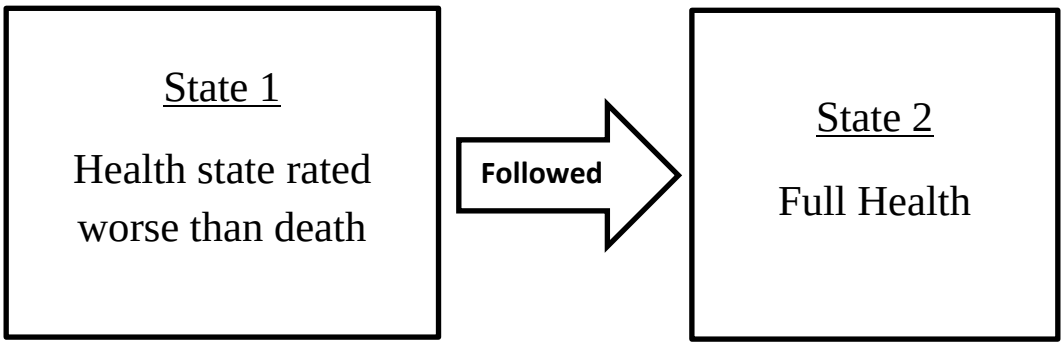
Place a "✓" if you prefer Life "A"

Place an "**X**" if you prefer Life "B"

Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

HEALTH STATE RATED WORSE THAN DEATH

LIFE "A"



LIFE "A"



HEALTH STATE RATED WORSE THAN DEATH

LIFE "A"			LIFE "B"	FOR INTER VIEWER USE
STATE 1	**STATE 2 (full health)**			
0 Months 2 Weeks	9 Months 2 Weeks		Immediate Death	–19.00
1 Month	9 Months		Immediate Death	– 09.00
1 Month 2 Weeks	8 Months 2 Weeks		Immediate Death	– 05.67
2 Months	8 Months		Immediate Death	– 04.00
2 Months 2 Weeks	7 Months 2 Weeks		Immediate Death	– 03.00
3 Months	7 Months		Immediate Death	– 02.33
3 Months 2 Weeks	6 Months 2 Weeks		Immediate Death	– 01.86
4 Months	6 Months		Immediate Death	– 01.50
4 Months 2 Weeks	5 Months 2 Weeks		Immediate Death	– 01.22
5 Months	5 Months		Immediate Death	– 01.00
5 Months 2 Weeks	4 Months 2 Weeks		Immediate Death	– 00.82
6 Months	4 Months		Immediate Death	– 00.67
6 Months 2 Weeks	3 Months 2 Weeks		Immediate Death	– 00.54
7 Months	3 Months		Immediate Death	– 00.43
7 Months 2 Weeks	2 Months 2 Weeks		Immediate Death	– 00.33
8 Months	2 Months		Immediate Death	– 00.25
8 Months 2 Weeks	1 Month 2 Weeks		Immediate Death	– 00.18
9 Months	1 Month		Immediate Death	– 00.11
9 Months 2 Weeks	0 Months 2 Weeks		Immediate Death	– 00.05
10 Months	0 Months		Immediate Death	00.00

Place a "✓" if you prefer Life "A"

Place an "**X**" if you prefer Life "B"

Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

Respondent Serial Number

TIME TRADE-OFF: SELF-COMPLETION METHOD

HEALTH STATE X

VERBATIM RESPONSE

10.3.8 Health state cards

Block 1

Health state 6 (2101100) – Block 1
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have not been affected by pain
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 13 (2222112) – Block 1
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation severely or overwhelmingly
I have been affected by pain severely or overwhelmingly
I have been feeling depressed most of the time or always
I have been feeling anxious occasionally or sometimes
I have unresolved practical matters
I have not felt good about myself at all

Health state 1 (0000000) – Block 1
My family and friends have not been anxious about me
I have not been affected by other symptoms e.g. nausea, cough or constipation
I have not been affected by pain
I have not been feeling depressed
I have not been feeling anxious
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 12 (2221112) – Block 1
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation severely or overwhelmingly
I have been affected by pain severely or overwhelmingly
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I have unresolved practical matters
I have not felt good about myself at all

Health state 3 (1100000) – Block 1
My family and friends have been anxious about me occasionally or sometimes
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have not been affected by pain
I have not been feeling depressed
I have not been feeling anxious
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 4 (1100100) – Block 1
My family and friends have been anxious about me occasionally or sometimes **I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately** **I have not been affected by pain** **I have not been feeling depressed** **I have been feeling anxious occasionally or sometimes** **I do not have unresolved practical matters** **I have felt good about myself most of the time or always**

Health state 5 (2100100) – Block 1
My family and friends have been anxious about me most of the time or always **I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately** **I have not been affected by pain** **I have not been feeling depressed** **I have been feeling anxious occasionally or sometimes** **I do not have unresolved practical matters** **I have felt good about myself most of the time or always**

Health state 8 (2111110) – Block 1
My family and friends have been anxious about me most of the time or always **I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately** **I have been affected by pain slightly or moderately** **I have been feeling depressed occasionally or sometimes** **I have been feeling anxious occasionally or sometimes** **I have unresolved practical matters** **I have felt good about myself most of the time or always**

Block 2

Health state 6 (2101100) – Block 2
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have not been affected by pain
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 7 (2111100) – Block 2
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have been affected by pain slightly or moderately
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 9 (2111111) – Block 2
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have been affected by pain slightly or moderately
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I have unresolved practical matters
I have felt good about myself occasionally or sometimes

Health state 10 (2121111) – Block 2
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation slightly or moderately
I have been affected by pain severely or overwhelmingly
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I have unresolved practical matters
I have felt good about myself occasionally or sometimes

Health state 11 (2221111) – Block 2
My family and friends have been anxious about me most of the time or always
I have been affected by other symptoms e.g. nausea, cough or constipation severely or overwhelmingly
I have been affected by pain severely or overwhelmingly
I have been feeling depressed occasionally or sometimes
I have been feeling anxious occasionally or sometimes
I have unresolved practical matters
I have felt good about myself occasionally or sometimes

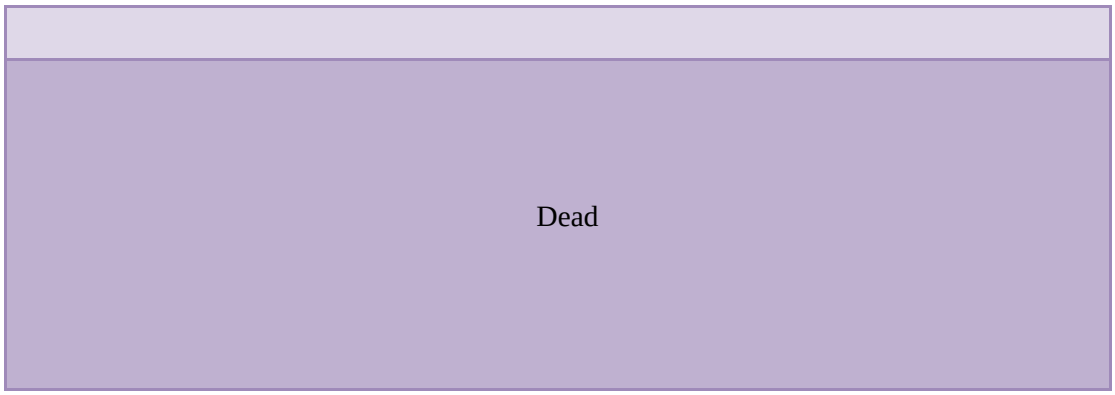
Health state 2 (1000000) – Block 2
My family and friends have been anxious about me occasionally or sometimes
I have not been affected by other symptoms e.g. nausea, cough or constipation
I have not been affected by pain
I have not been feeling depressed
I have not been feeling anxious
I do not have unresolved practical matters
I have felt good about myself most of the time or always

Health state 13 (2222112) – Block 2
My family and friends have been anxious about me <u>most of the time or always</u> **I have been affected by other symptoms e.g. nausea, cough or constipation <u>severely or overwhelmingly</u>** **I have been affected by pain <u>severely or overwhelmingly</u>** **I have been feeling depressed <u>most of the time or always</u>** **I have been feeling anxious <u>occasionally or sometimes</u>** **I have <u>unresolved</u> practical matters** **I have <u>not</u> felt good about myself <u>at all</u>**

Other health state cards

Full Health

Health state X (example)
I have been affected by pain <u>slightly or moderately</u> I have been affected by other symptoms <u>slightly or moderately</u> I have been feeling depressed <u>occasionally or sometimes</u> I have been feeling anxious <u>occasionally or sometimes</u> I have felt good about myself <u>occasionally or sometimes</u> My family and friends have been anxious about me <u>occasionally or sometimes</u> I have <u>unresolved</u> practical matters


Dead

THE UNIVERSITY OF YORK

CENTRE FOR HEALTH ECONOMICS

TIME TRADE-OFF USER MANUAL:

Manual edited by C. Gudex

Aprill 1994

TIME TRADE-OFF

USER MANUAL:

PROPS AND SELF-COMPLETION METHODS

Procedures designed by:

Measurement and Valuation of Health Group Centre for Health Economics
University of York,
YOI SDD

and

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Manual edited by C. Gudex April 1994

INTRODUCTION

In 1992, the Measurement and Valuation of Health {MVH) Group at the Centre for Health Economics conducted a study with Social and Community Planning Research (SCPR) comparing different methods of valuing health states (Dolan et al 1993). Random samples of 335 members of the general population were interviewed in their own homes by specially trained interviewers. Each respondent was asked to value a series of health states using two different valuation methods - Standard Gamble (SO) and Time Trade-Off (TTO).

Considerable time and energy went into the production of the protocols for the interviews. Standard methodology (derived primarily from research in Canada and the USA) for both the SG and TTO methods involves the use of specially designed boards and cards. The SG procedure typically uses a 'probability wheel' which allows different probabilities of health outcomes to be presented to the respondent, while the TTO typically uses a horizontal sliding scale which allows the length of time spent in a health state to be varied. SG and TTO boards based on the standard methodology were piloted as part of the MVH study and it was found that substantial modifications were required to simplify the material for both the interviewer and the respondent. In addition the standard boards were found to be too large and were difficult to operate. The substantive change made to the SG board during the course of the piloting was the use of a sliding scale rather than a wheel, and a new TTO board was designed so that both sides could be used - one for states considered better than death, and the other for states considered worse than death.

A fundamental question arising from the pilot work was the advantage of using props such as boards and cards in the interview. To address this issue, an alternative method of administering the SG and TTO tasks was developed, representing a significant departure from the standard methodology. In these modified procedures, the respondent was able to take a much more active role and in fact completed much of the valuation task by him/herself without the use of a board.

All four methods performed very well in the main study, to the extent that no single method proved decisively superior to all others from an administrative point of view. Ultimately the choice of method was based on empirical grounds, with the result that the TTO 'Props' (with board and cards) was selected as the 'best' method for valuing health states in population surveys.

Although the MVH Group is now concentrating on the TTO "Props" method in further work, there are certain to be other researchers who want to use the SG method or the TTO in its self-completion form. Thus, we want to ensure that all our methods are available to other interested parties in the field of health status measurement. The health states used in this study were based on the EuroQol descriptive system (Kind et al, 1994), but these valuation procedures have a general application and, can be used for any health state descriptive system. Being aware of the considerable work required in designing and piloting any new methods, we felt that it would be useful if other researchers were able to gain access to a detailed account of the procedures that we bad developed.

In order to maximize the availability of these designs, we have decided to supplement the initial report describing the piloting and interview design (Thomas and ·Thomson 1992) with specific User Guides detailing the four valuation methods:

Standard Gamble: Props and Self-completion
Time Trade-Off: Props and Self- completion

Revisions to the TTO Props method as a result of more recent survey work have also been included. We hope others will be able to pick up from where we have left off, either to make use of the methods in their current form or to modify them further as they wish. In either event we look forward with interest to hearing of the results.

For further information regarding the SG or TTO methods or the MVH study, please contact any member of the MVH Group: Paul Dolan, Claire Gudex, Paul Kind, Alan Williams or SCPR: Roger Thomas, Katarina Thomson.

The SG and TIO guides are available, at a price of £7.50 each (to cover the cost of publication, postage and packing), from:

The Publications Secretary.
Centre for Health Economics,
University of York,
York. YOl 500.

Cheques should be made payable to the University of York.

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THE TIME TRADE-OFF

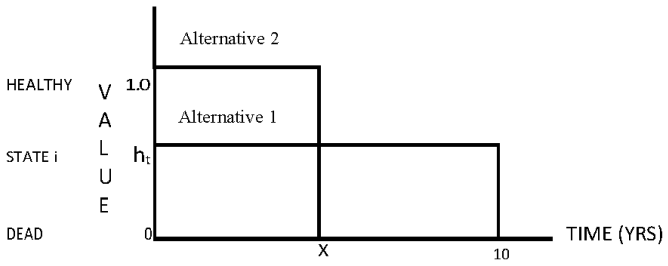
INTRODUCTION

The Time Trade-off produces valuation based on decision made under conditions of certainty. In the generally accepted 'standard' version described by Torrance (1986), the respondent is required to choose between two certain alternatives. For states better than death, one of these alternatives is to live in a state less than full health for a defined period of time (e.g. last 10 years of life). The other alternative is to live in full health but for a shorter period of time (i.e. less than 10 years). The aim is to find the number of years of full health at which the respondent is indifferent between the longer period of less than full health and the shorter period of full health. This indifference point generates a health state value between 1.00 and 0.00. When states worse than death are also used, the health state scores range between 1.00 and –ve infinity, on a scale in which full health and death are assigned values of 1.00 and 0.00 respectively.

The basic TTO procedure, for chronic states better than death, is shown in Figure 1. The respondent is offered two alternatives. Alternative 1 is a treatment with a certain outcome of a chronic state *i* for 10 years followed by death. Alternative 2 is a treatment with a certain outcome of full health for x number of years (where *x<10)* followed by death. Time x is varied until the respondent is indifferent between the two alternatives, at which point the utility value for state *i* is given by:

$$U(i) = x/10$$

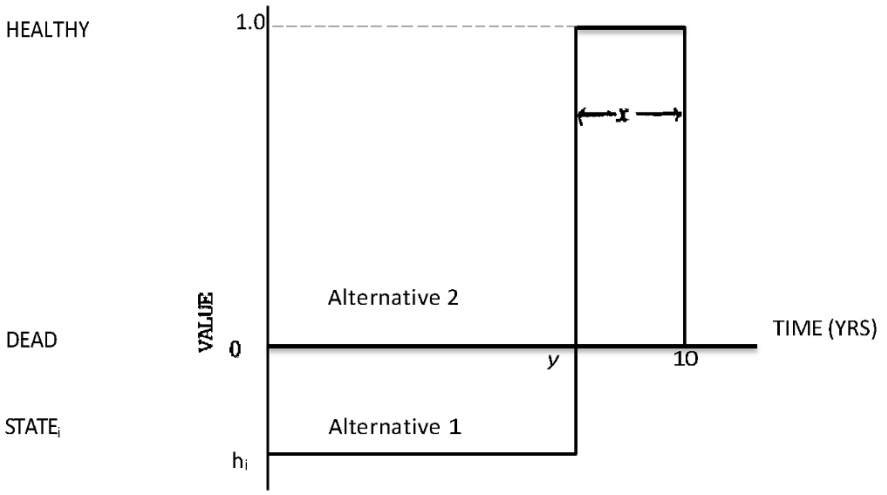
Figure 1: Time Trade-off for a Chronic State Considered Better than Death
(After Torrance 1986)



The format used in this manual for chronic states worse than death, is shown in Figure 2. The respondent is again offered two alternatives but this time Alternative 1 is a combination of chronic state i for y number of years followed by full health for x number of years (where x + y = 10), followed by death. Alternative 2 is the certain outcome of immediate death. Time x is again varied until the respondent is indifferent between the two alternatives, at which point the utility value for state i is given by:

$$U(i) = -x/(10-x)$$

Figure 2: Time Trade-off for a Chronic State Considered Worse than Death



Note that this method differs from that of Torrance (1986) who describes Alternative 1 as a period of full health first, followed by the period of poor health. It was felt that by having the poor health state first, the respondent is forced to think more directly about being in that state for y number of years and thus to recognize the sacrifice that must be made before being in full health for x number of years.

Note that in all cases the maximum time in a state is 10 years without any change, i.e. the respondent does not live beyond 10 years.

Note also that the health state descriptions used in this manual are based on the EuroQol classification system. This is for illustrative purposes only – any descriptive system can be used, as long as it provides a description of 'good' or 'full' health and of a series of dysfunctional health states.

INTERVIEWER TRAINING

Training was one of the key elements to the success of the MVH study and it is recommended that considerable effort be put into this. In the MVH study, professional interviewers registered with SCPR were specifically trained in the handling of these procedures. Although the interviewers were experienced in contacting and communicating with the general public; they were quite unused to manipulating boards and cards. The most productive method of training appeared to be a formal 1-day session with the following format:

- A short general explanation of theory behind the procedures
- Demonstration of the procedure with a 'dummy' interview
- Practice sessions in which the new interviewer conducted the interview with someone familiar with the techniques acting as respondent
- Debriefing session to resolve any problems

New interviewers were then asked to practice the methods at home, and then to conduct 5 formal interviews. These were checked and remedial training was provided if necessary.

REFERENCES

Dolan P., Gudex C., Kind P. & Williams A. 'Valuing Health States: A Comparison of Methods'. MVH Research Report, Centre for Health Economics, University of York, 1993.

Kind P., Gudex C., Williams A. & Dolan P. Practical and Methodological Issues in the Development of the EuroQol: The York experience. In Advances in Medical Sociology, Vol 5: Quality of Life in Health Care. Edited by Albrecht G L and Fitzpatrick R. I.A.I. Press, 1994 (forthcoming).

Thomas R. and Thomson K. Health Related Quality of Life: Technical Report, Joint Centre for Survey Methods, London; August 1992.

Torrance G.W. Measurement of Health State Utilities for Economic Appraisal: A Review, Journal of Health Economi1;&, 5:1-30, 1986.

TIME TRADE-OFF: SELF- COMPLETION METHOD

This is a version of the TTO that does not require a board. Instead, show cards are used to explain the task to the respondent who then completes a series of response booklets. When six states are valued the TTO self-completion method takes approximately 15 minutes.

ITEMS REQUIRED

1. Four show cards made of hard cardboard:

Showcard 1 (see Page 39) indicates 'Life A' and 'life B' boxes

Showcard 2 (see Page 40) describes a hypothetical scenario where the respondent is faced with a choice either to choose a treatment that gives a certain length of time in full health ('Life A') or to remain in a poor health state for 10 Months ('Life B'). The health state used in this example should not be one of those to be valued in the course of the interview.

Showcard 3 (see Page 41) shows the varying lengths of time in full health after treatment ('Life A'). The alternative of life B is always 10 months in the poor health state. An example answer indicates that a respondent is willing to choose the treatment when it is followed by 9 months of full health.

Showcard 4 (see Page 42) is another example answer when a respondent is willing to choose the treatment when it is followed by 5 months of full health.

2. A Response booklet is required for each state to be valued.

The front cover of the booklet identifies the state to be valued and the respondent's serial number.

Pages 2 and 3 are used where the state is rated better than death.

Page 2 presents the alternatives: 'Life A' with an outcome of full heal or 'Life B', with an outcome of the state to be valued.

Page 3 shows the varying lengths of time in full health ('Life A') as compared to 10 months in the 'Life B' state. The respondent answers in the middle blank column. A reminder of when to place a tick, cross or equals sign is provided for the respondent at the bottom of the page. Scores for data entry are in the far right hand column.

Page 4 and 5 are used where the state is rated worse than death.

Page 4 presents the alternatives: 'Life A' with an outcome of the state to be valued (left hand box) followed by full health (right hand box) or 'Life B' with an outcome of immediate death.

Page 5 shows the varying lengths of time in full health (and of being in the state to be valued) for 'Life A' as compared to immediate death ('Life B'). The respondent answers in the middle blank column. A reminder of when to place a tick, cross or equals sign is provided for the respondent at the bottom of the page. Scores for data entry are in the far right hand column.

Page 6 is for verbatim comments if the respondent gives an unusual answer (e.g. that 10 months in a 'less than full' state is better than 10 months in full health).

3. *Page TTO1* for recording time taken and the respondent's understanding of the task.

PROCEDURE

The interviewer first explains the procedure to the respondent using a series of example health states and response sheets. The respondent then completes the procedure him or herself, by working through the states one by one and filling in the appropriate response booklet.

Initially, it is assumed that all states are considered better than death. If the respondent offers an answer which suggests that the state is in fact worse than death, a new series of questions are asked.

The full script is reproduced here on pages 35-38.

1. The interviewer has the show cards and response booklets ready, notes the start time, and then takes the respondent through paragraphs 1 to 3 of the script. At the end of this time, the respondent should have a general understanding of what is required In particular (s)he will be aware that the choice to be made is between 'Life A' with an outcome of full health for a varying amount of time, or 'Life B' with a certain outcome of 10 months in the state to be valued. Also, (s)he will be aware that answers can be ticks, crosses, or equals signs, and that where (s)he is unsure, a 'best guess' can be made.

2. The response booklets are given to the respondent one by one (in a pre-determined order if desired), open at pages 2-3. For each state the respondent fills in ticks, crosses or equals signs on page 3 to indicate at what number of years of Life A (s)he would choose the treatment rather than remain in the health state indicated by Life B.

When the respondent has completed page 3 the interviewer proceeds as follows:

(a) If the respondent has answered with an '=' not in the bottom line, the interviewer circles the appropriate same in the right hand column and gives the respondent the booklet for the next state to be valued.

(b) If an '=' is placed in the bottom line, the interviewer needs to check whether the respondent thinks this state is equal to, or worse than being dead. Depending on the answer to this question, the interviewer either circles '0.00' and continues to the next state, or goes on to the script for states worse than death. (If the respondent thinks that the state is actually better than being dead, (s)he has made an error and is asked to think again about the choices in the bottom few rows on page 3)

(c) if the respondent answers with ticks all the way down page 3, the interviewer goes on to the script for states rated as worse than death.

(d) if the respondent answers with crosses all the way down page 3 the interviewer needs to check whether the respondent thinks this state is equal to, or better than full health. Depending on the answer to this question, the interviewer circles either '+1.00' or '+97.00' respectively, writes any comments of explanation on page 6 of the booklet, and then continues to the next state.

(If the respondent thinks that the state is actually worse than full health, (s)he has made an error and is asked to think again about the choices in the top few rows on page 3).

3. If a state is considered worse than death, the interviewer presents pages 4-5 of the booklet to the respondent and explains that the choices are changed. 'Life A' is now a combination of the state to be valued followed by full health, while 'Life B' is the outcome of immediate death. Page 5 is otherwise completed in just the same way as page 3.

When the respondent has completed page 5 the interviewer proceeds as follows:

(a) if the respondent has answered with an '=' not in the bottom line, the interviewer circles the appropriate score in the right hand column and gives the respondent the booklet for the next state to be valued.

(b) if an '=' is placed in the bottom line, the interviewer circles '0.00'.

(c) if the respondent answers with either all ticks or all crosses on page 5, the interviewer circles t+97.00' on page 3 of the booklet.

When all states have been scored, the finish time is recorded on page TTO1.

DATA ENTRY AND SCORING

In the MVH study, the TTO procedure was preceded by several warm-up' exercises in which the respondent first ranked and then rated the health states to be valued in the TTO. The respondents were thus familiar with the health states, and hence the reference to "states that you have seen before" at the beginning of the TTO procedure.

This is also the explanation for the numbering of the card records for computer entry which start at 12.

Cards 12 and 13-18 TTO Self-completion method: Card 12 was used to record the information from Page TTO1 regarding time taken and understanding of the task. Six states were valued in the MVH health study and the scoring for each one was entered onto a different record such that the score for the first state was entered onto Card 13, that for the second state onto Card 14 etc. Columns 07 to 12 were used if the state was

rated as better than death, and columns 13 to 18 if the state was rated as worse than death. Thus columns 19 to 80 were spare on all these cards. There is no necessity for each state to have a separate record, and if desired, all scores can be entered onto the same record.

The verbatim comments on the last page of the booklets in the Self-Completion Method were useful to explain any unusual or unexpected answers, but were neither coded nor entered onto the computer file.

Only the booklet for state 'X' (Card 13) is reproduced here.

Scoring of health states is incorporated into the interviewer instructions.

In resulting health state scores full health (represented by the 0000000 state) is given a value of 1.00, death is given a value of 0.00 and the minimum score is -19.00. The code +97.00 is used for unusual answers, while "999.99" is recommended for missing answers.

NOTES FOR CIRCLING SCORES IN BOOKLET

If the respondent has more than one '=', then circle the middle value.
If there are an even number of '=', then circle the lower middle value.
If the respondent has no '=', then circle the highest 'X' value.
For verbatim answers, either '+97.00' or '+1.00' will already be circled.

INTERVIEWER SCRIPT
TIME TRADE-OFF: SELF-COMPLETION METHOD

HAVE THE RESPONSE SHEET FOR TTO (PAGE TTO1) READY.
HAVE SHOWCARDS 1- 4 READY.
NOTE START TIME OF THE TIME TRADE-OFF ON PAGE TTO1

1. **PLACE TTO SHOWCARD 1 ON THE TABLE AND SAY TO RESPONDENT:**
"Now we are going to the next set of questions.
I am going to ask you about the state at the top which is LIFE A (POINT TO LIFE A) and the state at the bottom which is LIFE B (POINT TO LIFE B). The state in LIFE A will stay the same but the time for which you will be in this state will change. The state in LIFE B will change but the length of time of time will always be the same at 10 Months."

---

2. **TAKE BACK TTO SHOWCARD 1 AND PLACE TTO SHOWCARD 2 ON THE TABLE**

"First, let's go through an example together. Here is a choice between being in LIFE A for a certain length of time, or LIFE B for 10 Months."

PLACE TTO SHOWCARD 3 ON THE TABLE NEXT TO TTO SHOWCARD 2:

"This is an example of how I would like you to make your choice. Here are the two possibilities, LIFE A and Life B (POINT TO THE TWO COLUMNS). In the left hand column, is shown the different lengths of time that you could be, in LIFE A for. In the right hand column is shown the number of years that you could be in LIFE B for. This time is always the same at 10 months.

You would look at each row on this answer sheet, and then decide whether you would prefer to have either Life A or Life B. You would place a tick in the box if you would prefer Life A and a cross if you would prefer Life B. You would place an equal's sign if you feel Life A and Life B are equivalent (i.e. you could not choose between Life A and Life B).

In this example, being in Life A for nine months is seen as the same as being in Life B for 10 months.

---

3. TAKE TTO SHOWCARD 3 AWAY AND PLACE TTO SHOWCARD 4 ON THE TABLE NEXT TO TTO SHOWCARD 2.

"This is another example. This one shows that being in Life A for 5 months is the same as being in Life B for 10 months.

You will notice that in this example not all the boxes have been filled in. This is because it is sometimes hard to say whether you would definitely choose Life A or definitely choose life B. When this happens you will have a number of boxes where you find it difficult to choose between the two choices. In these cases, please place an equals sign in the one box which shows your 'best guess', for example at 5 months in Life A being the same as 10 months in Life B as shown here.

This is the kind of choice I will ask you to make. Do you understand what I would like you to do?"

IF YES: CIRCLE ANSWER ON PAGE TTO1, TAKE BACK SHOWCARDS 2 AND 4, GO TO 4

IF NO: CIRCLE ANSWER ON PAGE TTO1, TAKE BACK SHOWCARDS 2 AND 4, and GO BACK TO 1 AND SAY: "Let's go through this again."

---

4. PUT TTO SHOWCARDS 1 TO 4 AWAY

"Now we are ready to begin. From now on I would like you to imagine that you yourself are in these states without any change and that you had only 10 months to live.

HAND THE RESPONDENT THE ANSWER BOOKLET FOR STATE 'X' OPENED AT FIRST DOUBLE PAGE (i.e. pages 2 and 3):

This is the first choice that I would like you to make. Please read through carefully the states for Life A and Life B. These are both states that you have seen before. Please tell me when you have finished reading."

WHEN RESPONDENT HAS FINISHED READING, SAY:

"Now please mark your answer on this sheet. Remember that you would place a tick in the box if you would prefer Life A, and a cross if you would prefer Life B. You would place an equal's sign if you feel Life A and Life B are equivalent (i.e. you could not choose between Life A and Life B).

You may change your answer at any time by using the rubber provided. Please return the booklet to me when you have finished."

WHEN THE RESPONDENT HAS COMPLETED FILLING THE BOOKLET, TAKE BACK THE BOOKLET AND PROCEED AS FOLLOWS:

- **IF RESPONDENT HAS PLACED AN '=' WHICH IS NOT IN THE BOTTOM LINE, CIRCLE APPROPRIATE SCORE. THEN GO TO 5**
- **IF AN '=' IS PLACED ON THE BOTTOM LINE, SAY TO RESPONDENT: "I see that you have placed an equal sign on the bottom line. Do you think that being in Life B for 10 months is equal to immediate death or do you think or do you think it is worse than immediate death?"**

  IF EQUAL: LEAVE ANSWER AS IT IS, CIRCLE '0.00', AND GO TO 5

  IF WORSE: WRITE BESIDE THE BOTTOM LINE: 'WORSE THAN DEATH' Then GO TO TTO PROTOCOL FOR STATES WORSE THAN DEATH.
  IF BETTER: ASK RESPONDENT TO THINK AGAIN ABOUT THE CHOICES IN THE BOTTOM FEW ROWS.

- **IF RESPONDENT HAS PLACED TICKS FOR ALL CHOICES, GO TO TTO PROTOCOL FOR STATES WORSE THAN DEATH.**
- **IF RESPONDENT HAS PLACED CROSSES FOR ALL CHOICES, SAY: "I see that you have put a cross for all the choices. Do you think that 10 months in Life B is better, worse, or the same as 10 months in Life A"?**

  IF BETTER: ASK "Why", AND RECORD THE ANSWER VERBATIM ON THE LAST PAGE OF THE BOOKLET. CIRCLE "+97.00" ON PAGE 3 IN THE BOOKLET.

  IF WORSE: ASK RESPONDENT TO THINK AGAIN ABOUT THE CHOICES IN THE TOP FEW ROWS
  IF SAME: ASK "WHY", AND RECORD THE ANSWER VERBATIM ON THE LAST PAGE OF THE BOOKLET. CIRCLE '1.00' ON PAGE 3 IN THE BOOKLET.

---

5. TAKE BACK COMPLETED BOOKLET
GIVE THE RFSPONDENT THE BOOKLET FOR THE NEXT STATE

---

6. WHEN RESPONDENT HAS FINISHED ALL HEALTH STATES: NOTE FINISH TIME OF TTO ON PAGE TTO1.

TIME TRADE-OFF PROTOCOL FOR STATES RATED AS WORSE THAN DEATH: SELF COMPLETEION METHOD

1. SAY TO RESPONDENT:

"I need to ask you another question about this state."

TURN TO THE SECOND DOUBLE PAGE OF THE BOOKLET (i.e. PAGES 4 AND 5), AND THEN GIVE THE BOOKLET BACK TO THE RESPONDENT. SAY:

"As you can see, Life A and Life B are now different to the first page. Life B involves dying immediately **(POINT TO LIFE B)**.

Life A now involves experiencing two health states. First is the health state that you rated as worse than death **(POINT TO HEALTH STATE ON LEFT HAND SIDE OF LIFE A)** which is then followed by this health state **(POINT TO HEALTH STATE ON RIGHT BAND SIDE OF LIFE A).**

The number of months that you will be in each of these health states is shown on your answer sheet here (POINT TO THE COLUMNS).

I still want you to imagine that you yourself are in these states, and that they would last up to 10 months without any change and then you would die.

Please fill in your answer sheet in the same as before and when you have finished hand the booklet back to me and we will move on to the next question".

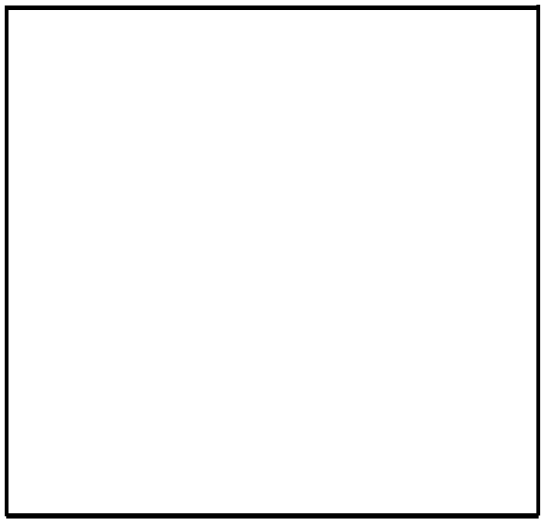
WHEN RESPONDENT HAS FINISHED GO TO NEXT STATE.

NOTE FOR CODING RESPONSES (STATES WORSE THAN DEATH)

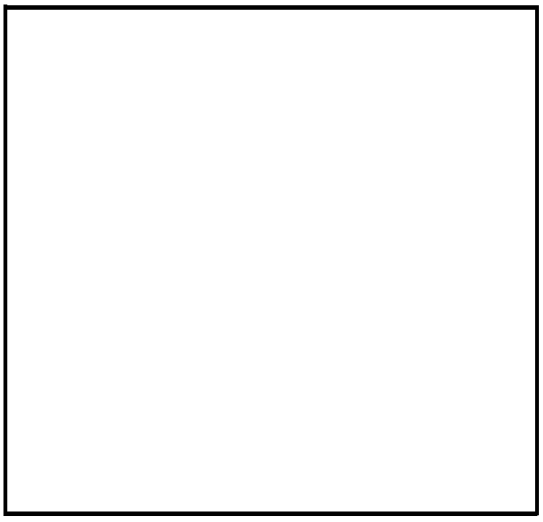
IF AN '=' IS PLACED ON THE BOTTOM LINE, CIRCLE '0.00' ON PAGE 5 OF THE BOOKLET
IF THE RESPONDENT HAS PLACED TICKS FOR ALL CHOICES, CIRCLE '+97.00' ON PAGE 3 OF THE BOOKLET
IF THE RESPONDENT HAS PLACED CROSSES FOR ALL CHOICES, CIRCLE '+97.00' ON· PAGE 3 OF THE BOOKLET

TTO SHOWCARD 1: EXAMPLE

LIFE "A"



LIFE "B"



TTO SHOWCARD 2: EXAMPLE

LIFE "A"

Full Health

LIFE "B"

I HAVE BEEN AFFECTED BY PAIN **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN AFFECTED BY OTHER SYMPTOMS **SLIGHTLY** OR **MODERATELY**

I HAVE BEEN FEELING DEPRESSED **OCCASIONALLY** OR **SOMETIMES**

I HAVE BEEN FEELING ANXIOUS **OCCASIONALLY** OR **SOMETIMES**

I HAVE FELT GOOD ABOUT MYSELF **OCCASIONALLY** OR **SOMETIMES**

MY FAMILY AND FRIENDS HAVE BEEN ANXIOUS ABOUT ME **OCCASIONALLY** OR **SOMETIMES**

TTO SHOWCARD 3: EXAMPLE ANSWER SHEET (1)

LIFE "A"		LIFE "B"
10 Months	✓	10 Months
9 Months 2 Weeks	=	10 Months
9 Months	X	10 Months
8 Months 2 Weeks	X	10 Months
8 Months	X	10 Months
7 Months 2 Weeks	X	10 Months
7 Months	X	10 Months
6 Months 2 Weeks	X	10 Months
6 Months	X	10 Months
5 Months 2 Weeks	X	10 Months
5 Months	X	10 Months
4 Months 2 Weeks	X	10 Months
4 Months	X	10 Months
3 Months 2 Weeks	X	10 Months
3 Months	X	10 Months
2 Months 2 Weeks	X	10 Months
2Months	X	10 Months
1 Month 2 Weeks	X	10 Months
1 Month	X	10 Months
0 Months 2 Weeks	X	10 Months
0 Months	X	10 Months

Place a "✓" if you prefer Life "A"
Place an "X" if you prefer Life "B"
Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

TTO SHOWCARD 4: EXAMPLE ANSWER SHEET (2)

LIFE "A"		LIFE "B"
10 Months	✓	10 Months
9 Months 2 Weeks	✓	10 Months
9 Months	✓	10 Months
8 Months 2 Weeks	✓	10 Months
8 Months	✓	10 Months
7 Months 2 Weeks	✓	10 Months
7 Months	✓	10 Months
6 Months 2 Weeks		10 Months
6 Months		10 Months
5 Months 2 Weeks		10 Months
5 Months	=	10 Months
4 Months 2 Weeks		10 Months
4 Months		10 Months
3 Months 2 Weeks	X	10 Months
3 Months	X	10 Months
2 Months 2 Weeks	X	10 Months
2 Months	X	10 Months
1 Month 2 Weeks	X	10 Months
1 Month	X	10 Months
0 Months 2 Weeks	X	10 Months
0 Months	X	10 Months

Place a "✓" if you prefer Life "A"
Place an "X" if you prefer Life "B"
Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

Respondent Serial Number

Health state No.:
Card block:

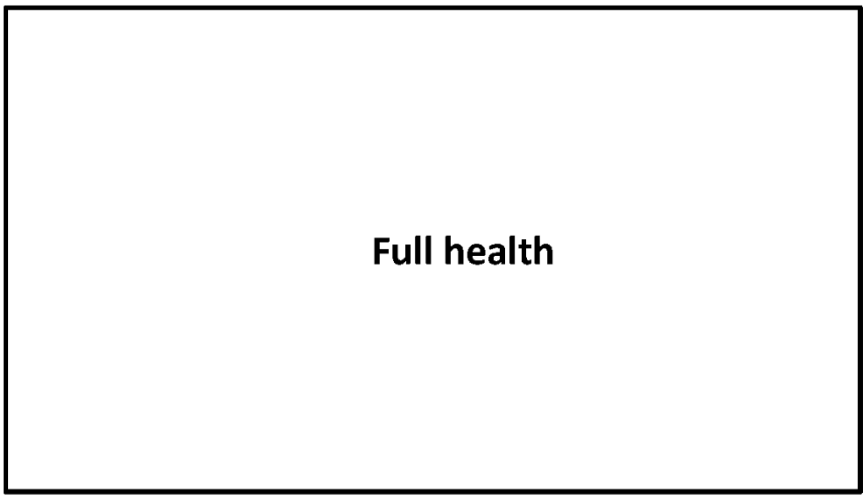
TIME TRADE-OFF: SELF-COMPLETION METHOD

RESPONSE BOOKLET FOR STATE

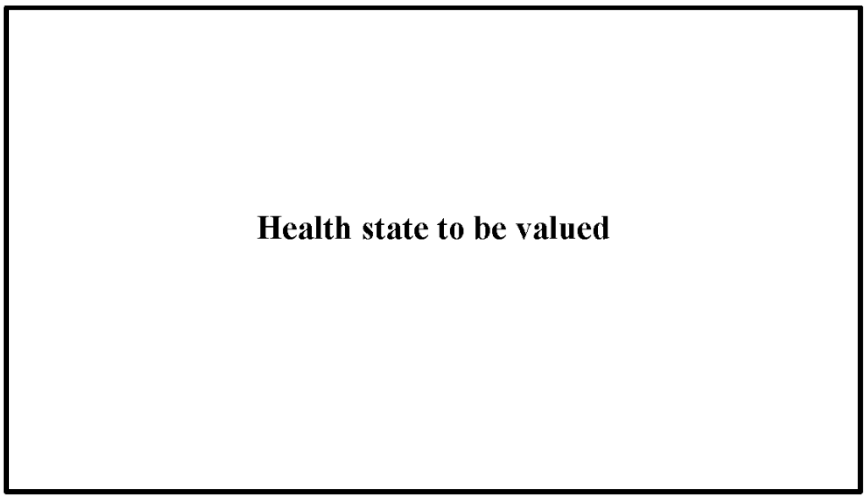
X

HEALTH STATE RATED BETTER THAN DEATH

LIFE "A"



LIFE "B"



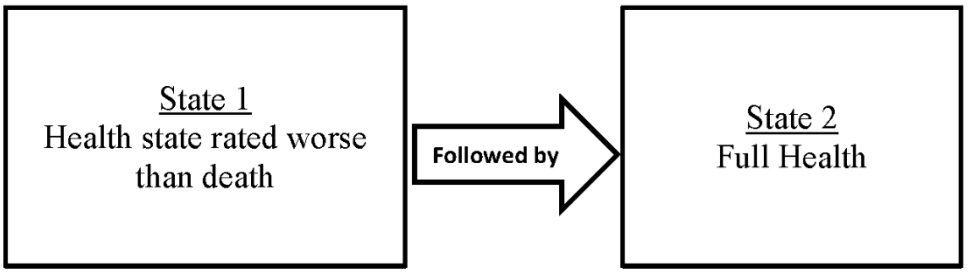
HEALTH STATE: **X RATED BETTER THAN DEATH**

LIFE "A"		LIFE "B"	FOR INTER VIEWER USE
10 Months		10 Months	+01.00
9 Months 2 Weeks		10 Months	+00.95
9 Months		10 Months	+00.90
8 Months 2 Weeks		10 Months	+00.85
8 Months		10 Months	+00.80
7 Months 2 Weeks		10 Months	+00.75
7 Months		10 Months	+00.70
6 Months 2 Weeks		10 Months	+00.65
6 Months		10 Months	+00.60
5 Months 2 Weeks		10 Months	+00.55
5 Months		10 Months	+00.50
4 Months 2 Weeks		10 Months	+00.45
4 Months		10 Months	+00.40
3 Months 2 Weeks		10 Months	+00.35
3 Months		10 Months	+00.30
2 Months 2 Weeks		10 Months	+00.25
2 Months		10 Months	+00.20
1 Month 2 Weeks		10 Months	+00.15
1 Month		10 Months	+00.10
0 Months 2 Weeks		10 Months	+00.05
0 Months		10 Months	+00.00
			+97.00

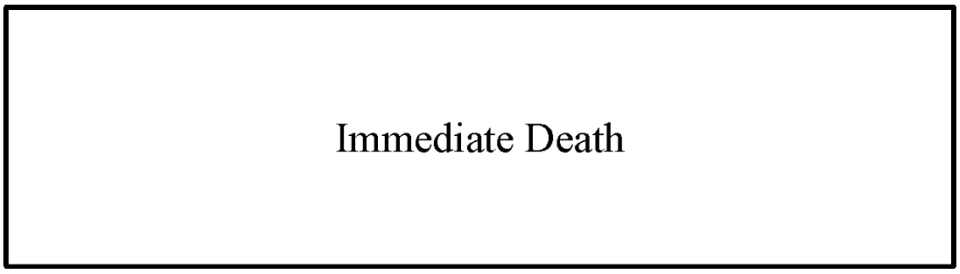
Place a "✓" if you prefer Life "A"
Place an "X" if you prefer Life "B"
Place a "=" if Life "A" and "B" are equivalent (cannot chose between life "A" or "B")

HEALTH STATE RATED WORSE THAN DEATH

LIFE "A"



LIFE "B"



HEALTH STATE: **X RATED WORSE THAN DEATH**

LIFE "A" STATE 1	STATE 2		LIFE "B"	FOR INTER VIEWER USE
0 Months 2 Weeks	9 Months 2 Weeks		Immediate Death	–19.00
1 Month	9 Months		Immediate Death	– 09.00
1 Month 2 Weeks	8 Months 2 Weeks		Immediate Death	– 05.67
2 Months	8 Months		Immediate Death	– 04.00
2 Months 2 Weeks	7 Months 2 Weeks		Immediate Death	– 03.00
3 Months	7 Months		Immediate Death	– 02.33
3 Months 2 Weeks	6 Months 2 Weeks		Immediate Death	– 01.86
4 Months	6 Months		Immediate Death	– 01.50
4 Months 2 Weeks	5 Months 2 Weeks		Immediate Death	– 01.22
5 Months	5 Months		Immediate Death	– 01.00
5 Months 2 Weeks	4 Months 2 Weeks		Immediate Death	– 00.82
6 Months	4 Months		Immediate Death	– 00.67
6 Months 2 Weeks	3 Months 2 Weeks		Immediate Death	– 00.54
7 Months	3 Months		Immediate Death	– 00.43
7 Months 2 Weeks	2 Months 2 Weeks		Immediate Death	– 00.33
8 Months	2 Months		Immediate Death	– 00.25
8 Months 2 Weeks	1 Month 2 Weeks		Immediate Death	– 00.18
9 Months	1 Month		Immediate Death	– 00.11
9 Months 2 Weeks	0 Months 2 Weeks		Immediate Death	– 00.05
10 Months	0 Months		Immediate Death	00.00

Respondent Serial Number

TIME TRADE-OFF: SELF-COMPLETION METHOD
HEALTH STATE X
VERBATIM RESPONSE

Respondent Serial Number

TIME RECORD SHEET FOR THE TIME TRADE-OFF: SELF COMPLETION METHOD

1. Time at start of trade-off exercise

24 hour clock

2. Time at end of trade-off exercise

24 hour clock

3. Time taken for the time trade-off exercise

Minutes

4. Did the respondent understand the exercise the first time?

Yes	1: continue exercise
No	2: repeat script

5. Did the respondent understand the exercise the second time?

Yes	1: continue exercise
No	2: continue exercise

PAGE TTO1

10.4. Ethics and R&D approval for the POS-E valuation survey

Ethical approval was obtained from the London South East REC. R&D approval was obtained initially via the IRAS portal and subsequently brought under HRA as a minor amendment as the study was still recruiting new research sites when the entire governance and approval process was taken over by the HRA.

NHS
Health Research Authority

Professor Irene Higginson
Assistant Medical Director (Research), King's College Hospital
King's College London
Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London London SE5 9PJ

Email: hra.approval@nhs.net

15 June 2016

Dear Professor Higginson,

Letter of HRA Approval for a study with an existing UK study wide review

Study title:	**Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)**
IRAS project ID:	**159556**
Sponsor:	**King's College London**

Thank you for your request to bring the above referenced study under HRA Approval.

I am pleased to confirm that the study has been given **HRA Approval.** This has been issued on the basis that a study wide review has previously been undertaken, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to add a new site between 23 March 2016 and the date of this letter, the addition of the new site is also approved.

Participation of NHS Organisations in England

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study.

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the HRA website.

Your IRAS project ID is **159556.** Please quote this on all correspondence.

Yours sincerely

Elizabeth Bottomley
Application Administrator

Email: hra.approval@nhs.net

Copy to: *Mr Keith Brennan*

Ms Liba Stones
Senior Research Facilitator (Grants)

Notification of Non-Substantial/Minor Amendments(s) for NHS Studies

This template **must only** be used to notify NHS/HSC R&D office(s) of amendments, which are **NOT** categorised as Substantial Amendments.
If you need to notify a Substantial Amendment to your study then you MUST use the appropriate Substantial Amendment form in IRAS.

Instructions for using this template

- For guidance on amendments refer to http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/
- This template should be completed by the CI and optionally authorised by Sponsor, if required by sponsor guidelines.
- This form should be submitted according to the instructions provided for NHS/HSC R&D at http://www.hra.nhs.uk/research-community/during-your-research-project/amendments/which-review-bodies-need-to-approve-or-be-notified-of-which-types-of-amendments/ . If you do not submit your notification in accordance with these instructions then processing of your submission may be significantly delayed.

1. Study Information

Full title of study:	Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)
IRAS Project ID:	159556
Sponsor Amendment Notification number:	
Sponsor Amendment Notification date:	14/06/2016
Details of Chief Investigator:	
Name [first name and surname]	Professor Irene J. Higginson
Address:	King's College London; Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation.
Postcode:	SE5 9PJ
Contact telephone number:	02078485585
Email address:	irene.higginson@kcl.ac.uk
Details of Lead Sponsor:	
Name:	Keith Brennan
Contact email address:	keith.brennan@kcl.ac.uk
Details of Lead Nation:	
Name of lead nation *delete as appropriate*	England
If England led is the study going through CSP? *delete as appropriate*	No
Name of lead R&D office:	Research & Innovation Office; Kings College Hospital NHS Foundation Trust.

NHS REC Form | Reference: | IRAS Version 5.0.0

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Development of a preference-based outcome measure for Palliative Care

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
(●) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No
b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No
c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

[✓] England
[ ] Scotland
[ ] Wales
[ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (●) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which review bodies are you applying to?

- [ ] HRA Approval
- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

(●) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

( ) Yes (●) No

If yes and you have selected HRA Approval in question 4 above, your study will be processed through HRA Approval.

If yes, and you have not selected HRA Approval in question 4 above, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

(●) Yes ( ) No

If yes, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before submitting other applications. If you have selected HRA Approval in question 4 above your study will be processed through HRA Approval. If not, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

6. Do you plan to include any participants who are children?

( ) Yes (●) No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

( ) Yes (●) No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory

Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
Part of this study contributes to PhD work for Dr Mendwas Dzingina.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study

NHS
Health Research Authority

Application to NHS/HSC Research Ethics Committee

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Development of a preference-based outcome measure for Palliative Care

Please complete these details after you have booked the REC application for review.

REC Name:

REC Reference Number: Submission date:

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)

A2-1. Educational projects

Name and contact details of student(s):

Student 1

	Title Forename/Initials Surname
	Dr Mendwas Dzingina
Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London
Post Code	SE5 9PJ
E-mail	mendwas.dzingina@kcl.ac.uk
Telephone	02078485572
Fax	02078485517

Give details of the educational course or degree for which this research is being undertaken:
Name and level of course/degree:
Doctor of philosophy (PhD) in palliative care research

Name of educational establishment:
King's College London

Name and contact details of academic supervisor(s):

Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Irene J.	Higginson
Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
Post Code	SE5 9PJ		
E-mail	irene.higginson@kcl.ac.uk		
Telephone	02078485585		
Fax	02078485517		

Academic supervisor 2

	Title	Forename/Initials	Surname
	Professor	Paul	McCrone
Address	King's Health Economics		
	Box 024, David Goldberg Centre, Institute of Psychiatry		
	King's College London		
Post Code	SE5 8AF		
E-mail	paul.mccrone@kcl.ac.uk		
Telephone	0207 8480874		
Fax			

Academic supervisor 3

	Title	Forename/Initials	Surname
	Dr	Fliss	Murtagh
Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
Post Code	SE5 9PJ		
E-mail	fliss.murtagh@kcl.ac.uk		
Telephone	02078485583		
Fax	02078485517		

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Dr Mendwas Dzingina	☑ Professor Irene J. Higginson

☑ Professor Paul McCrone

☑ Dr Fliss Murtagh

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

- ○ Student
- ◉ Academic supervisor
- ○ Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Irene	Higginson
Post	Assistant Medical Director (Research), King's College Hospital		
Qualifications	OBE BMedSci BMBS PhD FMedSci FRCP FFPHM		
Employer	King's College London		
Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
	London		
Post Code	SE5 9PJ		
Work E-mail	irene.higginson@kcl.ac.uk		
* Personal E-mail			
Work Telephone	02078485585		
* Personal Telephone/Mobile			
Fax	02078485517		

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Mr	Keith	Brennan
Address	Room 1.8, Hodgkin Building		
	King's College London, Guy's Campus		
	Great Maze Pond, London		
Post Code	SE1 4UL		
E-mail	keith.brennan@kcl.ac.uk		
Telephone	02078486960		
Fax	02078486394		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number:

Protocol Version: 1

Protocol Date: 20/11/2014

Funder's reference number: RP-PG-1210-12015

Project website: www.kcl.ac.uk/palliative/research/studies/c-change

Additional reference number(s):

Ref.Number Description	Reference Number
additional funder's reference number	24611

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

A5-2. Is this application linked to a previous study or another current application?

(•) Yes ( ) No

Please give brief details and reference numbers.
This study is linked to the C-CHANGE project (NIHR Programme Grants for Applied Research - RP-PG-1210-12015) and Cicely Saunders International BuildCARE Fellowships (24611)

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

The aim of this study is to develop a method for evaluating economic aspects of the treatment and care of people with far advanced illness. There is no existing questionnaire which can tell us how patients or the public value different health states in the context of advanced illness.
We will administer a questionnaire which asks individual participants to state how much value (in numerical terms) they attach to different health states. This questionnaire will be developed from an existing, validated patient reported tool called the POS (Patient Outcome Scale). The POS is based on what patients with advanced illness themselves prioritize as important. It is routinely used in clinical practice and in research studies, to assess changes in patients' health status but it cannot be used for economic evaluation without adaptation.

This work is important because it provides information to policy-makers and health decision-makers which enables them to make choices about providing healthcare resources which match the priorities of patients and public. Without this work, it is not possible for the views and perspectives of patients with advanced illness, and the public, to be directly taken into account, when making value judgements about palliative care interventions / treatments.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex

organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

This study presents a minimal risk to patients since it does not involve any change in routine care or new intervention/treatment.

It involves asking around 130 participants (including 65 patients with advanced disease; and 65 healthy volunteers sampled as a proxy for the general population) to complete a questionnaire asking them to value different health states.

The main ethical issues are:
1. potential distress arising from completing the questionnaire
2. ensuring informed consent is obtained from all participants

We do not expect high levels of distress from the questionnaire. Sometimes, participants, particularly those with advanced illness, are distressed by their illness, and questionnaires can uncover this. Thus, in the unlikely event that a participant becomes distressed during the study, a distress protocol developed based on the experiences and expertise of the research department will be followed to reduce any risk and/or burden to participants.

We will obtain informed consent from participants prior to enrolment to the study. All potential participants will be given the opportunity to ask questions at the point of invitation to the study, when expressing interest in participating, at the time of consent, and during questionnaire completion.
Patients will need to have the capacity to give consent to participate.
Only patients who are deemed by the clinical team to have capacity to give consent will be invited to participate. The capacity to give consent will be assessed by clinical staff involved in their care.

A6-3. Proportionate review of REC application *The initial project filter has identified that your study may be suitable for proportionate review by a REC sub-committee. Please consult the current guidance notes from NRES and indicate whether you wish to apply through the proportionate review service or, taking into account your answer to A6-2, you consider there are ethical issues that require consideration at a full REC meeting.*

○ Yes - proportionate review ◉ No - review by full REC meeting

Further comments (optional):

Note: This question only applies to the REC application.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply:*

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☑ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☑ Questionnaire, interview or observation study
- ☐ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The principal research objective is to determine patient- and public -derived weights of health status (or health utility) for an existing validated outcome measure called the Patient Outcome Scale (POS) - for use in economic evaluations of treatments or interventions in palliative care.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

This study also aims to determine whether patients value health states differently from healthy volunteers (the general public).

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

The world's population is ageing and the numbers of people with progressive disease is increasing(10), and as a result, we need effective treatments. There is now evidence to support the effectiveness of specialist palliative care teams, however, evidence on the cost-effectiveness (value for money) of palliative care is scarce and we do not have the appropriate economic tools to measure this.
Palliative care is currently being incorporated into main stream health service provision in the UK. In order to provide resources required to meet the needs of dying patients, health policy makers require information on the 'value for money' of palliative care treatments and interventions. Economic evaluation using cost-utility analysis (CUA) is the recommended means for generating such information.(1) There is a dearth of economic evaluations, especially CUAs, in advanced disease.(2)
CUAs compare interventions in terms of their cost per quality adjusted life years (QALYs) gained. QALYs combine life expectancy (in years) and quality of life (expressed in the form of "health state values") into a single metric, based on peoples' preferences. The quality of life (QOL) portion is estimated by assigning a numerical value to each health state experienced by a patient on a scale from one to zero.(3)

A common way of estimating health-state values is to use a "generic" preference-based measure (PBM), such as the EuroQOL five dimensions questionnaire (EQ-5D).(4) All PBMs have a preference-based algorithm for assigning values to each health state. In other words, a PBM could be regarded as a quality-of-life tool whose item-levels have been assigned 'preference weights' which reflect the desirability (or importance) of each item-level relative to the others. These preference weights are usually obtained by asking members of the general public (or patients) preference elicitation questions, such as 'time-trade-off or 'standard gamble'.(5) Generic PBMs were developed on the basis that they can be used in all patients, irrespective of their medical condition because they concentrate on core aspects of health-related quality of life (HRQoL).(6)

However, for certain medical conditions, generic PBMs have been found to be inappropriate or insensitive to "small but important changes". Among patients with advanced disease and in palliative care, there are concerns that generic PBMs are heavily focused on physical function (e.g. 4 of the 5 dimensions of the EQ-5D measure physical aspects of HRQoL), and so do not incorporate many aspects of HRQoL important to patients with symptoms and advanced disease.(7,8) This has led to proposals for the development of a PBM that would be appropriate for patients with advanced disease.(7,9) Presently, no such measure exists. The Patient Care Outcome Scale (POS) has been suggested as suitable for this purpose.(7) The POS is a validated questionnaire which was developed to measure domains that impact on the quality of life of patients with advanced disease.
We aim to develop a preference-based measure for use in economic evaluations of palliative care interventions / treatments, and to determine whether patients value health states differently from the healthy volunteers (general public).

References:
(1) Earnshaw J and Lewis G. NICE Guide to the Methods of Technology Appraisal: pharmaceutical industry perspective. PharmacoEconomics. 2008; 26: 725-7.
(2) Smith S, Brick A, O'Hara S and Normand C. Evidence on the cost and cost-effectiveness of palliative care: a literature review. Palliative medicine. 2014; 28: 130-50.
(3) Whitehead SJ. Health outcomes in economic evaluation: The QALY and utilities. British Medical Bulletin. 2010; 96: 5-21.
(4) Gusi N, Olivares PR and Rajendram R. The EQ-5D Health-Related Quality of Life Questionnaire. In: Preedy V and Watson R, (eds.). Handbook of Disease Burdens and Quality of Life Measures. Springer New York, 2010, p. 87-99.
(5) Brazier JE, Ratcliffe J, Salomon J and A T. Measuring and valuing health benefits for economic evaluation. Oxford/New York: Oxford University Press, 2007.
(6) Marra CA, Woolcott JC, Kopec JA, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Social science & medicine. 2005; 60: 1571-82.
(7) Normand C. Measuring outcomes in palliative care: limitations of QALYs and the road to PalYs. Journal of Pain &

Symptom Management. 2009; 38: 27-31.
(8) Hughes J. Palliative care and the QALY problem. Health Care Analysis. 2005; 13: 289-301.
(9) Round J. Is a QALY still a QALY at the end of life? Journal of Health Economics. 2012; 31: 521-7.
(10) Dzingina MD, Higginson IJ. Public Health and Palliative Care in 2015. Clinics in Geriatric Medicine. 2015
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A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study design is a cross-sectional valuation study.
Two groups of study participants will be recruited into this study.
(1) Patients with advanced illness who meet the following inclusion criteria: are 18 years or older; have advanced disease (all patients being seen by specialist palliative care services): such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease; are able to provide informed consent; are willing to participate; and are English-literate.
(2) Healthy volunteers who meet the following inclusion criteria: are 18 years or older; are able to provide informed consent; are willing to participate; and are English-literate.

Participants will be asked to complete a one-off interviewer-administered questionnaire.

65 Patients will be recruited from specialist palliative care services at King's College Hospital (KCH), Guy's and St. Thomas' (GSTT) hospital, St Georges hospital, St. Christopher's hospice, St. Joseph's hospice and services in similar hospital settings in the UK. Recruitment will be through the patients' clinical and/or community outpatient teams. All patients seen by specialist palliative care services have, by definition, advanced disease.

65 healthy volunteers will be recruited through the volunteer services departments of the participating sites.

Participants will be presented with scenarios (health states) where they will be ask to imagine living in a health state that is less than perfect health, for a given amount of time (10 months). They will then be asked to express how much time (months of life) they would be willing to give up in order to be returned to full health, a technique called the time-trade-off approach. Completion of this questionnaire should take 30 to 45 minutes and participants are required to complete this task only once.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [ ] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Cicely Saunders Institute has a patient and public involvement panel. This protocol and all materials have been reviewed by the panel before being finalized.
Also, the doctoral student has attended the department's Dissemination, Engagement and Empowerment Advisory Group which comprises of service users and academic and clinical staff for review of the project. This group's input will also be sought at one of their quarterly meetings, for advice on the dissemination of the findings.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Two groups of study participants will be recruited into this study:
a) Patients with advanced disease
b) Healthy volunteers
Inclusion criteria
Patients who are:
1. 18 years or older;
2. with advanced disease (receiving palliative care): such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease;
3. able to provide informed consent; and
4. English-literate
5. willing to participate
Healthy volunteers who are:
1. 18 years or older;
2. able to provide informed consent;
3. English-literate; and
4. willing to participate

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Patients who are too unwell (unable to converse over a sustained time or with impaired capacity), too symptomatic or distressed to participate, as judged by the clinical team, or do not have advanced disease.

- All participants that are unable to give informed consent.

- All participants that are unable to understand written and verbal communication in English.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Obtain informed consent from participants	1	NA	15 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.
Participants complete self/interviewer administered questionnaire	1	NA	45 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.

A21. How long do you expect each participant to be in the study in total?

This is a cross sectional study which requires a survey to be completed once. Time from consent to completion of questionnaire is expected to be less than two weeks. No future contact is planned after completion of interview.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The proposed study involves neither invasive procedures nor novel therapeutic interventions, and taking part will not

affect the participants' medical management in any way. Participants will be advised they are under no obligation to take part.
The purpose and intent of the work will be explained. Participants will be given the choice not to answer any particular question. They may skip the question and move on, return to the question later, omit the question altogether, or stop the interview or questionnaire. Patients will be made aware that they can withdraw from the study at anytime, with no adverse implications for their clinical care.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

It is possible that patient participants may become distressed or raise issues during data collection related to their illness. Should this be the case, then a member of the research team will seek consent from the participant to raise matters with the relevant member(s) of the patient's clinical team for review. We anticipate distress will be very infrequent, if at all, given the general nature of the valuation questions, and is likely to reflect advanced disease and not the questionnaires themselves.
During the data collection process there will be on-going monitoring for any indications of distress, both actively with frequent verbal checks that the participant is okay and would like to continue, as well as non-verbal indicators that may suggest the participant is distressed such as a change in the level of engagement with the interview or appearing nervous/anxious. Breaks will be used should participants wish and the interview will be terminated early if required. Any participant who is distressed will also be offered additional support, for example, details of the Macmillan support centre will be provided if appropriate.
All of the research team will have completed Good Clinical Practice (GCP) training, and specific training on addressing distress in palliative care.

Also, as with any research project, there are risks related to the safety and security of participants' personal data. To address these risks all data collected will be completely anonymised and kept in a locked filing cabinet, in a secure office, within the Department of Palliative Care, Policy and Rehabilitation, King's College London. All data protection requirements will be fulfilled. The recruitment log will be kept separately (and securely) to the anonymised data.

A23. Will interviews/questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

(●) Yes ( ) No

If Yes, please give details of procedures in place to deal with these issues:

Although there is only a minimal risk of a disclosure occurring, a verbal discussion will take place that highlights that although this research is confidential, there is a limit to confidentiality if patients disclose information that indicate they would/have put themselves or others in danger or, any illegal activities, then this would have to be disclosed to a senior clinician.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

A24. What is the potential for benefit to research participants?

Patients
Although we are not proposing to offer any specific benefits to patients by taking part, patients may be encouraged to raise issues regarding their quality of life and well-being with their clinicians.
Also, there is a substantial and growing body of evidence, including two systematic reviews, suggesting that patients experience benefit from participating in research (1, 2). Qualitative studies of terminally ill patients' experiences of research have highlighted themes of benefit through social interaction and information provision (3) as well as enhanced problem-solving skills, better coping mechanisms and feelings of empowerment, support and reassurance (4). Studies have also found that research participants often value the opportunity to contribute to research that might help others, and can gain a sense of "usefulness" from participating in research despite their deteriorating health.

Healthy volunteers:
Likewise, we are not proposing to offer any specific benefits to healthy volunteers, however, the information provided during the study will help enhance and improve future clinical care.

REFERENCES
1) White C, Hardy J. What do palliative care patients and their relatives think about research in palliative care?a systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2010 Aug;18(8):905-11. PubMed PMID: 19705165.
2) Gysels MH, Evans C, Higginson IJ. Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. Bmc Med Res Methodol. 2012;12:123. PubMed PMID: 22900965. Pubmed Central PMCID: 3489694.

3) Gysels M, Shipman C, Higginson IJ. Is the qualitative research interview an acceptable medium for research with palliative care patients and carers? BMC medical ethics. 2008;9:7. PubMed PMID: 18435846. Pubmed Central PMCID: 2383914.
4) Maloney C, Lyons KD, Li Z, Hegel M, Ahles TA, Bakitas M. Patient perspectives on participation in the ENABLE II randomized controlled trial of a concurrent oncology palliative care intervention: benefits and burdens. Palliative medicine. 2013 Apr;27(4):37583. PubMed PMID: 22573470. Pubmed Central PMCID: 3657725.

A26. What are the potential risks for the researchers themselves? *(if any)*

Dealing with distressed participants can lead to distress within the research team. Informal peer support will be available during the study and regular supervision for all members of the research team.
We will offer participants the option of completing questionnaires at a time and place convenient to them. This may therefore require members of the research team to visit them in the community. All those working offsite in this way are required to follow the department's home-worker policy and required to complete a log showing where they are going to conduct an interview. All researchers will be paired with a partner to ensure that a named individual within the department knows their whereabouts at all times.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used? *For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified as follows:
(1) IDENTIFICATION OF POTENTIAL PATIENT PARTICIPANTS
Potential patient participants will be screened in the first instance by a member of their clinical team against the inclusion and exclusion criteria. If screened as appropriate and eligible by the clinical team, potential participants will be given the information sheet by a clinician and have a further discussion about the study, with the opportunity to ask questions. A member of the research team will then visit patients who have expressed an interest in taking part at least 24 hours after initial identification. If they are still willing to take part full informed written consent will be obtained. Patients will be allowed to participate in a way comfortable to them, and be offered flexibility around the time and place of interviewing completion.

(2) IDENTIFICATION OF POTENTIAL HEALTHY VOLUNTEERS :
Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at King's College London (KCL) directly to express interest in participating and for further information.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:
Potential patient participants will be identified by their clinical team.

Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

(●) Yes ( ) No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Healthy volunteers will be recruited through the Volunteer Service Departments at each study site via general e-mail invitations, and volunteer recruitment web pages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information.

A29. How and by whom will potential participants first be approached?

Potential participants will be identified as follows:
(1) PATIENT PARTICIPANTS
Potential patient participants will be screened in the first instance by a member of their clinical team against the inclusion and exclusion criteria. Potential participants will not be approached whilst in the emergency department. Eligible patients identified will first be approached by a clinical member of the palliative care team. When first approached, the clinical team member will introduce the study, explain that participation is entirely voluntary, and provide the patient with an information leaflet about the study. Patients will mostly be approached whilst in hospital or hospice. Only patients who express an interest in the research and who are agreeable to meeting with a member of the research team will have their names passed on to the research team. For these patients, Dr Mendwas Dzingina (PhD training fellow), or another member of the research team (including clinical research nurses), will follow up the initial contact and be available to explain the study in detail, answer questions and address any concerns.

(2)IDENTIFICATION OF HEALTHY VOLUNTEERS:
Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information. Dr Dzingina, or another member of the research team (including research nurses) will explain those who have expressed interest that participation is entirely voluntary, and provide more details about the study.

A30-1. Will you obtain informed consent from or on behalf of research participants?

(●) Yes ( ) No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

(1) PATIENT PARTICIPANTS:
All potential patient participants will have the study explained to them (initially by a clinical member of the palliative care team) and be provided with an information leaflet outlining the purpose of the study, including details of what participation would involve. An in-depth further explanation of the study will subsequently be given by Dr Dzingina (PhD training fellow) or another member of the research team.
For patients who would like to participate, and after a minimum of 24 hours from first contact with a member of the research team, informed written consent to complete a questionnaire survey will be obtained. A minimum period of 24 hours between full explanation of the study and completion of the consent form will be offered to all participants in order to provide an opportunity for patients to reflect on the study and their involvement. If, after 24 hours, potential patient participants would like additional time to consider their involvement, a future meeting time will be organised. However, some potential participants may feel that they do not require 24 hours to consider their involvement, and are comfortable to consent, or decline, earlier than this, for example some soon-to-be discharged patients may prefer to complete the questionnaire before leaving hospital. In these situations the researcher will be guided by the patients' preferences.
Patients will be required to fully comprehend the risks, benefits and burden of their taking part, and give written informed consent to do so. Dr Dzingina, or another member of the research team (including clinical research nurses), who are trained and experienced in the consent process, will be responsible for obtaining consent from all participants.
Patients will be allowed to participate in a way comfortable to them, and be offered flexibility around the time and place of questionnaire completion.
All members of the research team have completed Good Clinical Practice training at Kings College London.

2) HEALTHY VOLUNTEERS:

Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information. Dr Dzingina, or another member of the research team (including research nurses) will explain those who have expressed interest that participation is entirely voluntary, and provide more details about the study.

Full informed written consent will be obtained from healthy volunteers who have agreed to participate in the study by Dr Dzingina, or another member of the research team (including clinical research nurses).

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form (s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

A minimum of 24 hours.
However, some potential participants may feel that they do not require 24 hours to consider their involvement, and are comfortable to consent, or decline, earlier than this, for example some soon-to-be discharged patients may prefer to complete the questionnaire before leaving hospital. In these situations the researcher will be guided by the participants' preferences, but 24 hours will always be allowed if desired.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters)*

Patients unable to understand written and verbal communication in English are excluded from this study.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

( ) The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.

(●) The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

( ) The participant would continue to be included in the study.

( ) Not applicable – informed consent will not be sought from any participants in this research.

( ) Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:
This study involves a one-time collection of survey data, so monitoring of subsequent capacity does not apply. However, if a potential participant loses capacity between the time of identification/consent and completion of the survey, they will be excluded from the study.

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? *(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☑ Manual files including X-rays
  - ☐ NHS computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

Further details:
Study participants will be assigned a unique identifier (code number) at the time of data collection.
We will log names and unique identifiers of all participants in a recruitment log which will be locked securely in a cabinet and kept separate from research data (see example in the attached questionnaire). Otherwise, person-identifiable details of participants will not be collected.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All participants will be assured of the procedures below that will be taken to ensure confidentiality:
All data collected will be anonymised according to departmental and college guidelines, (Department of Palliative Care, Policy & Rehabilitation, King's College London, (updated April 2010)).
Study participants will be assigned a unique identifier (code number) at the time of data collection. We will log names and unique identifiers of all participants in a recruitment log which will be locked securely in a cabinet and kept separate from research data (see example in the attached questionnaire).

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The Chief Investigator, Prof. Irene Higginson (IH), the doctoral candidate, Dr Mendwas Dzinigna, other academic supervisors; Prof. Paul McCrone (PM) and Dr Fliss Murtagh (FM); and other designated members of the research team, supervised by IH, PM and FM, will have access to the participants' data during the study.

Storage and use of data after the end of the study

A43. How long will personal data be stored or accessed after the study has ended?

- ◉ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years

○ Over 3 years

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

○ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

○ Yes ◉ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

◉ Yes ○ No

Please give details, or justify if not registering the research.
UKCRN Portfolio Database

Registration of research studies is encouraged wherever possible.
You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

☑ Peer reviewed scientific journals
☑ Internal report
☑ Conference presentation
☑ Publication on website

☐ Other publication

☐ Submission to regulatory authorities

☑ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators

☐ No plans to report or disseminate the results

☑ Other (please specify)

Dissemination through Cicely Saunders Institute's organised training days for healthcare professionals and researchers about the use of preference-based outcome measures in economic evaluations of palliative care interventions/services, where the newly developed preference-based outcome measure will be discussed.

A53. Will you inform participants of the results?

◉ Yes ○ No

Please give details of how you will inform participants or justify if not doing so.

A lay summary of the findings will be offered to the participating palliative care units and hospices for inclusion in their respective patient news letters and websites.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

☐ Independent external review

☐ Review within a company

☑ Review within a multi-centre research group

☑ Review within the Chief Investigator's institution or host organisation

☑ Review within the research team

☑ Review by educational supervisor

☐ Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

☐ Review by independent statistician commissioned by funder or sponsor

☐ Other review by independent statistician

☐ Review by company statistician

☐ Review by a statistician within the Chief Investigator's institution

☐ Review by a statistician within the research team or multi-centre group

☑ Review by educational supervisor

☑ Other review by individual with relevant statistical expertise

☐ No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has

been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Paul	McCrone
Department	King's Health Economics, Institute of Psychiatry, Psychology & Neuroscience.		
Institution	King's College London		
Work Address	King's Health Economics		
	Box 024, David Goldberg Centre, Institute of Psychiatry		
	King's College London		
Post Code	SE5 8AF		
Telephone	442078480874		
Fax	442078480458		
Mobile			
E-mail	paul.mccrone@kcl.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

This is not an intervention study and as a result there is no primary outcome measure. It aims to develop a measure that can be used to derive utility weights for economic evaluations of palliative care interventions.

A58. What are the secondary outcome measures? *(if any)*

NA

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 130
Total international sample size (including UK):
Total in European Economic Area:

Further details:
A total sample size of 130 will be required as follows:
1) 65 patients; and
2) 65 healthy volunteers (32 for each of the two groups of health states).

The group of health states to be valued will be assigned to consecutive participants.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Valuation of the 14 states has two aims: (a) to produce mean values for each health state; and (b) to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests. Assuming a power of 0.8, significance level of 0.05, SD of 0.3 and an expected difference of 0.1, 73 valuations are required for each health state (37 from patients and 37 from healthy volunteers) and thus a total of 1,022 valuations for the 14 health states.(1) If we assume that participants are able to provide then a total sample size of 73 would be sufficient to achieve 73 valuations per health state. However, consultations with clinicians and patient representatives revealed that some participants, particularly patients with advanced disease, might find it too burdensome to value 14 health states. Also, previous valuation exercises have shown that respondents cannot value more than 13 health states at a time (Dolan et al., 1996),16 and typically they are asked to value between 6 and 8 health states (Brazier et al., 2002, 2005b & 2008; Dolan et al., 1996; Yang et al., 2011).(2-6) Conversely, reducing the number of health states to be valued by each participant will necessitate an increase in the sample size (of participants) required to achieve 73 valuations per health state.

In order to address this issue, health states will be divided into two blocks, with each block comprising of 8 health states. In each of the two blocks there will be two health states that will be common to both blocks and 6 unique health states (i.e. 6 states unique to block 1; + 6 unique to block 2; + 2 common states = 14 states). Each participant will value only one block comprising of 8 health states. Based on this, a total of 130 participants will be required (65 patients and 65 healthy volunteers). The two health states common to both blocks will thus have 73 values each and so will be used to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests (aim b). The other health states will be used to calculate mean values for each health state (aim a) as a much smaller number of valuations per health is required for this. This method has been used in previous valuation studies.(1)

The group of health states to be valued will be assigned to consecutive participants.

Reference:
(1) Brazier JE, Rowen D, Mavranezouli I, Tsuchiya A, Young T, Yang Y, et al. Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). Health technology assessment. 2012;16(32):1-114. Epub 2012/07/27.
(2) Dolan P, Gudex C, Kind P and Williams A. The time trade-off method : results from a general population study. Health Econ. 1996; 5: 141-54.
(3) Brazier J, Roberts J and Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002; 21: 271-92.
(4) Brazier JE, Roberts J, Platts M and Zoellner YF. Estimating a preference-based index for a menopause specific health quality of life questionnaire. Health and quality of life outcomes. 2005; 3: 13.
(5) Brazier J. Measuring and valuing mental health for use in economic evaluation. Journal of health services research & policy. 2008; 13 Suppl 3: 70-5.
(6) Yang Y, Brazier JE, Tsuchiya A and Young TA. Estimating a preference-based index for a 5-dimensional health state classification for asthma derived from the asthma quality of life questionnaire. Medical decision making : an international journal of the Society for Medical Decision Making. 2011; 31: 281-91.

A61. Will participants be allocated to groups at random?

○ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The methods used for this study are based on recommendations in the Health Technology Assessment (HTA) guidance document on "developing and testing methods for deriving preference based measures of health from condition-specific measures (and other patient-based measures of outcome)".(1)

Deriving a preference-based-measure consists of 3 stages as follows.
Stage 1:
In the first stage, the aim is to construct a simplified health state classification (based on the Patient Outcome Scale - POS) containing a subset of items that are most representative of the POS. This involves conducting secondary analyses of pre-existing POS datasets using factor analysis, Rasch analysis, and other standard psychometric techniques. We have already completed this first stage.

Stage 2:
The second stage involves primary data collection via a cross sectional survey. The aim here is to directly derive health-state utility values/weights for a sub-sample of the health states derived from the first stage described above. The utility values for these health states will be derived directly by asking health professionals, managers, students, patients and carers, 'Time-Trade-Off (TTO) questions in a 'valuation' survey.
The TTO is a technique used in health economics to help determine the quality of life of an individual (or patient) or a group. The individual will be presented with a set of directions for example:
"Imagine that you are told that you have 10 years left to live. In connection with this you are also told that you can choose to live these 10 years in your current health state or that you can choose to give up some years-of-life to live for a shorter period in full health. Indicate with a cross on the line, the number of months in full health that you think is of equal value to 10 years in your current health state".(2)

The line usually ranges from 0 to 10 and the person's score is calculated by dividing the number corresponding to their cross by 10. For example if someone marks a cross at 6 on the TTO line, they would be given a TTO score of 0.60. This number is often used in turn to calculate quality-adjusted life years (QALYs). In our example if this person were to live for 2 years at their current health state (of 0.6) this would be equal to 1.2 QALYs (2 * 0.6). QALYs enable health care

decision makers to combine mortality and morbidity into a single interval scale, thereby enabling the comparison of interventions between different diseases and across a variety of disciplines.
However, for this study, we propose to use a modified version of the TTO which uses a time interval of 0 to 10 weeks (instead of 0 to 10 years). The rationale behind this is based on the fact that on average, palliative care patients usually have a life expectancy much shorter than 10 years, and so it may be inappropriate to ask them to trade-off lengths of time they know they don't have.(3)

Mean TTO values will be estimated for each of the 14 health states that will be valued. The mean values between the states that were valued by patients will be compared with those valued by non-patient participants using simple t-tests.

Stage 3:
The aim here is to indirectly derive utility values for all other health states that were not included in stage 2, through a combination of regression and Rasch analyses.(1) This technique involves using regression analysis to estimate utility values for all health states using the Rasch logit score.(4) Specifically, a series of regression analyses will be undertaken to explore the relationship between the utility values of each health state that was considered in the valuation survey and the respective Rasch model logit value corresponding to the health state, as calculated by previously undertaken Rasch analysis of POS data.
Ordinary Least Squares (OLS) models will be used to analyse the valuation data at an aggregate (mean) level first, i.e. regression analyses will be conducted on the mean utility values obtained for each health state included in the valuation survey, without taking into account individual respondent characteristics (such as age, gender, ethnicity, etc.), since aggregate utility data are used in cost-utility analyses of healthcare technologies. OLS regression analysis will also be conducted at the individual level to explore the impact of respondents' personal characteristics (such as age, gender, ethnicity, patient / member of general public, etc.). An important limitation of the OLS model is that it assumes a continuous variable without censoring; in this case, it does not allow for the dependent variable (utility value) to be bounded by a maximum value of +1 and a minimum value of -1. Therefore, Tobit models will be estimated, to allow censoring at both the top and bottom ends of the relationship.(5)
The fit of individual OLS models will be assessed using the coefficient of determination (i.e. the adjusted R-Squared) and the root mean squared error (RMSE)7. Tobit models will be assessed using the estimated standard error of the regression, which is analogous to the root mean square error (RMSE) in OLS regression. All regression analyses will be run on STATA version 12 (Stata Corp., 2011).

Reference:
(1) Brazier JE, Rowen D, Mavranezouli I, et al. Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). Health technology assessment. 2012; 16: 1-114.

(2) Burström K, Johannesson M, Diderichsen F. A comparison of individual and social time trade-off values for health states in the general population. Health policy. 2006;76(3):359-70.

(3) Normand C. Measuring outcomes in palliative care: limitations of QALYs and the road to PalYs. Journal of Pain & Symptom Management. 2009; 38: 27-31

(4) Mavranezouli I, Brazier JE, Rowen D, Barkham M. Estimating a Preference-Based Index from the Clinical Outcomes in Routine Evaluation–Outcome Measure (CORE-OM): Valuation of CORE-6D. Medical Decision Making. 2013;33 (3):381-95.

(5) Tobin J. Estimation of Relationships for Limited Dependent Variables. Econometrica. 1958;26(1):24-36.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co-applicants, protocol co-authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	Mendwas	Dzingina
Post	Cicely Saunders International PhD Training Fellow		
Qualifications	MBBS; DLSHTM; MSc		
Employer	King's College London		

Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London London
Post Code	SE5 9PJ
Telephone	442078485517
Fax	44207 848 5517
Mobile	
Work Email	mendwas.dzingina@kcl.ac.uk

Title	Forename/Initials	Surname
Professor	Irene J.	Higginson

Post	Professor and Head of Department of Palliative Care, Policy & Rehabilitation
Qualifications	PhD, FFPHM, BMBS, BMedSci
Employer	King's College London
Work Address	King's College London, Cicely Saunders Institute Bessemer Road Denmark Hill, London
Post Code	SE5 9PJ
Telephone	02078485516
Fax	02078485517
Mobile	
Work Email	irene.higginson@kcl.ac.uk

Title	Forename/Initials	Surname
Professor	Paul	McCrone

Post	Professor of Health Economics & Deputy Director, King's Health Economics
Qualifications	PhD Health Economics; MSc Economics; BA (Hons) Political Economy
Employer	King's College London
Work Address	P024 Institute of Psychiatry King's College London De Crespigny Park, London
Post Code	SE5 8AF
Telephone	4420 7848 0874
Fax	4420 7848 0458
Mobile	
Work Email	paul.mccrone@kcl.ac.uk

Title	Forename/Initials	Surname
Dr	Fliss	Murtagh

Post	Reader and Consultant in Palliative Medicine
Qualifications	FRCP; MRCGP; PhD
Employer	King's College London
Work Address	King's College London, Cicely Saunders Institute Bessemer Road Denmark Hill, London
Post Code	SE5 9PJ
Telephone	442078485583
Fax	442078485517
Mobile	
Work Email	fliss.murtagh@kcl.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status:

If Other, please specify:

Contact person

Name of organisation	King's College London
Given name	Keith
Family name	Brennan
Address	Room 1.8, Hodgkin Building, Guy's Campus
Town/city	London
Post code	SE1 4UL
Country	UNITED KINGDOM
Telephone	02078486960
Fax	02078486394
E-mail	keith.brennan@kcl.ac.uk

Is the sponsor based outside the UK?
○ Yes ◉ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

- ☑ Funding secured from one or more funders
- ☐ External funding application to one or more funders in progress
- ☐ No application for external funding will be made

What type of research project is this?

- ○ Standalone project
- ○ Project that is part of a programme grant
- ○ Project that is part of a Centre grant
- ○ Project that is part of a fellowship/ personal award/ research training award
- ◉ Other

Other – please state:
There are two funding sources: (1) C-CHANGE NIHR programme grant (RP-PG-1210-12015) is leading the work on development of outcome measures, including for economic evaluation. This is a five year research programme with many components, of which this is one. (2) The Build CARE programme is supporting the PhD fellowship.

Please give details of funding applications.

Organisation	National Institute for Health Research (NIHR)
Address	Room 132 Richmond House 79 Whitehall
Post Code	SW1A 2NS
Telephone	
Fax	
Mobile	
Email	enquiries@nihr.ac.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: £1,968,973

Duration
Years: 5
Months: 0

If applicable, please specify the programme/funding stream:

What is the funding stream/programme for this research project?
NIHR program grants for applied research

Organisation	Cicely Saunders International
Address	Cicely Saunders Institute Bessemer Road, Denmark Hill London
Post Code	SE5 9PJ
Telephone	02078485580
Fax	
Mobile	
Email	brenda.ferns@cicelysaundersinternational.org

Funding Application Status: (•) Secured ( ) In progress

Amount: £2,443,112.00

Duration
Years: 4
Months:

If applicable, please specify the programme/funding stream:

What is the funding stream/programme for this research project?
This project forms part of a larger programme of palliative care research, project BuildCARE, for which funding has been secured

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

○ Yes ◉ No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

	Title	Forename/Initials	Surname
	Mrs	Liba	Stones
Organisation	King's College Hospital NHS foundation Trust		
Address	1st Floor, 161 Denmark Hill		
	London		
Post Code	SE5 8EF		
Work Email	liba.stones@nhs.net		
Telephone	02032991980		
Fax	02032995515		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

South London

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 27/07/2015
Planned end date: 03/06/2016
Total duration:
Years: 0 Months: 10 Days: 8

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 5

Does this trial involve countries outside the EU?
○ Yes ◉ No

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☑ NHS organisations in England	3
☐ NHS organisations in Wales	
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Social care organisations	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☑ Independent hospitals	2
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	5

A76. Insurance/indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)
☑ Other insurance or indemnity arrangements will apply (give details below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
☑ Other insurance or indemnity arrangements will apply (give details below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)

☑ Research includes non-NHS sites (give details of insurance / indemnity arrangements for these sites below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Investigator identifier	Research site		Investigator Name	
IN1	(•) NHS site ( ) Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Fliss Murtagh fliss.murtagh@kcl.ac.uk PhD; MSc; MRCGP; MBBS UNITED KINGDOM
	Country: England			
	Organisation name	KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST		
	Address	DENMARK HILL LONDON GREATER LONDON		
	Post Code	SE5 9RS		
IN2	( ) NHS site (•) Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Victor Pace V.Pace@stchristophers.org.uk UNITED KINGDOM
	Institution name	St. Christopher's Hospice		
	Department name			
	Street address	51-59 Lawrie Park Road		
	Town/city	London		
	Post Code	SE26 6DZ		
	Country	UNITED KINGDOM		
IN3	(•) NHS site ( ) Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Teresa Beynon Teresa.Beynon@gstt.nhs.uk UNITED KINGDOM
	Country: England			
	Organisation name	GUY'S AND ST THOMAS' NHS FOUNDATION TRUST		
	Address	TRUST OFFICES GUY'S HOSPITAL		

	GREAT MAZE POND LONDON GREATER LONDON
Post Code	SE1 9RT

IN4

- (●) NHS site
- ( ) Non-NHS site

Country: England

Forename	Ollie
Middle name	
Family name	Minton
Email	ominton@sgul.ac.uk
Qualification (MD...)	PhD; FRCP; FHEA
Country	UNITED KINGDOM

Organisation name	ST GEORGE'S HEALTHCARE NHS TRUST
Address	ST GEORGE'S HOSPITAL
	BLACKSHAW ROAD
	TOOTING LONDON GREATER LONDON
Post Code	SW17 0QT

IN5

- ( ) NHS site
- (●) Non-NHS site

Forename	Margaret
Middle name	
Family name	Clifford
Email	M.Clifford@STJH.org.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Institution name	St Joseph's Hospice
Department name	
Street address	Mare Street
Town/city	London
Post Code	E8 4SA
Country	UNITED KINGDOM

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- (●) Chief Investigator
- ( ) Sponsor

- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Irene Higginson on 21/09/2015 08:10.

Job Title/Post:	Head of Division
Organisation:	King's College London, Cicely Saunders Institute
Email:	irene.higginson@kcl.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mr Keith Brennan on 18/09/2015 16:33.

Job Title/Post:	Director of Research Management and Innovation
Organisation:	King's College London
Email:	keith.brennan@kcl.ac.uk

D8. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Dr Fliss Murtagh on 18/09/2015 14:54.

Job Title/Post:	Reader in Palliative Medicine
Organisation:	King's College London
Email:	fliss.murtagh@kcl.ac.uk

Academic supervisor 2

This section was signed electronically by Professor Paul McCrone on 20/09/2015 18:25.

Job Title/Post:	Professor of Health Economics
Organisation:	KCL
Email:	paul.mccrone@kcl.ac.uk

Academic supervisor 3

This section was signed electronically by Professor Irene Higginson on 21/09/2015 08:08.

Job Title/Post:	Head of Division
Organisation:	King's College London, Cicely Saunders Institute
Email:	irene.higginson@kcl.ac.uk

NHS Research and Development application form: via IRAS

NHS R&D Form IRAS Version 5.2.1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Development of a preference-based outcome measure for Palliative Care

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

(•) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation?	( ) Yes	(•) No
b) Will you be taking new human tissue samples (or other human biological samples)?	( ) Yes	(•) No
c) Will you be using existing human tissue samples (or other human biological samples)?	( ) Yes	(•) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

[x] England

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☐ Scotland
☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

◉ England
○ Scotland
○ Wales
○ Northern Ireland
○ This study does not involve the NHS

4. Which review bodies are you applying to?

☐ HRA Approval
☑ NHS/HSC Research and Development offices
☐ Social Care Research Ethics Committee
☑ Research Ethics Committee
☐ Confidentiality Advisory Group (CAG)
☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

○ Yes ◉ No

If yes and you have selected HRA Approval in question 4 above, your study will be processed through HRA Approval.

If yes, and you have not selected HRA Approval in question 4 above, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

◉ Yes ○ No

If yes, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before submitting other applications. If you have selected HRA Approval in question 4 above your study will be processed through HRA Approval. If not, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

6. Do you plan to include any participants who are children?

○ Yes ◉ No

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7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
Part of this study contributes to PhD work for Dr Mendwas Dzingina.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

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Integrated Research Application System
Application Form for Research administering questionnaires/interviews for quantitative analysis or mixed methodology study

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
Development of a preference-based outcome measure for Palliative Care

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)

A2-1. Educational projects

Name and contact details of student(s):

Student 1

Title	Forename/Initials	Surname
Dr	Mendwas	Dzingina

Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London
Post Code	SE5 9PJ
E-mail	mendwas.dzingina@kcl.ac.uk
Telephone	02078485572
Fax	02078485517

Give details of the educational course or degree for which this research is being undertaken:

Name and level of course/ degree:
Doctor of philosophy (PhD) in palliative care research

Name of educational establishment:
King's College London

Name and contact details of academic supervisor(s):

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Academic supervisor 1

	Title	Forename/Initials	Surname
	Professor	Irene J.	Higginson
Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
Post Code	SE5 9PJ		
E-mail	irene.higginson@kcl.ac.uk		
Telephone	02078485585		
Fax	02078485517		

Academic supervisor 2

	Title	Forename/Initials	Surname
	Professor	Paul	McCrone
Address	King's Health Economics		
	Box O24, David Goldberg Centre, Institute of Psychiatry		
	King's College London		
Post Code	SE5 8AF		
E-mail	paul.mccrone@kcl.ac.uk		
Telephone	0207 8480874		
Fax			

Academic supervisor 3

	Title	Forename/Initials	Surname
	Dr	Fliss	Murtagh
Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
Post Code	SE5 9PJ		
E-mail	fliss.murtagh@kcl.ac.uk		
Telephone	02078485583		
Fax	02078485517		

Please state which academic supervisor(s) has responsibility for which student(s):
Please click "Save now" before completing this table. This will ensure that all of the student and academic supervisor details are shown correctly.

Student(s)	Academic supervisor(s)
Student 1 Dr Mendwas Dzingina	☑ Professor Irene J. Higginson ☑ Professor Paul McCrone ☑ Dr Fliss Murtagh

A copy of a current CV for the student and the academic supervisor (maximum 2 pages of A4) must be submitted with the application.

A2-2. Who will act as Chief Investigator for this study?

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- ○ Student
- ◉ Academic supervisor
- ○ Other

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Irene	Higginson
Post	Assistant Medical Director (Research), King's College Hospital		
Qualifications	OBE BMedSci BMBS PhD FMedSci FRCP FFPHM		
Employer	King's College London		
Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London London		
Post Code	SE5 9PJ		
Work E-mail	irene.higginson@kcl.ac.uk		
* Personal E-mail			
Work Telephone	02078485585		
* Personal Telephone/Mobile			
Fax	02078485517		

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Mr	Keith	Brennan
Address	Room 1.8, Hodgkin Building King's College London, Guy's Campus Great Maze Pond, London		
Post Code	SE1 4UL		
E-mail	keith.brennan@kcl.ac.uk		
Telephone	02078486960		
Fax	02078486394		

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):	
Sponsor's/protocol number:	
Protocol Version:	1
Protocol Date:	20/11/2014
Funder's reference number:	RP-PG-1210-12015
Project website:	www.kcl.ac.uk/palliative/research/studies/c-change

Additional reference number(s):

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Ref.Number Description	Reference Number
additional funder's reference number	24611

Registration of research studies is encouraged wherever possible. You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you have registered your study please give details in the "Additional reference number(s)" section.

A5-2. Is this application linked to a previous study or another current application?

(•) Yes ( ) No

Please give brief details and reference numbers.
This study is linked to the C-CHANGE project (NIHR Programme Grants for Applied Research - RP-PG-1210-12015) and Cicely Saunders International BuildCARE Fellowships (24611)

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

The aim of this study is to develop a method for evaluating economic aspects of the treatment and care of people with far advanced illness. There is no existing questionnaire which can tell us how patients or the public value different health states in the context of advanced illness.
We will administer a questionnaire which asks individual participants to state how much value (in numerical terms) they attach to different health states. This questionnaire will be developed from an existing, validated patient reported tool called the POS (Patient Outcome Scale). The POS is based on what patients with advanced illness themselves prioritize as important. It is routinely used in clinical practice and in research studies, to assess changes in patients' health status but it cannot be used for economic evaluation without adaptation.

This work is important because it provides information to policy-makers and health decision-makers which enables them to make choices about providing healthcare resources which match the priorities of patients and public. Without this work, it is not possible for the views and perspectives of patients with advanced illness, and the public, to be directly taken into account, when making value judgements about palliative care interventions / treatments .

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, R&D office or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

This study presents a minimal risk to patients since it does not involve any change in routine care or new intervention/treatment.

It involves asking around 130 participants (including 65 patients with advanced disease; and 65 healthy volunteers sampled as a proxy for the general population) to complete a questionnaire asking them to value different health states.

The main ethical issues are:
1. potential distress arising from completing the questionnaire

2. ensuring informed consent is obtained from all participants

We do not expect high levels of distress from the questionnaire. Sometimes, participants, particularly those with advanced illness, are distressed by their illness, and questionnaires can uncover this. Thus, in the unlikely event that a participant becomes distressed during the study, a distress protocol developed based on the experiences and expertise of the research department will be followed to reduce any risk and/ or burden to participants.

We will obtain informed consent from participants prior to enrolment to the study. All potential participants will be given the opportunity to ask questions at the point of invitation to the study, when expressing interest in participating, at the time of consent, and during questionnaire completion.
Patients will need to have the capacity to give consent to participate.
Only patients who are deemed by the clinical team to have capacity to give consent will be invited to participate. The capacity to give consent will be assessed by clinical staff involved in their care.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply:*

- ☐ Case series/ case note review
- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☑ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☑ Questionnaire, interview or observation study
- ☐ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The principal research objective is to determine patient- and public -derived weights of health status (or health utility) for an existing validated outcome measure called the Patient Outcome Scale (POS) - for use in economic evaluations of treatments or interventions in palliative care.

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

This study also aims to determine whether patients value health states differently from healthy volunteers (the general public).

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

The world's population is ageing and the numbers of people with progressive disease is increasing(10), and as a result, we need effective treatments. There is now evidence to support the effectiveness of specialist palliative care teams, however, evidence on the cost-effectiveness (value for money) of palliative care is scarce and we do not have the appropriate economic tools to measure this.
Palliative care is currently being incorporated into main stream health service provision in the UK. In order to provide resources required to meet the needs of dying patients, health policy makers require information on the 'value for

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money' of palliative care treatments and interventions. Economic evaluation using cost-utility analysis (CUA) is the recommended means for generating such information.(1) There is a dearth of economic evaluations, especially CUAs, in advanced disease.(2)
CUAs compare interventions in terms of their cost per quality adjusted life years (QALYs) gained. QALYs combine life expectancy (in years) and quality of life (expressed in the form of "health state values") into a single metric, based on peoples' preferences. The quality of life (QOL) portion is estimated by assigning a numerical value to each health state experienced by a patient on a scale from one to zero.(3)

A common way of estimating health-state values is to use a "generic" preference-based measure (PBM), such as the EuroQOL five dimensions questionnaire (EQ-5D).(4) All PBMs have a preference-based algorithm for assigning values to each health state. In other words, a PBM could be regarded as a quality-of-life tool whose item-levels have been assigned 'preference weights' which reflect the desirability (or importance) of each item-level relative to the others. These preference weights are usually obtained by asking members of the general public (or patients) preference elicitation questions, such as 'time-trade-off' or 'standard gamble'.(5) Generic PBMs were developed on the basis that they can be used in all patients, irrespective of their medical condition because they concentrate on core aspects of health-related quality of life (HRQoL).(6)

However, for certain medical conditions, generic PBMs have been found to be inappropriate or insensitive to "small but important changes". Among patients with advanced disease and in palliative care, there are concerns that generic PBMs are heavily focused on physical function (e.g. 4 of the 5 dimensions of the EQ-5D measure physical aspects of HRQoL), and so do not incorporate many aspects of HRQoL important to patients with symptoms and advanced disease.(7,8) This has led to proposals for the development of a PBM that would be appropriate for patients with advanced disease.(7,9) Presently, no such measure exists. The Patient Care Outcome Scale (POS) has been suggested as suitable for this purpose.(7) The POS is a validated questionnaire which was developed to measure domains that impact on the quality of life of patients with advanced disease.
We aim to develop a preference-based measure for use in economic evaluations of palliative care interventions / treatments, and to determine whether patients value health states differently from the healthy volunteers (general public).

References:
(1) Earnshaw J and Lewis G. NICE Guide to the Methods of Technology Appraisal: pharmaceutical industry perspective. PharmacoEconomics. 2008; 26: 725-7.
(2) Smith S, Brick A, O'Hara S and Normand C. Evidence on the cost and cost-effectiveness of palliative care: a literature review. Palliative medicine. 2014; 28: 130-50.
(3) Whitehead SJ. Health outcomes in economic evaluation: The QALY and utilities. British Medical Bulletin. 2010; 96: 5-21.
(4) Gusi N, Olivares PR and Rajendram R. The EQ-5D Health-Related Quality of Life Questionnaire. In: Preedy V and Watson R, (eds.). Handbook of Disease Burdens and Quality of Life Measures. Springer New York, 2010, p. 87-99.
(5) Brazier JE, Ratcliffe J, Salomon J and A T. Measuring and valuing health benefits for economic evaluation. Oxford/New York: Oxford University Press, 2007.
(6) Marra CA, Woolcott JC, Kopec JA, et al. A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. Social science & medicine. 2005; 60: 1571-82.
(7) Normand C. Measuring outcomes in palliative care: limitations of QALYs and the road to PalYs. Journal of Pain & Symptom Management. 2009; 38: 27-31.
(8) Hughes J. Palliative care and the QALY problem. Health Care Analysis. 2005; 13: 289-301.
(9) Round J. Is a QALY still a QALY at the end of life? Journal of Health Economics. 2012; 31: 521-7.
(10) Dzingina MD, Higginson IJ. Public Health and Palliative Care in 2015. Clinics in Geriatric Medicine. 2015(0).available from http://dx.doi.org/10.1016/j.cger.2015.01.002

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study design is a cross-sectional valuation study.
Two groups of study participants will be recruited into this study.
(1) Patients with advanced illness who meet the following inclusion criteria: are 18 years or older; have advanced disease (all patients being seen by specialist palliative care services): such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease; are able to provide informed consent; are willing to participate; and are English-literate.
(2) Healthy volunteers who meet the following inclusion criteria: are 18 years or older; are able to provide informed consent; are willing to participate; and are English-literate.

Participants will be asked to complete a one-off interviewer-administered questionnaire.

65 Patients will be recruited from specialist palliative care services at King's College Hospital (KCH), Guy's and St. Thomas' (GSTT) hospital, St Georges hospital, St. Christopher's hospice, St. Joseph's hospice and services in similar hospital settings in the UK. Recruitment will be through the patients' clinical and/or community outpatient teams. All patients seen by specialist palliative care services have, by definition, advanced disease.

65 healthy volunteers will be recruited through the volunteer services departments of the participating sites.

Participants will be presented with scenarios (health states) where they will be ask to imagine living in a health state that is less than perfect health, for a given amount of time (10 months). They will then be asked to express how much time (months of life) they would be willing to give up in order to be returned to full health, a technique called the time-trade-off approach. Completion of this questionnaire should take 30 to 45 minutes and participants are required to complete this task only once.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [ ] Management of the research
- [ ] Undertaking the research
- [ ] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
Cicely Saunders Institute has a patient and public involvement panel. This protocol and all materials have been reviewed by the panel before being finalized.
Also, the doctoral student has attended the department's Dissemination, Engagement and Empowerment Advisory Group which comprises of service users and academic and clinical staff for review of the project. This group's input will also be sought at one of their quarterly meetings, for advice on the dissemination of the findings.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [x] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [x] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System

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- ☐ Injuries and Accidents
- ☐ Mental Health
- ☐ Metabolic and Endocrine
- ☐ Musculoskeletal
- ☐ Neurological
- ☐ Oral and Gastrointestinal
- ☐ Paediatrics
- ☐ Renal and Urogenital
- ☐ Reproductive Health and Childbirth
- ☐ Respiratory
- ☐ Skin
- ☐ Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Two groups of study participants will be recruited into this study:
a) Patients with advanced disease
b) Healthy volunteers
Inclusion criteria
Patients who are:
1. 18 years or older;
2. with advanced disease (receiving palliative care): such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease;
3. able to provide informed consent; and
4. English-literate
5. willing to participate
Healthy volunteers who are:
1. 18 years or older;
2. able to provide informed consent;
3. English-literate; and
4. willing to participate

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

- Patients who are too unwell (unable to converse over a sustained time or with impaired capacity), too symptomatic or distressed to participate, as judged by the clinical team, or do not have advanced disease.

- All participants that are unable to give informed consent.

- All participants that are unable to understand written and verbal communication in English.

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research,

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how many of the total would be routine?

3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Obtain informed consent from participants	1	NA	15 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.
Participants complete self/interviewer administered questionnaire	1	NA	45 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.

A21. How long do you expect each participant to be in the study in total?

This is a cross sectional study which requires a survey to be completed once. Time from consent to completion of questionnaire is expected to be less than two weeks. No future contact is planned after completion of interview.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

The proposed study involves neither invasive procedures nor novel therapeutic interventions, and taking part will not affect the participants' medical management in any way. Participants will be advised they are under no obligation to take part.
The purpose and intent of the work will be explained. Participants will be given the choice not to answer any particular question. They may skip the question and move on, return to the question later, omit the question altogether, or stop the interview or questionnaire. Patients will be made aware that they can withdraw from the study at any time, with no adverse implications for their clinical care.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

It is possible that patient participants may become distressed or raise issues during data collection related to their illness. Should this be the case, then a member of the research team will seek consent from the participant to raise matters with the relevant member(s) of the patient's clinical team for review. We anticipate distress will be very infrequent, if at all, given the general nature of the valuation questions, and is likely to reflect advanced disease and not the questionnaires themselves.
During the data collection process there will be on-going monitoring for any indications of distress, both actively with frequent verbal checks that the participant is okay and would like to continue, as well as non-verbal indicators that may suggest the participant is distressed such as a change in the level of engagement with the interview or appearing nervous/ anxious. Breaks will be used should participants wish and the interview will be terminated early if required. Any participant who is distressed will also be offered additional support, for example, details of the Macmillan support centre will be provided if appropriate.
All of the research team will have completed Good Clinical Practice (GCP) training, and specific training on addressing distress in palliative care.

Also, as with any research project, there are risks related to the safety and security of participants' personal data. To address these risks all data collected will be completely anonymised and kept in a locked filing cabinet, in a secure office, within the Department of Palliative Care, Policy and Rehabilitation, King's College London. All data protection requirements will be fulfilled. The recruitment log will be kept separately (and securely) to the anonymised data.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

(●) Yes ( ) No

If Yes, please give details of procedures in place to deal with these issues:

Although there is only a minimal risk of a disclosure occurring, a verbal discussion will take place that highlights that although this research is confidential, there is a limit to confidentiality if patients disclose information that indicate they would/have put themselves or others in danger or, any illegal activities, then this would have to be disclosed to

a senior clinician.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

A24. What is the potential for benefit to research participants?

Patients
Although we are not proposing to offer any specific benefits to patients by taking part, patients may be encouraged to raise issues regarding their quality of life and well-being with their clinicians.
Also, there is a substantial and growing body of evidence, including two systematic reviews, suggesting that patients experience benefit from participating in research (1, 2). Qualitative studies of terminally ill patients' experiences of research have highlighted themes of benefit through social interaction and information provision (3) as well as enhanced problem-solving skills, better coping mechanisms and feelings of empowerment, support and reassurance (4). Studies have also found that research participants often value the opportunity to contribute to research that might help others, and can gain a sense of "usefulness" from participating in research despite their deteriorating health.

Healthy volunteers:
Likewise, we are not proposing to offer any specific benefits to healthy volunteers, however, the information provided during the study will help enhance and improve future clinical care.

REFERENCES
1) White C, Hardy J. What do palliative care patients and their relatives think about research in palliative care?a systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2010 Aug;18(8):90511. PubMed PMID: 19705165.
2) Gysels MH, Evans C, Higginson IJ. Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. Bmc Med Res Methodol. 2012;12:123. PubMed PMID: 22900965. Pubmed Central PMCID: 3489694.
3) Gysels M, Shipman C, Higginson IJ. Is the qualitative research interview an acceptable medium for research with palliative care patients and carers? BMC medical ethics. 2008;9:7. PubMed PMID: 18435846. Pubmed Central PMCID: 2383914.
4) Maloney C, Lyons KD, Li Z, Hegel M, Ahles TA, Bakitas M. Patient perspectives on participation in the ENABLE II randomized controlled trial of a concurrent oncology palliative care intervention: benefits and burdens. Palliative medicine. 2013 Apr;27(4):37583. PubMed PMID: 22573470. Pubmed Central PMCID: 3657725.

A26. What are the potential risks for the researchers themselves? *(if any)*

Dealing with distressed participants can lead to distress within the research team. Informal peer support will be available during the study and regular supervision for all members of the research team.
We will offer participants the option of completing questionnaires at a time and place convenient to them. This may therefore require members of the research team to visit them in the community. All those working offsite in this way are required to follow the department's home-worker policy and required to complete a log showing where they are going to conduct an interview. All researchers will be paired with a partner to ensure that a named individual within the department knows their whereabouts at all times.
We will train interviewers at each study site on how to conduct valuation surveys using the time-trade method.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).*

Potential participants will be identified as follows:
(1) IDENTIFICATION OF POTENTIAL PATIENT PARTICIPANTS
Potential patient participants will be screened in the first instance by a member of their clinical team against the inclusion and exclusion criteria. If screened as appropriate and eligible by the clinical team, potential participants will be given the information sheet by a clinician and have a further discussion about the study, with the opportunity to ask questions. A member of the research team will then visit patients who have expressed an interest in taking part at

least 24 hours after initial identification. If they are still willing to take part full informed written consent will be obtained. Patients will be allowed to participate in a way comfortable to them, and be offered flexibility around the time and place of interviewing completion.

(2) IDENTIFICATION OF POTENTIAL HEALTHY VOLUNTEERS :
Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at King's College London (KCL) directly to express interest in participating and for further information.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

○ Yes ◉ No

Please give details below:
Potential patient participants will be identified by their clinical team.

Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

◉ Yes ○ No

If Yes, please give details of how and where publicity will be conducted, and enclose copy of all advertising material (with version numbers and dates).

Healthy volunteers will be recruited through the Volunteer Service Departments at each study site via general e-mail invitations, and volunteer recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information.

A29. How and by whom will potential participants first be approached?

Potential participants will be identified as follows:
(1) PATIENT PARTICIPANTS
Potential patient participants will be screened in the first instance by a member of their clinical team against the inclusion and exclusion criteria. Potential participants will not be approached whilst in the emergency department. Eligible patients identified will first be approached by a clinical member of the palliative care team. When first approached, the clinical team member will introduce the study, explain that participation is entirely voluntary, and provide the patient with an information leaflet about the study. Patients will mostly be approached whilst in hospital or hospice. Only patients who express an interest in the research and who are agreeable to meeting with a member of the research team will have their names passed on to the research team. For these patients, Dr Mendwas Dzingina (PhD training fellow), or another member of the research team (including clinical research nurses), will followup the initial contact and be available to explain the study in detail, answer questions and address any concerns.

(2)IDENTIFICATION OF HEALTHY VOLUNTEERS:
Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information. Dr Dzingina, or another member of the research team (including research nurses) will explain those who have expressed interest that participation is entirely voluntary, and provide more details about the study.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be

done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

(1) PATIENT PARTICIPANTS:
All potential patient participants will have the study explained to them (initially by a clinical member of the palliative care team) and be provided with an information leaflet outlining the purpose of the study, including details of what participation would involve. An in-depth further explanation of the study will subsequently be given by Dr Dzingina (PhD training fellow) or another member of the research team.
For patients who would like to participate, and after a minimum of 24 hours from first contact with a member of the research team, informed written consent to complete a questionnaire survey will be obtained. A minimum period of 24 hours between full explanation of the study and completion of the consent form will be offered to all participants in order to provide an opportunity for patients to reflect on the study and their involvement. If, after 24 hours, potential patient participants would like additional time to consider their involvement, a future meeting time will be organised. However, some potential participants may feel that they do not require 24 hours to consider their involvement, and are comfortable to consent, or decline, earlier than this, for example some soon-to-be discharged patients may prefer to complete the questionnaire before leaving hospital. In these situations the researcher will be guided by the patients' preferences.
Patients will be required to fully comprehend the risks, benefits and burden of their taking part, and give written informed consent to do so. Dr Dzingina, or another member of the research team (including clinical research nurses), who are trained and experienced in the consent process, will be responsible for obtaining consent from all participants.
Patients will be allowed to participate in a way comfortable to them, and be offered flexibility around the time and place of questionnaire completion.
All members of the research team have completed Good Clinical Practice training at Kings College London.

2) HEALTHY VOLUNTEERS:
Healthy volunteers will be recruited through the volunteer service departments at each study site via general e-mail invitations, and Volunteer Recruitment webpages of participating study sites. The volunteers will be invited to contact the research team at KCL directly to express interest in participating and for further information. Dr Dzingina, or another member of the research team (including research nurses) will explain those who have expressed interest that participation is entirely voluntary, and provide more details about the study.

Full informed written consent will be obtained from healthy volunteers who have agreed to participate in the study by Dr Dzingina, or another member of the research team (including clinical research nurses).

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

(●) Yes ( ) No

A31. How long will you allow potential participants to decide whether or not to take part?

A minimum of 24 hours.
However, some potential participants may feel that they do not require 24 hours to consider their involvement, and are comfortable to consent, or decline, earlier than this, for example some soon-to-be discharged patients may prefer to complete the questionnaire before leaving hospital. In these situations the researcher will be guided by the participants' preferences, but 24 hours will always be allowed if desired.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Patients unable to understand written and verbal communication in English are excluded from this study.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the

study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ◉ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ○ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:

This study involves a one-time collection of survey data, so monitoring of subsequent capacity does not apply. However, if a potential participant loses capacity between the time of identification/consent and completion of the survey, they will be excluded from the study.

If you plan to retain and make further use of identifiable data/tissue following loss of capacity, you should inform participants about this when seeking their consent initially.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☐ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☐ Electronic transfer by magnetic or optical media, email or computer networks
- ☐ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☐ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☑ Manual files (includes paper or film)
  - ☐ NHS computers
  - ☐ Social Care Service computers
  - ☐ Home or other personal computers
  - ☑ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

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Further details:
Study participants will be assigned a unique identifier (code number) at the time of data collection.
We will log names and unique identifiers of all participants in a recruitment log which will be locked securely in a cabinet and kept separate from research data (see example in the attached questionnaire). Otherwise, person-identifiable details of participants will not be collected.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Any paper copies of study data will be stored in a locked cabinet at the Cicely Saunders Institute on the site of King's College Hospital. Any electronic data will be stored on encrypted data sticks, encrypted hard drives, or on password protected computers within the Cicely Saunders Institute, King's College London. Only members of the research team will have access to the keys or passwords required to access the data.

A38. How will you ensure the confidentiality of personal data? *Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All participants will be assured of the procedures below that will be taken to ensure confidentiality:
All data collected will be anonymised according to departmental and college guidelines, (Department of Palliative Care, Policy & Rehabilitation, King's College London, (updated April 2010)).
Study participants will be assigned a unique identifier (code number) at the time of data collection. We will log names and unique identifiers of all participants in a recruitment log which will be locked securely in a cabinet and kept separate from research data (see example in the attached questionnaire).

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

The Chief Investigator, Prof. Irene Higginson (IH), the doctoral candidate, Dr Mendwas Dzinigna, other academic supervisors; Prof. Paul McCrone (PM) and Dr Fliss Murtagh (FM); and other designated members of the research team, supervised by IH, PM and FM, will have access to the participants' data during the study.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

The data will be analysed within the Department of Palliative Care, Policy & Rehabilitation, King's College London by the doctoral candidate (Dr Mendwas Dzingina), the Chief Investigator, Prof. Irene Higginson (IH), other academic supervisors; Prof. Paul McCrone (PM) and Dr Fliss Murtagh (FM); and other designated members of the research team, supervised by IH, PM and FM.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Dr	Mendwas	Dzingina
Post	Cicely Saunders International PhD Training Fellow		
Qualifications	MBBS; DLSHTM; MSc		
Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation		
	King's College London		
	London		
Post Code	SE5 9PJ		
Work Email	mendwas.dzingina@kcl.ac.uk		
Work Telephone	442078485572		
Fax	442078485517		

A43. How long will personal data be stored or accessed after the study has ended?

- (•) Less than 3 months
- ( ) 3 – 6 months
- ( ) 6 – 12 months
- ( ) 12 months – 3 years
- ( ) Over 3 years

A44. For how long will you store research data generated by the study?

Years: 10
Months: 0

A45. Please give details of the long term arrangements for storage of research data after the study has ended. *Say where data will be stored, who will have access and the arrangements to ensure security.*

Any paper copies of study data will be stored in a locked cabinet at the Cicely Saunders Institute on the site of King's College Hospital. Any electronic data will be stored on encrypted data sticks, encrypted hard drives, or on password protected computers within the Cicely Saunders Institute, King's College London. All data will be archived in line with KCL policy.
The Chief Investigator (Prof Irene Higginson), the doctoral candidate (Dr Mendwas Dzingina), and his academic supervisors (Dr Fliss Murtagh and Professor Paul McCrone) will have access to the encrypted hard drive.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

( ) Yes (•) No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

( ) Yes (•) No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

( ) Yes (•) No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

( ) Yes (•) No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

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PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

(•) Yes ( ) No

Please give details, or justify if not registering the research.
UKCRN Portfolio Database

Registration of research studies is encouraged wherever possible.
You may be able to register your study through your NHS organisation or a register run by a medical research charity, or publish your protocol through an open access publisher. If you are aware of a suitable register or other method of publication, please give details. If not, you may indicate that no suitable register exists. Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study? *Tick as appropriate:*

- [x] Peer reviewed scientific journals
- [x] Internal report
- [x] Conference presentation
- [x] Publication on website
- [ ] Other publication
- [ ] Submission to regulatory authorities
- [x] Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- [ ] No plans to report or disseminate the results
- [x] Other (please specify)

Dissemination through Cicely Saunders Institute's organised training days for healthcare professionals and researchers about the use of preference-based outcome measures in economic evaluations of palliative care interventions/services, where the newly developed preference-based outcome measure will be discussed.

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

No identifiable personal data will be used.
Only general information of the participants will be published (gender, age and diagnosis).

A53. Will you inform participants of the results?

(•) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
A lay summary of the findings will be offered to the participating palliative care units and hospices for inclusion in their respective patient news letters and websites.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed? *Tick as appropriate:*

- [ ] Independent external review

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- [ ] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [x] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed? *Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [ ] Review by a statistician within the Chief Investigator's institution
- [ ] Review by a statistician within the research team or multi−centre group
- [x] Review by educational supervisor
- [x] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Professor	Paul	McCrone
Department	King's Health Economics, Institute of Psychiatry, Psychology & Neuroscience.		
Institution	King's College London		
Work Address	King's Health Economics Box O24, David Goldberg Centre, Institute of Psychiatry King's College London		
Post Code	SE5 8AF		
Telephone	442078480874		
Fax	442078480458		
Mobile			
E-mail	paul.mccrone@kcl.ac.uk		

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

This is not an intervention study and as a result there is no primary outcome measure. It aims to develop a measure that can be used to derive utility weights for economic evaluations of palliative care interventions.

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A58. What are the secondary outcome measures? *(if any)*

NA

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size: 130
Total international sample size (including UK):
Total in European Economic Area:

Further details:
A total sample size of 130 will be required as follows:
1) 65 patients; and
2) 65 healthy volunteers (32 for each of the two groups of health states).

The group of health states to be valued will be assigned to consecutive participants.

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

Valuation of the 14 states has two aims: (a) to produce mean values for each health state; and (b) to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests. Assuming a power of 0.8, significance level of 0.05, SD of 0.3 and an expected difference of 0.1, 73 valuations are required for each health state (37 from patients and 37 from healthy volunteers) and thus a total of 1,022 valuations for the 14 health states.(1) If we assume that participants are able to provide then a total sample size of 73 would be sufficient to achieve 73 valuations per health state. However, consultations with clinicians and patient representatives revealed that some participants, particularly patients with advanced disease, might find it too burdensome to value 14 health states. Also, previous valuation exercises have shown that respondents cannot value more than 13 health states at a time (Dolan et al., 1996),16 and typically they are asked to value between 6 and 8 health states (Brazier et al., 2002, 2005b & 2008; Dolan et al., 1996; Yang et al., 2011).(2-6) Conversely, reducing the number of health states to be valued by each participant will necessitate an increase in the sample size (of participants) required to achieve 73 valuations per health state.
In order to address this issue, health states will be divided into two blocks, with each block comprising of 8 health states. In each of the two blocks there will be two health states that will be common to both blocks and 6 unique health states (i.e. 6 states unique to block 1; + 6 unique to block 2; + 2 common states = 14 states). Each participant will value only one block comprising of 8 health states. Based on this, a total of 130 participants will be required (65 patients and 65 healthy volunteers). The two health states common to both blocks will thus have 73 values each and so will be used to compare mean values between the health states valued by patients and those valued by healthy volunteers using simple t-tests (aim b). The other health states will be used to calculate mean values for each health state (aim a) as a much smaller number of valuations per health is required for this. This method has been used in previous valuation studies.(1)

The group of health states to be valued will be assigned to consecutive participants.

Reference:
(1) Brazier JE, Rowen D, Mavranezouli I, Tsuchiya A, Young T, Yang Y, et al. Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). Health technology assessment. 2012;16(32):1-114. Epub 2012/07/27.
(2) Dolan P, Gudex C, Kind P and Williams A. The time trade-off method: results from a general population study. Health Econ. 1996; 5: 141-54.
(3) Brazier J, Roberts J and Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002; 21: 271-92.
(4) Brazier JE, Roberts J, Platts M and Zoellner YF. Estimating a preference-based index for a menopause specific health quality of life questionnaire. Health and quality of life outcomes. 2005; 3: 13.
(5) Brazier J. Measuring and valuing mental health for use in economic evaluation. Journal of health services research & policy. 2008; 13 Suppl 3: 70-5.
(6) Yang Y, Brazier JE, Tsuchiya A and Young TA. Estimating a preference-based index for a 5-dimensional health state classification for asthma derived from the asthma quality of life questionnaire. Medical decision making : an international journal of the Society for Medical Decision Making. 2011; 31: 281-91.

A61. Will participants be allocated to groups at random?

○ Yes ◉ No

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

The methods used for this study are based on recommendations in the Health Technology Assessment (HTA) guidance document on "developing and testing methods for deriving preference based measures of health from condition-specific measures (and other patient-based measures of outcome)".(1)

Deriving a preference-based-measure consists of 3 stages as follows.
Stage 1:
In the first stage, the aim is to construct a simplified health state classification (based on the Patient Outcome Scale - POS) containing a subset of items that are most representative of the POS. This involves conducting secondary analyses of pre-existing POS datasets using factor analysis, Rasch analysis, and other standard psychometric techniques. We have already completed this first stage.

Stage 2:
The second stage involves primary data collection via a cross sectional survey. The aim here is to directly derive health-state utility values/weights for a sub-sample of the health states derived from the first stage described above. The utility values for these health states will be derived directly by asking health professionals, managers, students, patients and carers, 'Time-Trade-Off' (TTO) questions in a 'valuation' survey.
The TTO is a technique used in health economics to help determine the quality of life of an individual (or patient) or a group. The individual will be presented with a set of directions for example:
"Imagine that you are told that you have 10 years left to live. In connection with this you are also told that you can choose to live these 10 years in your current health state or that you can choose to give up some years-of-life to live for a shorter period in full health. Indicate with a cross on the line, the number of months in full health that you think is of equal value to 10 years in your current health state".(2)

The line usually ranges from 0 to 10 and the person's score is calculated by dividing the number corresponding to their cross by 10. For example if someone marks a cross at 6 on the TTO line, they would be given a TTO score of 0.60. This number is often used in turn to calculate quality-adjusted life years (QALYs). In our example if this person were to live for 2 years at their current health state (of 0.6) this would be equal to 1.2 QALYs (2 * 0.6). QALYs enable health care decision makers to combine mortality and morbidity into a single interval scale, thereby enabling the comparison of interventions between different diseases and across a variety of disciplines.
However, for this study, we propose to use a modified version of the TTO which uses a time interval of 0 to 10 weeks (instead of 0 to 10 years). The rationale behind this is based on the fact that on average, palliative care patients usually have a life expectancy much shorter than 10 years, and so it may be inappropriate to ask them to trade-off lengths of time they know they don't have.(3)

Mean TTO values will be estimated for each of the 14 health states that will be valued. The mean values between the states that were valued by patients will be compared with those valued by non-patient participants using simple t-tests.

Stage 3:
The aim here is to indirectly derive utility values for all other health states that were not included in stage 2, through a combination of regression and Rasch analyses.(1) This technique involves using regression analysis to estimate utility values for all health states using the Rasch logit score.(4) Specifically, a series of regression analyses will be undertaken to explore the relationship between the utility values of each health state that was considered in the valuation survey and the respective Rasch model logit value corresponding to the health state, as calculated by previously undertaken Rasch analysis of POS data.
Ordinary Least Squares (OLS) models will be used to analyse the valuation data at an aggregate (mean) level first, i.e. regression analyses will be conducted on the mean utility values obtained for each health state included in the valuation survey, without taking into account individual respondent characteristics (such as age, gender, ethnicity, etc.), since aggregate utility data are used in cost-utility analyses of healthcare technologies. OLS regression analysis will also be conducted at the individual level to explore the impact of respondents' personal characteristics (such as age, gender, ethnicity, patient / member of general public, etc.). An important limitation of the OLS model is that it assumes a continuous variable without censoring; in this case, it does not allow for the dependent variable (utility value) to be bounded by a maximum value of +1 and a minimum value of -1. Therefore, Tobit models will be estimated, to allow censoring at both the top and bottom ends of the relationship.(5)
The fit of individual OLS models will be assessed using the coefficient of determination (i.e. the adjusted R-Squared) and the root mean squared error (RMSE)7. Tobit models will be assessed using the estimated standard error of the

regression, which is analogous to the root mean square error (RMSE) in OLS regression. All regression analyses will be run on STATA version 12 (Stata Corp., 2011).

Reference:
(1) Brazier JE, Rowen D, Mavranezouli I, et al. Developing and testing methods for deriving preference-based measures of health from condition-specific measures (and other patient-based measures of outcome). Health technology assessment. 2012; 16: 1-114.

(2) Burström K, Johannesson M, Diderichsen F. A comparison of individual and social time trade-off values for health states in the general population. Health policy. 2006;76(3):359-70.

(3) Normand C. Measuring outcomes in palliative care: limitations of QALYs and the road to PalYs. Journal of Pain & Symptom Management. 2009; 38: 27-31

(4) Mavranezouli I, Brazier JE, Rowen D, Barkham M. Estimating a Preference-Based Index from the Clinical Outcomes in Routine Evaluation–Outcome Measure (CORE-OM): Valuation of CORE-6D. Medical Decision Making. 2013;33(3):381-95.

(5) Tobin J. Estimation of Relationships for Limited Dependent Variables. Econometrica. 1958;26(1):24-36.

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	Mendwas	Dzingina
Post	Cicely Saunders International PhD Training Fellow		
Qualifications	MBBS; DLSHTM; MSc		
Employer	King's College London		
Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation King's College London London		
Post Code	SE5 9PJ		
Telephone	442078485517		
Fax	44207 848 5517		
Mobile			
Work Email	mendwas.dzingina@kcl.ac.uk		

	Title	Forename/Initials	Surname
	Professor	Irene J.	Higginson
Post	Professor and Head of Department of Palliative Care, Policy & Rehabilitation		
Qualifications	PhD, FFPHM, BMBS, BMedSci		
Employer	King's College London		
Work Address	King's College London, Cicely Saunders Institute Bessemer Road Denmark Hill, London		
Post Code	SE5 9PJ		
Telephone	02078485516		
Fax	02078485517		
Mobile			

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Work Email	irene.higginson@kcl.ac.uk

Title	Forename/Initials	Surname
Professor	Paul	McCrone

Post	Professor of Health Economics & Deputy Director, King's Health Economics
Qualifications	PhD Health Economics; MSc Economics; BA (Hons) Political Economy
Employer	King's College London
Work Address	P024 Institute of Psychiatry King's College London De Crespigny Park,London
Post Code	SE5 8AF
Telephone	4420 7848 0874
Fax	4420 7848 0458
Mobile	
Work Email	paul.mccrone@kcl.ac.uk

Title	Forename/Initials	Surname
Dr	Fliss	Murtagh

Post	Reader and Consultant in Palliative Medicine
Qualifications	FRCP; MRCGP; PhD
Employer	King's College London
Work Address	King's College London, Cicely Saunders Institute Bessemer Road Denmark Hill, London
Post Code	SE5 9PJ
Telephone	442078485583
Fax	442078485517
Mobile	
Work Email	fliss.murtagh@kcl.ac.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status:

If Other, please specify:

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Contact person

Name of organisation	King's College London
Given name	Keith
Family name	Brennan
Address	Room 1.8, Hodgkin Building, Guy's Campus
Town/city	London
Post code	SE1 4UL
Country	UNITED KINGDOM
Telephone	02078486960
Fax	02078486394
E-mail	keith.brennan@kcl.ac.uk

Is the sponsor based outside the UK?

◯ Yes ◉ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

☑ Funding secured from one or more funders

☐ External funding application to one or more funders in progress

☐ No application for external funding will be made

What type of research project is this?

◯ Standalone project

◉ Project that is part of a programme grant

◯ Project that is part of a Centre grant

◯ Project that is part of a fellowship/ personal award/ research training award

◯ Other

Other – please state:
There are two funding sources: (1) C-CHANGE NIHR programme grant (RP-PG-1210-12015) is leading the work on development of outcome measures, including for economic evaluation. This is a five year research programme with many components, of which this is one. (2) The BuildCARE programme is supporting the PhD fellowship.

Please give details of funding applications.

Organisation	National Institute for Health Research (NIHR)
Address	Room 132 Richmond House 79 Whitehall
Post Code	SW1A 2NS
Telephone	
Fax	
Mobile	

DRAFT

Email enquiries@nihr.ac.uk

Funding Application Status: (•) Secured ( ) In progress

Amount: £1,968,973

Duration
Years: 5
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
NIHR program grants for applied research

Organisation Cicely Saunders International
Address Cicely Saunders Institute
Bessemer Road, Denmark Hill
London
Post Code SE5 9PJ
Telephone 02078485580
Fax
Mobile
Email brenda.ferns@cicelysaundersinternational.org

Funding Application Status: (•) Secured ( ) In progress

Amount: £2,443,112.00

Duration
Years: 4
Months:

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
This project forms part of a larger programme of palliative care research, project BuildCARE, for which funding has been secured

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (•) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (•) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

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	Title	Forename/Initials	Surname
	Mrs	Liba	Stones
Organisation	King's College Hospital NHS foundation Trust		
Address	1st Floor, 161 Denmark Hill		
	London		
Post Code	SE5 8EF		
Work Email	liba.stones@nhs.net		
Telephone	02032991980		
Fax	02032995515		
Mobile			

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A69-1. How long do you expect the study to last in the UK?

Planned start date: 27/07/2015
Planned end date: 03/06/2016
Total duration:
Years: 0 Months: 10 Days: 8

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☐ Scotland
- ☐ Wales
- ☐ Northern Ireland
- ☐ Other countries in European Economic Area

Total UK sites in study 5

Does this trial involve countries outside the EU?

○ Yes ◉ No

A72. Which organisations in the UK will host the research? *Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	3
☐ NHS organisations in Wales	
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	

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☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Joint health and social care agencies (eg community mental health teams)	
☐ Local authorities	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☑ Independent (private or voluntary sector) organisations	2
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	5

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

We conduct internal audits of all governance for studies annually.
The research and development department at King's College Hospital are also required to audit 10% of ongoing studies.
This study may be subject to this.

The Chief Investigators (Professor Irene Higginson) and the the academic supervisors of the Doctoral student (Dr Mendwas Dzingina) will review a sample of completed questionnaires to check for accuracy, authenticity, and standards of interviewing.

There will also be regular meetings of the steering group for the project, where the progress and findings will be reviewed.

A76. Insurance/ indemnity to meet potential legal liabilities

Note: in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

☐ NHS indemnity scheme will apply (NHS sponsors only)

☑ Other insurance or indemnity arrangements will apply (give details below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

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A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- [ ] NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- [x] Other insurance or indemnity arrangements will apply (give details below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- [x] NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- [x] Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

King's College London Standard Indemnity.

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

- (•) Yes
- ( ) No
- ( ) Not sure

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PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Investigator identifier	Research site		Investigator Name	
IN1 ☐	◉ NHS site ○ Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Fliss Murtagh fliss.murtagh@kcl.ac.uk PhD; MSc; MRCGP; MBBS UNITED KINGDOM
	Country: England			
	Organisation name Address Post Code	KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST DENMARK HILL LONDON GREATER LONDON SE5 9RS		
IN2 ☐	○ NHS site ◉ Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Victor Pace V.Pace@stchristophers.org.uk UNITED KINGDOM
	Institution name Department name Street address Town/city Post Code Country	St. Christopher's Hospice 51-59 Lawrie Park Road London SE26 6DZ UNITED KINGDOM		
IN3 ☐	◉ NHS site ○ Non-NHS site		Forename Middle name Family name Email Qualification (MD...) Country	Shaheen Khan Shaheen.Khan@gstt.nhs.uk UNITED KINGDOM
	Country: England			
	Organisation name Address	GUY'S AND ST THOMAS' NHS FOUNDATION TRUST TRUST OFFICES		

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GUY'S HOSPITAL
GREAT MAZE POND LONDON
GREATER LONDON
Post Code SE1 9RT

IN4 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name ST GEORGE'S HEALTHCARE NHS TRUST
Address ST GEORGE'S HOSPITAL
BLACKSHAW ROAD
TOOTING LONDON GREATER LONDON
Post Code SW17 0QT

Forename Ollie
Middle name
Family name Minton
Email ominton@sgul.ac.uk
Qualification (MD...) PhD; FRCP; FHEA
Country UNITED KINGDOM

IN5 ☐

○ NHS site
◉ Non-NHS site

Institution name St Joseph's Hospice
Department name
Street address Mare Street
Town/city London
Post Code E8 4SA
Country UNITED KINGDOM

Forename Margaret
Middle name
Family name Clifford
Email M.Clifford@STJH.org.uk
Qualification (MD...)
Country UNITED KINGDOM

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PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.
4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.
5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.
6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.
7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.
8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.
9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:
    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.
10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
11. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication *(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

◉ Chief Investigator

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- ◯ Sponsor
- ◯ Study co-ordinator
- ◯ Student
- ◯ Other – please give details
- ◯ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☐ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Professor Irene Higginson on 14/01/2016 13:51.

Job Title/Post:	Professor of Palliative care
Organisation:	KIng's College London
Email:	irene.higginson@kcl.ac.uk

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D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.
3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.
4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*
7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.
8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Mr Keith Brennan on 11/01/2016 19:00.

Job Title/Post:	Director of Research Management & Innovation
Organisation:	King's College London
Email:	keith.brennan@kcl.ac.uk

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D3. Declaration for student projects by academic supervisor(s)

1. I have read and approved both the research proposal and this application. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level.

2. I undertake to fulfil the responsibilities of the supervisor for this study as set out in the Research Governance Framework for Health and Social Care.

3. I take responsibility for ensuring that this study is conducted in accordance with the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research, in conjunction with clinical supervisors as appropriate.

4. I take responsibility for ensuring that the applicant is up to date and complies with the requirements of the law and relevant guidelines relating to security and confidentiality of patient and other personal data, in conjunction with clinical supervisors as appropriate.

Academic supervisor 1

This section was signed electronically by Dr Fliss Murtagh on 11/01/2016 14:32.

Job Title/Post:	Reader in Palliative Medicine
Organisation:	King's College London
Email:	fliss.murtagh@kcl.ac.uk

Academic supervisor 2

This section was signed electronically by Professor Paul McCrone on 07/01/2016 19:09.

Job Title/Post:	
Organisation:	
Email:	

Academic supervisor 3

This section was signed electronically by Professor Irene Higginson on 14/01/2016 13:50.

Job Title/Post:	Professor of Palliative care
Organisation:	KIng's College London
Email:	irene.higginson@kcl.ac.uk

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NHS SSI IRAS Version 5.2.1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Development of a preference-based outcome measure for Palliative Care

1. Is your project research?

(•) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product
( ) Clinical investigation or other study of a medical device
( ) Combined trial of an investigational medicinal product and an investigational medical device
( ) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
( ) Basic science study involving procedures with human participants
(•) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
( ) Study involving qualitative methods only
( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
( ) Study limited to working with data (specific project only)
( ) Research tissue bank
( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (•) No
b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (•) No
c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (•) No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

[x] England
[ ] Scotland

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☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

◉ England
○ Scotland
○ Wales
○ Northern Ireland
○ This study does not involve the NHS

4. Which review bodies are you applying to?

☐ HRA Approval
☑ NHS/HSC Research and Development offices
☐ Social Care Research Ethics Committee
☑ Research Ethics Committee
☐ Confidentiality Advisory Group (CAG)
☐ National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D offices, the CI must create Site-Specific Information Forms for each site, in addition to the study-wide forms, and transfer them to the PIs or local collaborators.

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

○ Yes ◉ No

If yes and you have selected HRA Approval in question 4 above, your study will be processed through HRA Approval.

If yes, and you have not selected HRA Approval in question 4 above, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) support and inclusion in the NIHR Clinical Research Network (CRN) Portfolio? Please see information button for further details.

◉ Yes ○ No

If yes, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before submitting other applications. If you have selected HRA Approval in question 4 above your study will be processed through HRA Approval. If not, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent

for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
Part of this study contributes to PhD work for Dr Mendwas Dzingina.

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

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Site-Specific Information Form (NHS sites)

Is the site hosting this research a NHS site or a non-NHS site? *NHS sites include Health and Social Care organisations in Northern Ireland. The sites hosting the research are the sites in which or through which research procedures are conducted. For NHS sites, this includes sites where NHS staff are participants.*

- (●) NHS site
- ( ) Non-NHS site

This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.

One Site-Specific Information Form should be completed for each research site and submitted to the relevant R&D office with the documents in the checklist. See guidance notes.

The data in this box is populated from Part A:

Title of research:
Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)

Short title: Development of a preference-based outcome measure for Palliative Care

Chief Investigator:

Title	Forename/Initials	Surname
Professor	Irene	Higginson

Name of NHS Research Ethics Committee to which application for ethical review is being made:

Project reference number from above REC:

1-2. Give the name of the NHS organisation responsible for this research site

KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST
If this site has not been included in the list of sites submitted to the main REC in Part C, please submit a Notice of Amendment to the main REC, copied to MHRA for information.

1-3. In which country is the research site located?

- (●) England
- ( ) Wales
- ( ) Scotland
- ( ) Northern Ireland

1-4. Is the research site a GP practice or other Primary Care Organisation?

( ) Yes (●) No

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2. Who is the Principal Investigator or Local Collaborator for this research at this site?

Select the appropriate title: (•) Principal Investigator ( ) Local Collaborator

	Title	Forename/Initials	Surname
	Dr	Fliss	Murtagh
Post	Reader and Consultant in Palliative Medicine		
Qualifications	PhD; MSc; MRCGP; MBBS		
Organisation	King's College London		
Work Address	Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation Faculty of Life Sciences & Medicine Bessemer Road, London		
PostCode	SE5 9PJ		
Work E-mail	fliss.murtagh@kcl.ac.uk		
Work Telephone	+44 (0) 207 848 5583		
Mobile			
Fax	+44 (0) 207 848 5517		

a) Approximately how much time will this person allocate to conducting this research? *Please provide your response in terms of Whole Time Equivalents (WTE).*
0.2 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (•) Yes ( ) No

A copy of a current CV for the Principal Investigator (maximum 2 pages of A4) must be submitted with this form.

3. Please give details of all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

Please list all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Give details of any research procedures to be carried out off site, for example in participants' homes.

	Location	Activity/facilities
1	All King's College Hospital (KCH) hospital inpatient wards	Recruitment, consenting and questionnaire completion by patients
2	All KCH out-patient and community clinics (oncology, respiratory, palliative care)	Recruitment, consenting and questionnaire completion by patients
3	The Cicely Saunders Institute	Consenting and questionnaire completion by patients and healthy volunteers

5. Please give details of all other members of the research team at this site.

1

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	Title	Forename/Initials	Surname
	Professor	Irene J.	Higginson
Work E-mail	irene.higginson@kcl.ac.uk		
Employing organisation	Kings College London		
Post	Head of Department, Professor of Palliative Care and Policy, Honorary Consultant in Palliative Medicine		
Qualifications	BMedSci, BMBS, FFPHM, FRCP, PhD		
Role in research team:	researcher		

a) Approximately how much time (approximately) will this person allocate to conducting this research? *Please provide your response in terms of Whole Time Equivalents (WTE).*
0.1 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

2

	Title	Forename/Initials	Surname
	Dr	Fliss	Murtagh
Work E-mail	fliss.murtagh@kcl.ac.uk		
Employing organisation	Kings College London		
Post	Reader and senior consultant in Palliative Medicine		
Qualifications	FRCP MRCGP PhD		
Role in research team:	researcher		

a) Approximately how much time (approximately) will this person allocate to conducting this research? *Please provide your response in terms of Whole Time Equivalents (WTE).*
0.1 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

3

	Title	Forename/Initials	Surname
	Dr	Mendwas	Dzingina
Work E-mail	mendwas.dzingina@kcl.ac.uk		
Employing organisation	King's College London		
Post	Cicely Saunders International PhD Training Fellow		
Qualifications	MBBS; DLSHTM; MSc		
Role in research team:	researcher		

a) Approximately how much time (approximately) will this person allocate to conducting this research? *Please*

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provide your response in terms of Whole Time Equivalents (WTE).
0.8 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

4

	Title	Forename/Initials	Surname
	Miss	Caty	Pannell
Work E-mail	caty.pannell@nhs.net		
Employing organisation	Kings College Hospital NHS Trust		
Post	Senior Research Nurse		
Qualifications	RGN		
Role in research team:	research nurse		

a) Approximately how much time (approximately) will this person allocate to conducting this research? *Please provide your response in terms of Whole Time Equivalents (WTE).*
0.2 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

5

	Title	Forename/Initials	Surname
	Mrs	Paramjote	Kaler
Work E-mail	p.kaler@nhs.net		
Employing organisation	Kings College Hospital NHS Trust		
Post	Research Nurse		
Qualifications	RGN		
Role in research team:	research nurse		

a) Approximately how much time (approximately) will this person allocate to conducting this research? *Please provide your response in terms of Whole Time Equivalents (WTE).*
0.1 WTE

b) Does this person hold a current substantive employment contract, Honorary Clinical Contract or Honorary Research Contract with the NHS organisation or accepted by the NHS organisation? (●) Yes ( ) No

A copy of a current CV for the research team member (maximum 2 pages of A4) must be submitted to the R&D office.

6. Does the Principal Investigator or any other member of the site research team have any direct personal involvement (e.g. financial, share-holding, personal relationship etc) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?

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○ Yes ◉ No

7. What is the proposed local start and end date for the research at this site?

Start date:	08/02/2016
End date:	18/07/2016
Duration (Months):	5

8-1. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *(These include seeking consent, interviews, non-clinical observations and use of questionnaires.)*

Columns 1-4 have been completed with information from A18 as below:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.

2. If this intervention would have been routinely given to participants as part of their care, how many of the total would have been routine?

3. Average time taken per intervention (minutes, hours or days)

4. Details of who will conduct the procedure, and where it will take place

Please complete Column 5 with details of the names of individuals or names of staff groups who will conduct the procedure at this site.

Intervention or procedure	1	2	3	4	5
Obtain informed consent from participants	1	NA	15 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.	Dr Mendwas Dzingina, Caty Pannell (research nurse), Dr Fliss Murtagh, Prof Irene Higginson or any other researcher working under Professor Higginson
Participants complete self/interviewer administered questionnaire	1	NA	45 Min	Dr Mendwas Dzingina or another member of the research team (including research nurses). Consenting will be completed in a place agreeable to both the participant and researcher.	Dr Mendwas Dzingina, Caty Pannell (research nurse), Dr Fliss Murtagh, Prof Irene Higginson or any other researcher working under Professor Higginson

8-2. Will any aspects of the research at this site be conducted in a different way to that described in Part A or the protocol?

○ Yes ◉ No

If Yes, please note any relevant changes to the information in the above table.

Are there any changes other than those noted in the table?

10. How many research participants/samples is it expected will be recruited/obtained from this site?

50 participants (20 patients and 30 healthy volunteers)

11. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study.

1) Adult patients (18 years or older) with advanced disease will be identified and approached initial by a member of

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their clinical team and asked if they would be interested in participating and also offered an information leaflet. Patients who have expressed interest will subsequently be approached by the research team. This will be supported by embedded research nurses.
2) Adult (18 years or older) healthy volunteers will be recruited through the King's College hospital volunteer service via email invitations, leaflets and posters at KCH. The volunteers will be invited to contact the research team at KCH directly to express interest in participating and for further information.

12. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

Name	Expertise/training
Dr Mendwas Dzingina	Dr Dzingina is a qualified medical doctor and has received training during his clinical career in the consent process and capacity assessments. Dr Dzingina has attended Good Clinical Practice (GCP) training at KCL in 2015
Miss Caty Pannell	Caty Pannell is a senior research nurse in the Department of Palliative Care, Policy & Rehabilitation. She is experienced in the consent process and has attended GCP training.
Mrs Paramjote Kaler	Paramjote Kaler is a research nurse in the Department of Palliative Care, Policy & Rehabilitation. She is experienced in the consent process and has attended GCP training.

15-1. Is there an independent contact point where potential participants can seek general advice about taking part in research?

The Patient Advice and Liaison Service (PALS) at Kings College Hospital.
All participants will be advised that they can seek support, or raise any concerns regarding the study through PALS at KCH. The phone number for PALS at KCH is provided on the information leaflets that will be received by all study participants.

15-2. Is there a contact point where potential participants can seek further details about this specific research project?

Dr Mendwas Dzingina, Department of Palliative Care, Policy & Rehabilitation, Cicely Saunders Institute, Bessemer Road, London, SE5 9PJ. mendwas.dzingina@kcl.ac.uk. Tel: 020 7848 5572.

Dr Fliss Murtagh, Department of Palliative Care, Policy & Rehabilitation, Cicely Saunders Institute, Bessemer Road, London, SE5 9PJ. fliss.murtagh@kcl.ac.uk. Tel: 020 7848 5583.

Professor Irene Higginson Department of Palliative Care, Policy & Rehabilitation, Cicely Saunders Institute, Bessemer Road, London, SE5 9PJ. palliativecare@kcl.ac.uk; 020 7848 5531.

The contact details for Dr Mendwas Dzingina and Professor Irene Higginson are also provided on the information leaflets that will be received by all study participants.

16. Are there any changes that should be made to the generic content of the information sheet to reflect site-specific issues in the conduct of the study? *A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.*

No

Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. Unless indicated above, this must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).

17. What local arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? *(e.g. translation, use of interpreters etc.)*

Participants that who do not adequately understand verbal explanations or written information given in English are excluded from this study.

18. What local arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

N/A.
It will not be necessary to inform the GP(s) of participants as the study only involves completing a one-off questionnaire and study participation will not impact on the care/treatment of patients.

19. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

In the unlikely event that distress is experienced during the study or because of it, a distress protocol, which has been developed based on those successfully used by researchers in the Department of Palliative Care, Policy & Rehabilitation for previous studies. During questionnaire completion, there will be ongoing monitoring for any indications of distress, both actively with frequent verbal checks that
the participant is okay and would like to continue, as well as non-verbal indicators that may suggest the participant is distressed such as a change in the level of engagement with the interview or appearing nervous/ anxious. Breaks will be used should participants become distressed and the interview will be terminated early if required. Any participant who is distressed will be offered additional support from the research team and the wider cancer support community, for example Macmillan support centre details will be provided, in accordance with the distress protocol.
It will be explained to all participants that they have the option of withdrawing from the study at any time and for any reason. Participants will also be advised that they do not need to answer every interview question, and can come back to questions at a later stage in the interview process if they wish. All data collected will remain strictly confidential unless any unsafe practice is revealed, i.e. information that represents a risk to the participant, others, and/ or is required to be disclosed by law. In this situation confidentiality will be breached and the participant will be informed of this. Information will then be reported following local guidelines, as well as being discussed with the research and clinical team leads to ensure safe and best practice is maintained. This is indicated in the participant information leaflet.
Both the study's Chief Investigator, Professor Irene Higginson, all academic supervisors, and the doctoral student, Dr Mendwas Dzingina have completed Good Clinical Practice training at King's College London.

20. What are the arrangements for the supervision of the conduct of the research at this site? *Please give the name and contact details of any supervisor not already listed in the application.*

The research and development department at King's College Hospital are required to audit 10% of ongoing studies. This study may be subject to this.
The Chief Investigator (Prof Irene Higginson) and the the academic supervisors of the Doctoral student (Dr Mendwas Dzingina) will review a sample of the data to check for accuracy, and authenticity.
There will also be regular meetings of the steering group for the project.

21. What external funding will be provided for the research at this site?

- ○ Funded by commercial sponsor
- ◉ Other funding
- ○ No external funding

Please give details of the funding:

Type of funding	Details (including breakdown over years if appropriate)
(i) Block grant	
(ii) Per participant	

There are two funding sources: (1) C-CHANGE NIHR programme grant (RP-PG-1210-12015) is

(iii) Other (give details)	leading the work on development of outcome measures, including for economic evaluation. This is a five year research programme with many components, of which this is one. (2) The BuildCARE programme is supporting the PhD fellowship through the Cicely Saunders International BuildCARE Fellowships (24611)

Which organisation will receive and manage this funding?
King's College London

23. Authorisations required prior to R&D approval

The local research team are responsible for contacting the local NHS R&D office about the research project. Where the research project is proposed to be coordinated centrally and therefore there is no local research team, it is the responsibility of the central research team to instigate this contact with local R&D.

NHS R&D offices can offer advice and support on the set-up of a research project at their organisation, including information on local arrangements for support services relevant to the project. These support services may include clinical supervisors, line managers, service managers, support department managers, pharmacy, data protection officers or finance managers depending on the nature of the research.

Obtaining the necessary support service authorisations is not a pre-requisite to submission of an application for NHS research permission, but all appropriate authorisations must be in place before NHS research permission will be granted. Processes for obtaining authorisations will be subject to local arrangements, but the minimum expectation is that the local R&D office has been contacted to notify it of the proposed research project and to discuss the project's needs **prior** to submission of the application for NHS research permission via IRAS.

Failure to engage with local NHS R&D offices **prior** to submission may lead to unnecessary delays in the process of this application for NHS research permissions.

Declaration:

☑ **I confirm that the relevant NHS organisation R&D office has been contacted to discuss the needs of the project and local arrangements for support services. I understand that failure to engage with the local NHS R&D office before submission of this application may result in unnecessary delays in obtaining NHS research permission for this project.**

Please give the name and contact details for the NHS R&D office staff member you have discussed this application with:

Please note that for some sites the NHS R&D office contact may not be physically based at the site. For contact details refer to the guidance for this question.

	Title	Forename/Initials	Surname
	Ms	Esther	Davies
Work E-mail	esther.davies1@nhs.net		
Work Telephone	020 3299 2763		

Declaration by Principal Investigator or Local Collaborator

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.

4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.

5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.

6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.

7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.

8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.

9. I undertake to complete any progress and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.

10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.

11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.

12. I understand that information relating to this research, including the contact details on this application, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

13. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

This section was signed electronically by Dr Fliss Murtagh on 05/02/2016 14:28.

Job Title/Post:	Reader in Palliative Medicine
Organisation:	King's College London
Email:	fliss.murtagh@kcl.ac.uk

DRAFT

Health Research Authority (HRA) approval: statement of activities for participating NHS organisations in England and Schedule of events

Site Type: 2 (All research activities including consent and data collection)

Organisation: Multiple GP practices within the North east and north Cumbria Clinical Research Network (CRN)

Locations within participating organisation: Newcastle and Gateshead Clinical Commissioning Group (CCG); Sunderland CCG; South Tyneside CCG; North Tyneside CCG; and Northumberland CCG.

HRA Statement of Activities

Health Research Authority

for Participating NHS Organisations in England (template version 4.1)

For non-commercial studies, one Statement of Activities should be completed as a template for each site-type in the study. Each Statement of Activities should be accompanied by a completed HRA Schedule of Events, as part of the submission via IRAS for HRA Approval.

Blue shaded fields (also marked with an asterisk) should be completed by the sponsor/applicant prior to submission to the HRA*
Where appropriate, for the purpose of confirming capacity and capability, green shaded fields (also marked with a caret^) should be completed by the participating organisation before returning the document to the sponsor.
Other questions may be completed either by the sponsor/applicant or participating organisation (or collaboratively between both parties), as appropriate.

For participating organisations in Northern Ireland, Scotland or Wales, the sponsor should transfer a Site Specific Information Form to each local research team for completion and submission to their research management support function.

To provide an answer in the form, click in a box with the blue text and over-write this text, or select the relevant option if presented with drop-down text. A separate guidance document is provided and should be consulted prior to completion of this template. Please also read the question specific guidance where present.

IRAS ID*	159556
Short Study Title*	Development of a preference-based outcome measure for Palliative Care
Full Study Title*	Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)
Contact details of sponsor, or sponsor's delegated point of contact (e.g. Study Manager), for questions relating to study set-up*	Dr Mendwas Dzingina mendwas.dzingina@kcl.ac.uk 02078485572
Site Type*	All Site Activities *Select one option. If 'Other', give details.* If 'Other', insert details here

Name of Participating Organisation	*Where this statement is to be used as the agreement between sponsor and participating organisation, the name of the participating organisation should be entered here prior to agreement. If this Statement is being agreed to cover multiple separate entities (e.g. multiple GP practices within a single LCRN geography) please make this clear here.* Multiple GP practices within the North East and North Cumbria Clinical Research Network
Location/s within Participating Organisation	*Where the research is planned to take place only at specified hospitals or other locations within the participating organisation (as may be the case in an NHS Trust comprised of more than one hospital) please name those hospitals/locations here.* Newcastle Gateshead CCG Sunderland CCG South Tyneside CCG

	North Tyneside CCG Northumberland CCG

Date *HRA Office Use Only*	*Date template assessed by HRA*
Version Number *HRA Office Use Only*	Applicant version assessed by HRA

1. Does the sponsor intend that this document forms the agreement between itself and the participating organisation/s in England?*

For non-commercial studies other than clinical trials and clinical investigations, the HRA encourages use of the Statement of Activities as the only form of agreement between sponsor and an English participating organisation, in place of bespoke agreements created by sponsors. For research in primary care settings, the Statement may be used for a geographical area, e.g. at the LCRN level, although agreement should be between the sponsor and independent legal entity (e.g. GP Practice). For clinical trials and clinical investigations the HRA expects that sponsors will use the relevant model agreement, where one exists.

Yes

2. Date this Statement of Activities confirmed by participating organisation, if applicable.^

15/09/2016

3. Confirmation on behalf of participating organisation provided by (insert name and job title), if applicable.^

Sally Dunn

Research Facilitator

Primary Care Team

NIHR Clinical Research Network North East and North Cumbria

It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the sponsor and participating organisation. Instead, sponsors are expected to accept confirmation by email from an individual empowered by the participating organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).

4. If this Statement is not intended to form the agreement with the participating organisation/s in England, will the sponsor be using an unmodified model non-commercial agreement?*

Select 'yes' or 'no'

5. If no, please provide details of the modifications made to the model agreement and the reasons for them. If the sponsor intends to use an agreement not based on the model agreement, please provide detailed justification for this (templates of all 'site agreements' to be used, including for sites in the devolved administrations (where applicable) should be provided as part of the submission for HRA Approval).*

Provide details of modification made to model agreement and the reasons for them

6. Predicted Participant Recruitment, if applicable.
This is recruitment or identification at participating organisation, not overall for the study. Please clarify if this refers to participants, samples or data. Please clearly state if this is per month, per year, overall etc. Leave blank if not applicable to this site type.

4 patients

7. Proposed start date of research/participant identification activity at participating organisation.
Where it might otherwise be open to interpretation, please specify whether this date refers to the commencement of screening, the recruitment of the first participant, etc.

19/10/16

Commencment of screening

8. Predicted end date of research/participant identification activity at participating organisation.
Where it might otherwise be open to interpretation, please specify whether this date refers to the recruitment of the final participant, the final visit of the final participant, database lock, etc.

19/12/16

Recruitment of final pariticipant

9. Person responsible for research activities at site.*

Local Principal Investigator
The HRA expects Principal investigators to be in place at participating organisations where locally employed staff take responsibility for research procedures. Where this is not the case, the HRA expects Local Collaborators to be in place where central study staff will be present at site to undertake research procedures (the role of the Local Collaborator is to support practical arrangements for the presence of research staff under Letters of Access or Honorary Research Contracts). Where existing data is being provided for research purposes without additional research procedures and without the presence of central research team members at site, the HRA does not expect that a Principal Investigator or Local Collaborator is appointed and you should select Chief Investigator.

10. Are you requesting support to identify a Principal Investigator or Local Collaborator?*
Please indicate whether support from the host organisation is being requested to identify a Principal Investigator/Local Collaborator and provide further information on expectations below. Where a Principal Investigator or Local Collaborator has already been identified, their details appear on Part C of the IRAS Form.

No

11. Further Information (where applicable).*
Please provide further information on sponsor expectations for a Principal Investigator/Local Collaborator, to help participating organisations identify an appropriate individual if required (e.g. Profession, specialty, seniority etc.)

Provide information on the support required

12. The following capabilities and capacity are needed locally in order to deliver the study, e.g. specific equipment, patient/participant groups, service support nursing time, excess treatment costs, etc.*

Any funding or support from the sponsor/funder to the participating organisation is set out in the Finance Schedule.

Ability to recruit 4 patients by 19/12/2016.

Capacity: 2 participants per month.

13. Projected NHS Treatment Cost savings at this site type, if applicable.*

Although many studies incur Excess Treatment Costs (see AcoRD for information on cost attribution) many studies also give rise to treatment cost savings during the study (e.g. a two armed study comparing standard care to a less intensive, and less expensive, alternative treatment). Please describe below any projected treatment cost savings, so your participating organisations may include this information when considering the overall treatment costs/cost savings of their portfolio of research. Any funding or support from the sponsor/funder to the participating organisation is set out in the Finance Schedule. Excess Treatment Costs will be indicated above (question 12) and in the HRA Schedule of Events.

Provide information on projected treatment cost savings (or leave blank if not applicable)

14. The following training for local staff will be provided by the sponsor. Where only specific team members (e.g. the Principal Investigator) will receive this training, this is described below.*

We (the central research team/sponsor) have trained the local research memebers (Research Nurses) on how to apply the Time-Trade-Off survey method which will be used in this study. This will be a one-off, three-hour long training.

15. In addition to the above training, to be provided by the sponsor, the sponsor also expects that the following local research team members will undertake or have already undertaken the following training.*

It would not be usual for the sponsor to expect study specific training additional to that which it will provide, this section does however allow sponsors to state that they will accept, for example, NIHR CRN training in Good Clinical Practice where the study is a Clinical Trial of an Investigational Medicinal Product etc.

All members of the local research team will be required to undertake Good Clinical Practice training

Schedule 1 (Finance) (template version 4.1)

Please select one of the following*	
There are no funds/resources/equipment, etc. being provided to this/these organisation/s by the sponsor. *This schedule should be left blank.**	☒
The following funding/resources/equipment, etc. is to be provided to this/these local participating organisation/s. However, the finance schedule to cover such transfer is detailed in a separate agreement. *Please complete the information below but leave the schedule blank and submit your separate agreement to the HRA.**	☐
Enter information on funding, resource and/or equipment etc. to be provided to the site by the sponsor but do not complete the schedule below	
The following funding/resource/equipment, etc. is to be provided to this local participating organisation. This Statement of Activities is intended by the sponsor to form the agreement between them and the participating organisation. The finance schedule below details the funds to be provided to the site by the sponsor. *Please complete the information and the schedule below.[1]**	☐
Enter information on funding, resource and/or equipment etc. to be provided to the site by the sponsor and also complete the schedule below	

1 Payment Schedule (i.e. frequency or trigger for payments)*
Enter details of payment schedule
2 Area of Cost (e.g. set-up, procedure, overall cost, etc.)*
Enter details on area of cost

Payment Details:

If VAT is payable, then the Sponsor shall pay the VAT in addition to the payment on presentation of a VAT invoice. If VAT is not payable, then the Sponsor shall issue a VAT exemption certificate.

3 Invoices to be submitted to (insert job title, name of body and address)*
Enter address details

4 Payment to be made by cheque to^
Enter cheque payable details
4.1 AND remitted to (insert job title/position and address)
Enter job title/position and address
OR
5 Arrange BACS transfer to: Bank Name
Enter bank name

[1] The Statement of Activities is not intended for use with participating organisations in Northern Ireland, Scotland or Wales

5.1 Sort Code

Enter sort code

5.2 Account Number

Enter account number

5.3 And send the relevant paper work to the following address

Enter address details

Invoices should be presented promptly. No payment shall be made in the case where invoices are not presented in a complete, accurate and timely fashion and funding from an external funding body has been irrecoverably reclaimed by such external funding body as a result of such delay or inadequacy.

Schedule 2 (Material Transfer Provisions)

(template version 4.1)

These provisions do not remove the responsibility for a sponsor to clearly lay out in their protocol (and to potential participants in the patient information sheet/s) at a minimum the following information for all human biological material taken: 1) The nature of the materials, 2) The reason that the material is being taken, 3) where the material is to be sent, 4) what will happen to any remaining material once it has been processed/analysed, etc. for the purposes of this study (e.g. return, retention or destruction).

Detailed guidance on what information should be included in a protocol may be found on the HRA website http://www.hra.nhs.uk

Please select one of the following*	
This study does not involve the transfer of human biological material from this participating organisation to the sponsor or its agents. ***This schedule does not form part of this agreement.****	☒
The Sponsor has separately provided to the HRA and participating organisation an agreement for the transfer of human biological material. ***This schedule does not form part of this agreement.****	☐
These provisions form part of the agreement between the sponsor and this participating organisation. ***Select this option if no other agreement is provided, and the terms below constitute the arrangements for this study.**[2]	☐

1 Where the protocol requires the participating organisation to supply material to the sponsor/joint sponsor(s)/either of the co-sponsors, these provisions shall apply if stated above.

2 In accordance with the protocol, the participating organisation shall send material to the sponsor/joint sponsor(s)/a co-sponsor or, in accordance with provision 8 below, a third party nominated by the sponsor/joint sponsor(s)/either of the co-sponsors.

3 The participating organisation warrants that all material has been collected with appropriate informed consent and has been collected and handled in accordance with applicable law (including, without limitation, the Human Tissue Act 2004 or the Human Tissue (Scotland) Act 2006[3] (as the case may be)) and as required by the protocol.

4 Subject to provision 3 above, the materials are supplied without any warranty, expressed or implied including as to their properties, merchantable quality, fitness for any particular purpose, or that the materials are free of extraneous or biologically active contaminants which may be present in the Materials.

5 The sponsor/joint sponsor(s)/one of the co-sponsors shall ensure, or procure through an agreement with the sponsor/joint sponsor(s)/co-sponsors nominee as stated in provision 2 above that.

5.1 the material is used in accordance with the protocol, the consent of the participant, and the HRA Approval for the Study,

5.2 the material is handled and stored in accordance with applicable law,

[2] The HRA Statement of Activities is not intended for use with participating organisations in Northern Ireland, Scotland or Wales.

[3] Although the HRA Statement of Activities is not intended for use with participating organisations in Scotland, studies taking place in England might involve transfer of Human Tissue to Scotland for (for example) analysis in a central technical facility.

5.3 the material shall not be redistributed or released to any person other than in accordance with the protocol or for the purpose of undertaking other studies approved by an appropriate ethics committee and in accordance with the participant's consent, and

5.4 no alteration shall be made to the title, coding or acronym of the material.

6 The parties shall comply with all relevant laws, regulations and codes of practice governing the research use of human biological material.

7 The participating organisation and the sponsor/joint sponsors(s)/a co-sponsor shall each be responsible for keeping a record of the material that has been transferred according to these provisions.

8 To the extent permitted by law the participating organisation and its staff shall not be liable for any consequences of the supply to or the use by the sponsor/joint sponsors//co-sponsor of the material or of the supply to or the use by any third party to whom the sponsor/joint sponsors/co-sponsor subsequently provides the material or the Sponsor's/Joint Sponsors/Co-Sponsor's nominee as stated in provision 2 above, save to the extent that any liability which arises is a result of the negligence of the participating organisation.

9 The sponsor/joint sponsors/co-sponsor undertake(s) that, in the even that material is provided to a third party in accordance with provision 2 above, it/they shall require that such third party shall undertake to handle any data and Material related to the Study in accordance with all applicable statutory requirements and codes of practice and under terms no less onerous than those set out in these provisions.

10 Any surplus material that is not returned to the participating organisation or retained for future research (in line with participant consent) shall be destroyed in accordance with applicable law (including, without limitation, the Human Tissue Act 2004).

Schedule 3 (Confidentiality, Data Protection and Freedom of Information) (template version 4.1)

Please select one of the following*	
This study does not involve the transfer of Personal Data from this participating organisation to the sponsor or its agents, nor is there transfer of confidential information between the parties. ***This schedule does not form part of this agreement.****	☐
The Sponsor has separately provided to the HRA and participating organisation another agreement for the transfer of data. ***This schedule does not form part of this agreement.****	☐
These provisions form part of the agreement between the sponsor and this participating organisation. ***Select this option if no other agreement is provided, and the terms below constitute the arrangements for this study.***[4]	☒

1. Participant Confidentiality
   1.1. The parties agree to adhere to all applicable statutory requirements and mandatory codes of practice in respect of confidentiality (including medical confidentiality) in relation to participants
   1.2. Personal Data shall not be disclosed to the sponsor by the participating organisation, save where this is required directly or indirectly to satisfy the requirements of the Protocol, or for the purpose of monitoring or reporting adverse events, or in relation to a claim or proceeding brought by a participant in connection with the study.
   1.3. Neither the sponsor nor the participating organisation shall disclose the identity of participants to third parties without the prior written consent of the participant except in accordance with applicable statutory requirements and codes of practice, including HSCIC Code of Practice on Confidential Information.
   1.4. The sponsor agrees to act as Data Controller in relation to any processing of Personal Data under this agreement. This extends to all processing that would not have taken place but for this agreement regardless where that processing takes places. In particular, it extends to processing by the participating organisation where that processing is undertaken solely for the purposes of the study.
   1.5. The sponsor agrees to comply with the obligations placed on a Data Controller by the Data Protection Act 1998. This is not limited to, but includes, ensuring that:
      1.5.1. Personal Data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes
      1.5.2. Personal Data are adequate, relevant and not excessive in relation to the purpose or purposes described within the protocol.
      1.5.3. Personal Data shall be accurate and, where necessary, kept up to date.
      1.5.4. Personal Data shall be processed in accordance with the rights of data subjects under the Data Protection Act 1998.
   1.6. The Sponsor agrees to ensure appropriate training. In particular:
      1.6.1. To ensure that any persons (excluding employees, honorary employees, students, researchers, consultants and subcontractors of the Participating Site) processing

[4] The HRA Statement of Activities is not intended for use with participating organisations in Northern Ireland, Scotland or Wales.

Personal Data are subject to annual mandatory training in the information governance responsibilities and have appropriate contracts including sanctions, including for breach of confidence or misuse of data;

1.6.2. To ensure that the Senior Information Risk Owners, e.g. Caldicott Guardians, senior partners and board members of the sponsor (or organisational equivalent of each of these) complete additional data security training annually.

1.7. The participating organisation agrees to ensure that its employees, honorary employees, students, researchers, consultants and subcontractors processing Personal Data are subject to annual mandatory training in the information governance responsibilities and have appropriate contracts including sanctions, including for breach of confidence or misuse of data;

1.8. The sponsor agrees to use Personal Data solely in connection with the operation of this agreement and the study and not otherwise. In particular;

1.8.1. Not to disclose Personal Data in whole or in part to any person without the participating organisation's prior written consent;

1.8.2. Not to disclose other than pursuant to a data sharing agreement that conforms to the requirements set out in the Information Commissioner's data sharing code of practice.

1.9. The participating organisation agrees to act as Data Processor on behalf of the sponsor as Data Controller for processing undertaken under this agreement solely for the purposes of the study. The participating organisation agrees to comply with the obligations placed on it as the data controller by the seventh data protection principle ("the Seventh Principle") set out in the Data Protection Act 1998, namely:

1.9.3. to maintain technical and organisational security measures sufficient to comply at least with the obligations imposed on the Data Controller by the Seventh Principle;

1.9.4. only to process Personal Data for and on behalf of the Data Controller, in accordance with the instructions of the Data Controller and for the purpose of the study and to ensure the Data Controller's compliance with the Data Protection Act 1998;

1.9.5. to allow the sponsor to audit the participating organisation's compliance with the requirements of this clause on reasonable notice and/or to provide the Data Controller with evidence of its compliance with the obligations set out in this clause;

1.9.6. the participating organisation shall obtain prior agreement of the sponsor to store or process Personal Data at sites outside the European Economic Area (comprising the countries of the European Community, Norway, Iceland and Liechtenstein).

2. Freedom of Information

2.1. Parties to this agreement which are subject to the Environmental Information Regulations 2004 (EIR) and the Freedom of Information Act 2000 (FOIA) or the Freedom of Information (Scotland) Act 2002 (FOI(S)A) and which receive a request under EIR, FOIA or FOI(S)A to disclose any information that belongs to another party shall notify and consult that party, as soon as reasonably practicable, and in any event, not later than seven (7) calendar days after receiving the request.

2.2. The parties acknowledge and agree that the decision on whether any exemption applies to a request for disclosure of recorded information under EIR, FOIA or FOI(S)A is a decision solely for the party responding to the request.

2.3. Where the party responding to an EIR, FOIA or FOI(S)A request determines that it will disclose information it will notify the other party in writing, giving at least four (4) calendar days' notice of its intended disclosure.

3. Confidential information

3.1. The receiving party agrees to take all reasonable steps to protect the confidentiality of the confidential information and to prevent it from being disclosed otherwise than in accordance with this agreement.

3.2. Subject to clause 3.4 below, the participating organisation agrees to treat the results, excluding any clinical data of the study, as confidential information disclosed by the sponsor and the sponsor agrees to treat Personal Data as confidential information disclosed by the participating organisation.

3.3. The receiving party agrees:

- 3.3.1. To ensure that any of its employees, students, researchers, consultants or sub-contractors who participate in the operation of the study are made aware of, and abide by, the requirement of this clause 3 and, where relevant, clause 2.
- 3.3.2. To use confidential information solely in connection with the operation of the agreement and not otherwise.
- 3.3.3. Not to disclose confidential information in whole or in part to any person without the disclosing party's prior written consent.

3.4. The provision of clause 3 shall not apply to the whole or any part of the confidential information that is:

- 3.4.1. lawfully obtained by the receiving party free of any duty of confidentiality;
- 3.4.2. already in the possession of the receiving party and which the receiving party can show from written records was already in its possession (other than as a result of a breach of clause 3.1 or 3.2);
- 3.4.3. in the public domain (other than as a result of a breach of clause 3.1 or 3.2);
- 3.4.4. independently discovered by employees of the receiving party without access to or use of confidential information;
- 3.4.5. necessarily disclosed by the receiving party pursuant to a statutory obligation;
- 3.4.6. disclosed with prior written consent of the disclosing party;
- 3.4.7. necessarily disclosed by the receiving party by virtue of its status as a public authority in terms of the Freedom of Information Act 2000;
- 3.4.8. published in accordance with HRA expectations on research transparency.

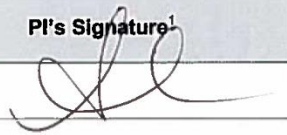
3.5. The restrictions contained in clauses 2 and 3 shall remain in force without limit in time in respect of Personal Data or which relates to a patient, his or her treatment and/or medical records. Save as aforesaid and unless otherwise expressly set out in this Agreement, these clauses shall remain in force for a period of 10 years after the termination or expiry of this Agreement.

Appendix 1 (Staff signature and delegation log) (template version 4.1)

This Appendix is for use at the discretion of the sponsor and participating organisation, to record the roles and responsibilities of the local research team (where applicable) and the authorisation of the Principal Investigator (PI) for this.

Please select one of the following*	
The sponsor intends to use this template as the delegation log for this participating organisation	☐
The sponsor intends to use a delegation log based on another template for this participating organisation	☐
The sponsor is not proposing that a delegation log is completed for this participating organisation	☐

IRAS ID	Name of Participating Organisation
159556	Imeary Street Surgery

Name of Principal Investigator	PI's Signature[1]	PI's Initials	Start (dd/mmm/yy)	End (dd/mmm/yy)
Dr Anji Curry		AC	07/10/2016	

[1]My signature confirms/acknowledges that the information contained in this delegation log is accurate and that:

a. I will conduct the study in accordance with the protocol and remain responsible for the overall study conduct at the participating organisation and for the reported data.
b. I will ensure study oversight.
c. I will authorise the delegation of study-related tasks to each individual as listed.
d. The study tasks listed will only be delegated by me to skilled and qualified staff appropriately trained for the role.
e. I will ensure that all personnel assisting in the conduct of the study are informed about their obligations and will not have performed any delegated study-related tasks prior to appropriate delegation and completion of study training appropriate to the role.
f. I will ensure that participating organisation staff receive, in a timely manner, the appropriate information and training.
g. I am not involved in any regulatory or misconduct litigation or investigation by any regulatory authority and no data produced by me in any previous clinical Study has been rejected because of concerns as to its accuracy or because it was generated by fraud.
h. Neither I, nor any dependents, have entered into and will not enter into arrangements, financial or otherwise, with any third party providing support, products and/or services to the study that would present a conflict of interests
i. I will ensure that any and all changes in staff or delegated study-related task will be recorded in a timely manner.
j. I consent to the sponsor, and to any relevant third party providing support, products and/or services to the Study, holding my name and other relevant details on an appropriate database for the purpose of communicating with me in relation to the study.

Study Task Key:

The sponsor may detail in the below key the main study activities that the PI can delegate to staff at the participating organisation. The task list and delegation log are intended to be maintained as an up to date document throughout the duration of the study at the participating organisation.

1. Screens/recruits study subjects	6. Enter other task here	11. Enter other task here	16. Enter other task here
2. Obtains Informed Consent	7. Enter other task here	12. Enter other task here	17. Enter other task here
3. Confirms eligibility (Inclusion/Exclusion)	8. Enter other task here	13. Enter other task here	18. Enter other task here
4. Enter other task here	9. Enter other task here	14. Enter other task here	19. Enter other task here
5. Enter other task here	10. Enter other task here	15. Enter other task here	20. Enter other task here

Name	Signature[2]	Initials	Study Role	Study Task(s) (Select from key)	Start of task(s) (dd/mmm/yy)	PI Initials	End of task(s) (dd/mmm/yy)	PI Initials
Anji Curry		AC	GP	1,	7/10/16	AC		
Jill Ducker		JD	RESEARCH NURSE	1,2,3,	07/10/2016.	AC		
Nicky Todd	Nicky Todd	NT	RESEARCH NURSE	1.2.3	07/10/2016	NT.		
Rachel Nixon								

[4]My signature confirms/acknowledges that I accept the assigned study task/s and that:

- I am not involved in any regulatory or misconduct litigation or investigation by any regulatory authority, and no data produced by me in any previous clinical Study has been rejected because of concerns as to its accuracy or because it was generated by fraud.
- I consent to the sponsor, and to any relevant third party providing support, products and/or services to the study, holding my name and other relevant details on an appropriate database for the purpose of communicating with me in relation to the study.

I confirm that the information contained in this delegation log is accurate and complete. (To be completed by the PI at the end of the study).

PI name: Signature: Date:

User Feedback (template version 4.1)

Please complete this form with your comments on the usability of the Statement of Activities and return by email to: hra.approvalprogramme@nhs.net

Comments

Enter comments here

What we will do with your response?

The HRA has a commitment to transparency. We will analyse the comments we receive, and publish a report on our website explaining how we will address the themes raised. The published report will compare the views of different organisations and groups of individuals.

Organisational responses: In the interest of transparency, all comments made on behalf of an organisation will normally be published and attributed unless an explanation is provided with your response as to why you consider the information should not be. (Please note the Confidentiality of Information section below.)

Individual responses:

Comments will be summarised in a way that does not identify individual respondents unless we have your permission to identify you.

Are you responding in an organisation or personal capacity?

Organisation Capacity	☐
Personal Capacity	☐

If you are replying in an organisational capacity, please note that your response may be published and quoted in the final report.

Organisational responses only

If you do not wish your organisational response, and any quotes used from it, to be identified in any consultation report and any future HRA publications, or published once the consultation has ended.

Please provide explanation of why you do not wish us to publish your organisational response

Individual responses only

I am responding primarily as a: (please check only one box):

Research Team Member	☐	NHS Staff	☐
Member of the public	☐	Industry	☐
REC Member	☐	Phase 1 Company	☐
REC Staff	☐	Regulatory Body	☐
R&D Community	☐	Academic	☐
Other (Please specify)	☐		

Please specify if answered 'Other'

I am willing for my response, and quotes used from it, to be used in non-identifiable form in any consultation report and any future HRA publications:

I am willing for my response, and quotes used from it, to be made identifiable in any consultation report and any future HRA publications:

Select 'yes' or 'no'

All responses

I am willing to be contacted by the HRA for further information in relation to this consultation or future consultations.

Select 'yes' or 'no'

If 'yes', please provide your contact details below. By providing these contact details, you are giving your consent for a member of HRA staff to contact you about your submission. The HRA takes data protection very seriously. We promise we will not pass your details on to any other organisations or use them for any other purposes.

Contact Name:

Enter contact name

Email:

Enter email address

Confidentiality of Information

The HRA will process your personal data in accordance with the DPA and in most circumstances this will mean that your personal data will not be disclosed to third parties without your permission or unless required by law. Information we receive, including personal information, may be published or disclosed in accordance with the access to information regimes (primarily the Freedom of Information Act 2000 (FOIA), the Data Protection Act 1998 (DPA) and the Environmental Information Regulations 2004). If you want the information that you provide to be treated as confidential, please be aware that, under the FOIA, there is a statutory Code of Practice with which public authorities must comply and which deals, amongst other things, with obligations of confidence. In view of this it would be helpful if you could explain to us why you regard the information you have provided as confidential. If we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. An automatic confidentiality disclaimer generated by your IT system will not, of itself, be regarded as binding on the HRA.

HRA Schedule of Events for Studies in Cohort 3 of HRA Approval

NHS Health Research Authority

What is the HRA Schedule of Events?

The HRA Schedule of Events is part of the document submission pack, to be submitted via IRAS for non-commercial studies applying for HRA Approval. It also forms part of the local document pack that sponsors should provide to participating organisations once the templates submitted to the HRA have been agreed and this agreement recorded in the HRA Initial Assessment Lettter (or HRA Approval letter, where no Initial Assessment letter is issued).

For non-commercial studies, one HRA Schedule of Events should be completed as a template for each site-type in the study. Each HRA Schedule of Events should be accompanied by a completed Statement of Activities for the same site-type, as part of the submission via IRAS for HRA Approval. Once agreed by the HRA, the sponsor/applicant should provide each participating organisation with the agreed Schedule and related agreed Statement relevent for its site-type. Applicants should refer to the full guidance in the Statement of Activities template for further information on use of the two tools.

Together with the Statement of Activities, the Schedule is designed to facilitate the conversation between sponsor/applicant and their partcipating organisations through which local capacity and capability to undertake the study are assessed and arranged and thereafter confirmed as being in place. The Schedule is designed to allow the sponsor/applicant to detail the activities to take place at the participating organisations that come under the site-type covered by the document and to indicate the cost attribution of each activity.

Each activity recorded in the Schedule should be given a cost attribution by the sponsor/applicant, in line with the DH AcoRD guidance available here: https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Each completed Schedule should reflect the activities to be undertaken at the organisations to be covered by the document. Studies where the activities undertaken at different organisations differ (i.e. there is more than one 'site-type' in the study) will require one Schedule submitted to the HRA per site type, with each Schedule reflecting the activities to be undertaken at one site-type.

What is a 'Site Type'?

Many research studies take place at more than one participating organisation. Where this is the case, each participating organisation may be undertaking the same research procedures, e.g. identifying, consenting, treating and following-up research participants. In such cases the study has only one 'site-type' and only one Schedule and one accompanying Statement are required. In other cases, different participating organisations may be required to undertake different sub-sets of the overall set of research procedures that make up the study, e.g. some participating organisations may identify and consent participants whilst others treat and follow-up. In such a case there would be two 'site-types' and two Schedules of Events and two Statements of Activities would be required, each Shedule/Statement covering one site-type. It is important to note that the number of Schedules required from the sponsor for HRA Approval is determined by the number of site-types, not by the number of sites.

How Do I Complete this Document?

Please answer the first four questions in the Study Information tab. Complete one HRA Schedule of Events per site-type, specifying the site-type under questions 3 (and 4, if necessary) of the Study Information tab.

Please complete the General Activities and Per-Participant tabs for the site-type covered by this document. Select an item from "Area of Activity" first, before selecting an item from

"Specific Activity" (the "Specific Activity" drop-down box is only present once an "Area of Activity" is selected. Activities should be selected from the drop-down lists where possilble (for ease of reference, all activities in the drop downs are listed alphabetically on the List of Activities tab). Where an activitiy is not listed, it should be entered in free-text. Only activities that take place per-participant should be listed on the per-participant tab. Where the study has more than one arm, or the activities otherwise differ between groups of participants, the tab may be copied and each arm/group recorded as a new tab. For each instance of each activity, a cost attribution should be selected from the drop-down list (e.g. Research Cost (Part A), Research Cost (Part B) etc.). Where an activity does not occur at a particular visit, the box may be left blank or "No Activity" may be selected. Each box may be populated individually from the drop down, or cost types may be 'pulled across' an entire row (see Hints and Tips tabs for further details).

Hints and Tips
Please read the Hints and Tips tab before completing the General Activities and Per-Participant tabs.

List of Activities
This section provides definitions of / more information on the activities given in the General Activities and Per-Participan drop-down lists. It is not an exhaustive list of all possible activities associated with a research project and applicants may enter additional activities by free-text in the general activities and/or participant activities tabs. Applicants are invited to use the User Feedback tab to comment on the usefulness of the activities given and to suggest the inclusion of additional activities in future versions of this tool.

How do I submit my HRA Schedule of Events to the HRA?
All submissions for HRA Approval should be made electronically through IRAS. The Schedule of Activities forms part of the document set that should be uploaded to the IRAS Form checklist tab prior to submission. To upload your Schedule/s please select 'Add New Row' at the bottom of the checklist tab . Please attach one Schedule per 'Other (please specify)' row.

Accessing Help and Support Completing this Document
Please refer in the first instance to the guidance below and the Hints & Tips tab. Additional queries may be addressed to hra.approval@nhs.net

User Feedback
The HRA wants to hear from you about this document. Whether you work for a sponsor or organisation hosting research, whether within cohort 3 or not, we want your views. Formal feedback may be provided by completing the User Feedback tab in this spreadsheet and returning it to hra.approval@nhs.net

End of General Guidance.

Study Information

Template Version 3.1

NHS Health Research Authority

The Sponsor/Applicant should provide answers to questions 1-4 below prior to submission for HRA Approval.

1. IRAS Reference Number:	**159556**
2. Short Study Title:	Development of a preference-based outcome measure for Palliative Care
3. Site Type, Please use drop-down Menu:	Site type 2: All site activities
4. If "Other", Please Specify:	
5. Date *(HRA Office Use Only)*:	
6. Version Number *(HRA Office Use Only)*:	

General Activities

Template Version 3.1

NHS Health Research Authority

Guidance

This tab should be completed for the 'site-type' covered by this Schedule of Events, including only those activities relevant to the organisations covered by this document (e.g. if the organisations will not be recruiting participants, do not include the activities related to participant recruitment). All activities should be given a cost attribution, in line with the DH AcoRD guidance. https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Please refer to the Hints and Tips tab before completing this section.

IRAS Reference Number:	159556

					Day -x to -y	Day 0	Day x
Area of Activity (Select this first. You can insert free text if the drop-down options are not suitable)	Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Site set-up	Screen	Base	Visit 1
Study Set Up	Attendance at training	180	External Staff (Central Research Team)	Research Cost (Part A)	No Activity	No Activity	No Activity
Consent Processes	Database search	90	GPs in North East and Cumbria	No Activity	Service Support Cost	No Activity	Research Cost (Part A)
Study Monitoring							

Per-Participant Activities

Template Version 3.1

NHS
Health Research Authority

Guidance

This tab should be completed for the 'site-type' covered by this Schedule of Events, including only those activities relevant to the organisations covered by this document (e.g. if the organisations will not be recruiting participants, do not include the activities related to participant recruitment). Where the study involves multiple arms, this tab may be copied and each arm entered as a new tab. All activities should be given a cost attribution, in line with the DH AcoRD guidance. https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Please refer to the Hints and Tips tab before completing this section.

IRAS Reference Number*:	159556

				Day -x to -y	Day 0
Area of Activity (Select this first. You can insert free text if the drop-down options are not suitable)	Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Screen	Base
Participant Consent Procedures	Approach potential participant in the first instance to introduce study, ask if they would be interested in participating, and take verbal consent	5	General practioners and nurses who work in the community, in North East and Cumbria	Service Support Cost	No Activity
Participant Consent Procedures	E-mail to research nurse to inform of verbal consent	3	General practioners and nurses who work in the community, in North East and Cumbria	Service Support Cost	No Activity
Participant Consent Procedures	Take informed consent	5	Research Nurses in North East and Cumbria CRN		Service Support Cost
Interventions non clinical	Administer questionnaire	50	Research Nurses in North East and Cumbria CRN		Service Support Cost
Other Procedures or Activities	Administer questionnaire	45	Research Nurses in North East and Cumbria CRN		Service Support Cost
Other Procedures or Activities					

Research Project Summary – information for GP practices

NHS National Institute for Health Research

Clinical Research Network
North East and North Cumbria

Study Title: Development of a preference based outcome measure for use in economic evaluations of palliative care services

Dr Mendwas Dzingina, Kings College London

Brief summary of the project	This study aims to improve the assessment of quality of life for palliative care patients. This will involve exploring different aspects of health and how they are valued by palliative care patients. The ultimate aim is to create a preference based outcome measure (similar to EQ-5D and SF-6D) specific to palliative care, which can be used as a tool to support economic evaluations of palliative care services.
What will the practice be expected to do?	• GPs who take part in the study will be asked to identify palliative care patients who they feel could be approached about taking part in the study. • The GP will inform the patient about the study during a practice appointment/home visit and ask for verbal consent to pass on contact details to the research team • The patients contact details will be transferred securely to CRN Research Nurses via NHS net email accounts.
Search criteria	**Inclusion** • 18 years or over • All receiving palliative care or being seen by specialist palliative care services – irrespective of diagnosis **Exclusion** Patients judged to be too distressed/ unwell/ symptomatic to participate by their clinical team.
What will the patient be expected to do?	• A member of the research team will contact consenting patients identified by their GP. • Following further discussion about the study, an appointment will be made with the patient at a location convenient to them. • Participants will be asked to complete a time-trade-off questionnaire which is led by the interviewer (Research Nurse). This will include information on socio-demographic information, an assessment of respondents own health and valuation tasks. • Valuation tasks will include comparing and prioritising states of health. **This may include references to dying and death**.
Service Support Costs	TBC

If you are interested in taking part or would like more information please contact your Research Facilitator

Apple– GP practices Version 1 December 2015

Template email for sponsors to share amendment documents with sites

This is an optional email for sponsors to use to notify participating NHS organisations in England of a Category A amendment, or a Category B amendment which does not add new participating NHS organisations. The notification should be sent to both the research management office and local research team.

The use of this template email will ensure clear and consistent communication between the sponsor and participating NHS organisations in England about implementation of Category A and B amendments, and is intended to be sent as soon as the categorisation email is issued to the sponsor.

The 35 day clock starts from the date that participating organisations in England are notified of the amendment by the sponsor.

Text that is highlighted in red should be amended by the sponsor as appropriate prior to issue of the email.

From: Sponsor (or representative)

To: Site research management function and local research team and, where applicable LCRN, (this template can be used to email multiple sites in one email, or one site). If sending to multiple sites, the use of the bcc function is recommended.

Subject: IRAS Number; Notification of Amendment

Attachments: HRA categorisation email, amendment package (including REC opinion if applicable and already issued); HRA assessment outcome letter (if already issued)

Body of Text:

Dear participating organisation/s, (name if sending to one site),

RE: IRAS Number; Short Study Title; Amendment Reference

We have submitted an amendment to the HRA for the above referenced study, and attached is the HRA categorisation email with the amendment package. Please read the documents carefully.

In line with the HRA categorisation email and UK wide policy on the handling of amendments, your site is given 35 days from the date of this notification to raise an objection about the amendment. If we do not hear from you by **insert date**, we will assume that the amendment may be implemented at your site. If you need more time to consider the amendment please contact us and we will assist with any queries you may have. If you are able to notify us ahead of this date that you are able to implement this amendment it will enable us to potentially implement it sooner.

Version 1.3, 7 April 2016

Please note that, in line with the HRA categorisation email, we will:

- Not implement this amendment until relevant regulatory approvals are in place
- Not implement this amendment at a site which requests more time to consider the amendment until that site is able to implement the amendment, or any that notifies us that they are unable to implement the amendment

If you need to discuss the impact of the amendment at your site please do not hesitate to contact me.

If not already attached, I will provide you with letter from the HRA assessment to communicate that you are able to implement the amendment. Please do not implement this amendment until this letter is received.

Kind regards

Sponsor (or representative of)

08 February 2016

King's College Hospital
NHS Foundation Trust

Dr Fliss Murtagh
Reader and Consultant in Palliative Medicine
King's College London
Cicely Saunders Institute
Dept of Palliative Care
Bessemer Road
London SE5 9PJ

Research & Innovation Office
Kings College Hospital NHS Foundation Trust
First Floor 161 Denmark Hill,
London, SE5 8EF

Direct tel: 020 3299 1980

www.kch.nhs.uk/research
R&I central mailbox kch-tr.research@nhs.net

Dear Dr Murtagh

Study Title: Development of a preference-based outcome measure for Palliative Care

Ethics ref: 15/LO/1774
Sponsor: King's College London
Location: Denmark Hill
Study end date as per SSI: 18 July 2016
Target Recruitment: 50
Protocol Version: V1

On behalf of **King's College Hospital NHS Foundation Trust,** I am pleased to inform you that your project is approved and you may proceed.

The study has been registered as **KCH16-013**. Please quote this reference in any communications with the R&I Office regarding your project.

All approved documents are listed at the end of this letter. Please ensure that any amendments to the documents or changes to the study team are notified to the office.

Investigator Responsibilities:

- You are expected to recruit to time and target. A condition of the approval is to notify the R&I Office (via the central mailbox) of the date on which you consent your first participant.
- The approval is conditional on the project being conducted as described within the application. The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures – especially those relating to research and data management.
- You must notify the office of all changes to the project, such as extension of study activity time at site, amendment to protocol, changes in study team and site closure. For all KCH

sponsored/co-sponsored studies, yearly REC progress reports and the end of study report should be submitted to R&I.

- You are responsible for ensuring that good research governance, conduct and practice, are maintained throughout the duration of the study.
- The Trust maintains oversight of all active projects and you may be subject to review and audit at any point by internal or external bodies.
- If the project is a clinical trial under the European Union (EU) Clinical Trials Directive the appropriate EU legislation must be complied with.
- In accordance with National and Trust guidelines on safety reporting requirements, you must notify the Sponsor, the R&I Office (via the central mailbox) and submit an Adverse Incidence report on the Trusts' Datix system for all SUSARS and suspected protocol breaches.

If appropriate it is recommended that you register with the Current Controlled Trials website;
http://isrctn.org/

The R&I office will support you throughout the duration of your project. Please contact us at the address above if and when you require further information or guidance.

We wish you every success with your project.

Yours sincerely,



Esther Davies
Asst Research Facilitator

cc. Chief Investigator: Irene Higginson, KCL - Irene.Higginson@kcl.ac.uk
cc. Sponsor: Keith Brennan, KCL - keith.brennan@kcl.ac.uk

List of Approved Documents:

Study protocol
Patient information Sheet
Consent forms
Feasibility form
Grant award letter
PI's CV
REC letter

V5 December 2015

Health Research Authority (HRA) approval: statement of activities for participating NHS organisations in England; and Schedule of events

Site Type: 1 (Consent and data collection by Central Research Team only)

Organisation: All NHS Trusts

Health Research Authority

Statement of Activities (template version 3.1)

IRAS ID:	*Insert the IRAS ID. It will populate the footer.* 159556
Short Study Title:	*Insert the short study title. It will populate the footer.* Development of a preference-based outcome measure for Palliative Care
Site Type:	Other *Select one option. If 'Other', give details.* Site type 1: Consent and data collection by Central Research Team
Date: *HRA Office Use Only*	*Date template assessed by HRA* Choose Assessment Date
Version Number: *HRA Office Use Only*	Enter Version Number.

For non-commercial studies, one Statement of Activities should be completed as a template for each site type in the study. Each Statement of Activities should be accompanied by a completed HRA Schedule of Events, as part of the submission via IRAS for HRA Approval. Questions denoted with a red asterisk should be completed by the sponsor/applicant prior to submission to the HRA. Where required, for the purpose of confirming capacity and capability, questions denoted by a green caret ^ should be completed by the participating organisation before returning the document to the sponsor. Other questions may be completed either by the sponsor/applicant or participating organisation, as appropriate.*

Guidance is provided at the end of this document. Please also read the question specific guidance where present.

Date this Statement of Activities confirmed by participating organisation, if applicable: ^

Click here to enter date confirmed.

Confirmation on behalf of participating organisation provided by (insert name and job title), if applicable: ^

Click here to enter name and job title.

It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the sponsor and participating organisation. Instead, sponsors are expected to accept confirmation by email from an individual empowered by the participating organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).

Health Research Authority

Part A (template version 3.1)

Part A should be completed only for staff research in England and research involving only primary care settings in England. For other studies, Part A is optional as the information will be provided in the Site Specific Information Form.

1. IRAS Study Type:*	Choose study type.
2. Full Study Title:*	Click here to enter full study title.
3. Name of Sponsor Organisation*	Click here to enter name of Sponsoring Organisation
4. Name of Chief Investigator*	Click here to enter name of Chief Investigator
5. Name of Participating Organisation *Where this statement is to be used as the agreement between sponsor and participating organisation, the name of the participating organisation should be entered here prior to agreement. If this Statement is being agreed to cover multiple separate entities (e.g. multiple GP practices within a single LCRN geography) please make this clear here.*	Click here to enter name of Participating Organisation

6 Predicted Participant Recruitment, if applicable:

This is recruitment at participating organisation, not overall for the study. Please clearly state if this is per month, per year, overall etc. State if not applicable to this site type.

Click here to enter predicted participant recruitment.

7 Proposed start date of research/participant identification activity at participating organisation

Where it might otherwise be open to interpretation, please specify whether this date refers to the commencement of screening, the recruitment of the first participant, etc.

Click here to select the proposed start date of research/participant identification activity.

Click here to specify the activity to which this date refers.

8 Predicted end date of research/participant identification activity at participating organisation

Where it might otherwise be open to interpretation, please specify whether this date refers to the recruitment of the final participant, the final visit of the final participant, database lock, etc.

Click here to choose end date of research/participant identification activity.

Click here to provide details on the activity to which this date refers.

Part B (template version 3.1)

Part B is to be completed for all studies.

1 Name of employing organisation of Chief Investigator*

King's College London

2 Name and contact details of clinical trials unit (or equivalent) delegated by the sponsor to coordinate the study (where applicable)*

NA

3 Does the sponsor intend that this Statement forms the agreement between itself and the participating organisations?*

For non-commercial studies other than clinical trials and clinical investigations, the HRA encourages use of the Statement of Activities as the only form of agreement between sponsor and an English participating organisation, in place of bespoke agreements created by sponsors. For research in primary care settings, the Statement may be used for a geographical area, e.g. at the LCRN level. For clinical trials and clinical investigations the HRA expects that sponsors will make use of the relevant model agreement.

Yes

4 If no, will the sponsor be using an unmodified model non-commercial agreement?*

Select 'yes' or 'no'.

5 If no, please provide details of the modifications made to the model agreement and the reasons for them. If the sponsor intends to use an agreement not based on the model agreement, please provide detailed justification for this (templates of all 'site agreements' to be used , including for sites in the devolved administrations (where applicable) should be provided as part of the submission for HRA Approval)*

Provide details of modifications made to model agreements and the reasons for them.

6 Person responsible for research activities at site*

The HRA expects Principal investigators to be in place at participating organisations where locally employed staff take responsibility for research procedures. Where this is not the case, the HRA expects Local Collaborators to be in place where central study staff will be present at site to undertake research procedures (the role of the Local Collaborator is to support practical arrangements for the presence of research staff under Letters of Access or Honorary Research Contracts). Where existing data is being provided for research purposes without additional research procedures and without the presence of central research team members at site, the HRA does not expect the appointment of a Principal Investigator or Local Collaborator is required, and you should select Chief Investigator.

Local Principal Investigator

6.1 Do you require any support to identify a Principal Investigator/Local Collaborator?*

Please indicate whether support from the host organisation is needed in identifying a Principal Investigator/Local Collaborator and provide further information on requirements below. Where a Principal Investigator or Local Collaborator has already been identified, their details appear on Part C of the IRAS Form.

No

6.2 Further Information (where applicable)*

*Please provide further information on support needed to identify a Principal Investigator/Local Collaborator, if required (e.g. Profession, specialty, seniority etc. required)**

Click here to provide information on further support required.

7 The following capabilities/capacity is/are needed locally in order to deliver the study, e.g. specific equipment, patient/participant groups, service support nursing time, excess treatment costs, etc. Any funding or support from the sponsor/funder to the participating organisation is set out in the Finance Schedule*.

Abilty to recruit 15 patients by 19/12/2016.

Capacity: 1 – 2 participants per week.

8 The following training for local staff will be provided by the sponsor. Where only specific team members (e.g. the Principal Investigator) will receive this training, this is described below*

Not applicable. GSTT staff will not be involved in data collection thus training is not required.

9 In addition to the above training, to be provided by the sponsor, the sponsor also requires that the following local research team members undertake the following training (N.B. it would not be usual for the sponsor to require study specific training additional to that which it will provide, this section does however allow sponsors to state that they will accept, for example, NIHR CRN training in Good Clinical Practice where the study is a Clinical Trial of an Investigational Medicinal Product etc.)*

Not applicable

Health Research Authority

Schedule 1 (Finance) (template version 3.1)

Please select one of the following*:

There are no funds/resources/equipment, etc. being provided to these organisations by the sponsor. *This schedule should be left blank.**	☒
The following funding/resources/equipment, etc. is to be provided to the local participating organisation. However, the finance schedule to cover such transfer is detailed in a separate agreement. *Please complete the information below but leave the schedule blank and submit your agreement to the HRA.**	☐

Click here to provide information on funding, resource and/or equipment etc.to be provided to the local participating organisation by the sponsor.

The following funding/resource/equipment, etc. is to be provided to the local participating organisation. The finance schedule below details the funds to be provided to the site by the sponsor. *Please complete the information and the schedule below.**	☐

Click here to provide information on funding, resource and/or equipment etc.to be provided to the site by the sponsor.

1 Payment Schedule (i.e. frequency or trigger for payments)*

Click here to enter details of payment schedule

2 Area of Cost (e.g. set-up, procedure, overall cost, etc.).*

Click here to enter details on area of cost.

Payment Details:

If VAT is payable, then the Sponsor shall pay the VAT in addition to the payment on presentation of a VAT invoice. If VAT is not payable, then the Sponsor shall issue a VAT exemption certificate.

3 Invoices to be submitted to (insert job title, name of body and address)*

Click here to enter address details.

4 Payment to be made by cheque to ^:

Click here to enter cheque payable details.

4.1 AND remitted to (insert job title/position and address): ^

Click here to add job title/position and address

OR

5 Arrange BACS transfer to: Bank Name^:

Click here to enter Bank Name.

5.1 Sort Code ^:

Click here to enter Sort Code.

5.2 Account Number^:

Click here to enter Account Number

5.3 And send the relevant paper work to the following address ^:

Click here to enter address details

Invoices must be presented promptly. No payment shall be made in the case where invoices are not presented in a complete, accurate and timely fashion and funding from an external funding body has been irrecoverably reclaimed by such external funding body as a result of such delay or inadequacy.

Health Research Authority

Schedule 2 (Material Transfer Provisions)

(template version 3.1)

These provisions do not remove the responsibility for a sponsor to clearly lay out in their protocol (and to potential participants in the patient information sheet/s) at a minimum the following information for all human biological material taken: 1) The nature of the materials, 2) The reason that the material is being taken, 3) where the material is to be sent, 4) what will happen to any remaining material once it has been processed/analysed, etc. for the purposes of this study (e.g. return, retention or destruction).

Detailed guidance on what information should be included in a protocol may be found on the HRA website http://www.hra.nhs.uk

Please select one of the following: *

This study does not involve the transfer of human biological material from this participating organisation to the sponsor or its agents. ***This schedule does not form part of this agreement.*** *	☒
The Sponsor has separately provided to the HRA and participating organisation an agreement for the transfer of human biological material. ***This schedule does not form part of this agreement.*** *	☐
These provisions form part of the agreement between the sponsor and this participating organisation. ***Select this option if no other agreement is provided, and the terms below constitute the arrangements for this study.*** *	☐

1 Where the protocol requires the participating organisation to supply material to the sponsor/joint sponsor(s)/either of the co-sponsors, these provisions shall apply if stated above.

2 In accordance with the protocol, the participating organisation shall send material to the sponsor/joint sponsor(s)/a co-sponsor or, in accordance with provision 8 below, a third party nominated by the sponsor/joint sponsor(s)/either of the co-sponsors.

3 The participating organisation warrants that all material has been collected with appropriate informed consent and has been collected and handled in accordance with applicable law (including, without limitation, the Human Tissue Act 2004 or the Human Tissue (Scotland) Act 2006 (as the case may be)) and as required by the protocol.

4 Subject to provision 3 above, the materials are supplied without any warranty, expressed or implied including as to their properties, merchantable quality, fitness for any particular purpose, or that the materials are free of extraneous or biologically active contaminants which may be present in the Materials.

5 The sponsor/joint sponsor(s)/one of the co-sponsors shall ensure, or procure through an agreement with the sponsor/joint sponsor(s)/co-sponsors nominee as stated in provision 2 above that.

5.1 the material is used in accordance with the protocol, the consent of the participant, and the HRA Approval for the Study,

5.2 the material is handled and stored in accordance with applicable law,

5.3 the material shall not be redistributed or released to any person other than in accordance with the protocol or for the purpose of undertaking other studies approved by an appropriate ethics committee and in accordance with the participant's consent, and

5.4 no alteration shall be made to the title, coding or acronym of the material.

6 The parties shall comply with all relevant laws, regulations and codes of practice governing the research use of human biological material.

7 The participating organisation and the sponsor/joint sponsors(s)/a co-sponsor shall each be responsible for keeping a record of the material that has been transferred according to these provisions.

8 To the extent permitted by law the participating organisation and its staff shall not be liable for any consequences of the supply to or the use by the sponsor/joint sponsors//co-sponsor of the material or of the supply to or the use by any third party to whom the sponsor/joint sponsors/co-sponsor subsequently provides the material or the Sponsor's/Joint Sponsors/Co-Sponsor's nominee as stated in provision 2 above, save to the extent that any liability which arises is a result of the negligence of the participating organisation.

9 The sponsor/joint sponsors/co-sponsor undertake(s) that, in the even that material is provided to a third party in accordance with provision 2 above, it/they shall require that such third party shall undertake to handle any data and Material related to the Study in accordance with all applicable statutory requirements and codes of practice and under terms no less onerous than those set out in these provisions.

10 Any surplus material that is not returned to the participating organisation or retained for future research (in line with participant consent) shall be destroyed in accordance with applicable law (including, without limitation, the Human Tissue Act 2004 or the Human Tissue (Scotland) Act 2006 (as the case may be).

Schedule 3 (Confidentiality, Data Protection and Freedom of Information) (template version 3.1)

Please select one of the following:*

This study does not involve the transfer of Personal Data from this participating organisation to the sponsor or its agents, nor is there transfer of confidential information between the parties. ***This schedule does not form part of this agreement.****	☒
The Sponsor has separately provided to the HRA and participating organisation another agreement for the transfer of data. ***This schedule does not form part of this agreement.****	☐
These provisions form part of the agreement between the sponsor and this participating organisation. ***Select this option if no other agreement is provided, and the terms below constitute the arrangements for this study.****	☐

1 Medical confidentiality

1.1 The parties agree to adhere to all applicable statutory requirements and mandatory codes of practice in respect of medical confidentiality in relation to participants.

1.2 Personal Data (as defined by the Data Protection Act) shall not be disclosed to the sponsor by the participating organisation, save where this is required directly or indirectly to satisfy the requirements of the protocol, or for the purpose of monitoring or reporting adverse events.

1.3 Neither the sponsor nor the participating organisation shall disclose the identity of participants to third parties without the prior written consent of the participants except in accordance with applicable statutory requirements and codes of practice.

2 Freedom of Information

2.1 Parties to this agreement which are subject to the Freedom of Information Act 2000 (FOIA) or the Freedom of Information (Scotland) Act 2002 (FOIS)A) and which receive a request under FOIA or FOI(S)A to disclose any information that belongs to another party shall notify and consult that party, as soon as reasonably practicable, and in any event, not later than seven calendar days after receiving the request.

2.2 The parties acknowledge and agree that the decision on whether any exemption applies to a request for disclosure of recorded information under FOIA or FOI(S)A is a decision solely for the party responding to the request.

2.3 Where the party responding to an FOIA or FOI(S)A request determines that it will disclose information it will notify the other party in writing, giving at least four calendar days' notice of its intended disclosure.

3 Confidential Information

3.1 The receiving party agrees to take all reasonable steps to protect the confidentiality of the confidential information and to prevent it from being disclosed otherwise than in accordance with this agreement.

3.2 The participating organisation agrees to treat the results excluding any clinical data of the study as confidential information disclosed by the sponsor and the sponsor agrees to treat personal data, including any clinical data as confidential information disclosed by the participating site.

3.3 The receiving party agrees:

3.3.1 To ensure that any of its employees, students, consultants or sub-contractors who participate in the operation of the study are made aware of, and abide by, the requirement of this clause 3.3.

3.3.2 To use confidential information solely in connection with the operation of the agreement and not otherwise.

3.3.3 Not to disclose confidential information in whole or in part to any person without the disclosing party's written consent.

3.4 The provision of clause 3.3 shall not apply to the whole or any part of the confidential information that is:

3.4.1 Lawfully obtained by the receiving party free of any duty of confidentiality.

3.4.2 Already in the possession of the receiving party and which the receiving party can show from written records (other than as a result of a breach of clause 3.3.1 or 3.3.2).

3.4.3 In the public domain (other than as a result of a breach of clause 3.3.1 or 3.3.2).

3.4.4 Independently discovered by employees of the receiving party without access to or use of confidential information.

3.4.5 Necessarily disclosed pursuant to a statutory obligation.

3.4.6 Disclosed with prior written consent of the disclosing party.

3.4.7 Necessarily disclosed by the receiving party by virtue of its status as a public authority in terms of the Freedom of Information Act 2000 or the Freedom of Information (Scotland) Act 2002.

4. The restrictions contained in clause 3.3 shall continue to apply after the end of the involvement of the participating organisation in this research project.

NHS
Health Research Authority

Appendix 1 (Staff signature and delegation log) (template version 3.1)

This Appendix is for use at the discretion of the participating organisation and sponsor, to record the roles and responsibilities of the local research team (where applicable) and the authorisation of the Principal Investigator for this.

Name	Study Role (e.g. sub-investigator, research nurse, etc.)	Task Codes (see below)	Date of start of study involvement	Date of end of study involvement	Usual Initials	PI Signature	Date of PI Signature	CV provided?
Dr Teresa Beynon	Principal Investigator	Insert code/s.	Select Start Date.	Select End Date.	TB	Teresa Beynon	01/04/2016	yes
Dr Mendwas Dzingina	Enter Study Role.	Insert code/s.	Select Start Date.	Select End Date.	MD	Mendwas Dzingina	01/04/2016	yes
Ms Caty Pannell	Enter Study Role.	Insert code/s.	Select Start Date.	Select End Date.	CP	Caty Pannell	01/04/2016	yes
Mrs Paramjote Kaler	Enter Study Role.	Insert code/s.	Select Start Date.	Select End Date.	PK	Paramjote Kaler	01/04/2016	yes
Enter Name	Enter Study Role.	Insert code/s.	Select Start Date.	Select End Date.	Initials	Enter PI signature	Enter Date	Yes/No
Enter Name	Enter Study Role.	Insert code/s.	Select Start Date.	Select End Date.	Initials	Enter PI signature	Enter Date	Yes/No

Please define delegated tasks (e.g. informed consent, CRF completion, medical care of the patient etc.)

1. Enter delegated task/s.	7. Enter delegated task/s.
2. Enter delegated task/s.	8. Enter delegated task/s.

General Activities

Template Version 3.1

NHS
Health Research Authority

Guidance

This tab should be completed for the 'site-type' covered by this Schedule of Events, including only those activities relevant to the organisations covered by this document (e.g. if the organisations will not be recruiting participants, do not include the activities related to participant recruitment). All activities should be given a cost attribution, in line with the DH AcoRD guidance. https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Please refer to the Hints and Tips tab before completing this section.

IRAS Reference Number:	159556

					Day -x to -y	Day 0	Day x
Area of Activity (Select this first. You can insert free text if the drop-down options are not suitable)	Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Site set-up	Screen	Base	Visit 1
Study Set Up	Site Initiation Visit	60	External Staff (Central Research Team)	Research Cost (Part A)	No Activity	No Activity	No Activity
Study Set Up	Archiving	90	External Staff (Central Research Team)	No Activity	No Activity	No Activity	Research Cost (Part A)
Study Monitoring							
Data collection							
Study Close Down							

Study Information

Template Version 3.1

NHS Health Research Authority

The Sponsor/Applicant should provide answers to questions 1-4 below prior to submission for HRA Approval.

1. IRAS Reference Number:	**159556**
2. Short Study Title:	Development of a preference-based outcome measure for Palliative Care
3. Site Type, Please use drop-down Menu:	Site type 1: Consent and data collection by Central Resea
4. If "Other", Please Specify:	
5. Date *(HRA Office Use Only)*:	
6. Version Number *(HRA Office Use Only)*:	

Per-Participant Activities

Template Version 3.1

NHS Health Research Authority

Guidance

This tab should be completed for the 'site-type' covered by this Schedule of Events, including only those activities relevant to the organisations covered by this document (e.g. if the organisations will not be recruiting participants, do not include the activities related to participant recruitment). Where the study involves multiple arms, this tab may be copied and each arm entered as a new tab. All activities should be given a cost attribution, in line with the DH AcoRD guidance. https://www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Please refer to the Hints and Tips tab before completing this section.

IRAS Reference Number*:	159556

				Day -x to -y	Day 0
Area of Activity (Select this first. You can insert free text if the drop-down options are not suitable)	Specific Activity (drop down only present when Area of Activity selected first - or use free text if the drop-down options are not suitable)	Duration (Minutes)	Undertaken by (drop down or free text)	Screen	Base
Participant Consent Procedures	Identify potential partipant during team meetings	3	Principal Investigator, and other memebers of the palliative care clinical team	Service Support Cost	
Participant Consent Procedures	Approach potential participant in the first instance and ask if they would be interested in participating in the study, and if they would be happy to be contacted by a member of the central research team who will discuss the study with them	5	Principal Investigator, and other memebers of the palliative care clinical team	Service Support Cost	
Participant Consent Procedures	Approach potential participants who have indicated that they are happy to be approached by a member of the central research team to discuss the study	8	External Staff (Central Research Team)	Research Cost (Part A)	
Participant Consent Procedures	Take informed consent	5	External Staff (Central Research Team)	Research Cost (Part A)	
Interventions non clinical	Administer questionnaire	45	External Staff (Central Research Team)	No Activity	Research Cost (Part B)

Minor amendment: 5 Month Extension Study from 18/07/2016-19/12/2016

NHS
Health Research Authority
London - South East Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

15 July 2016

Professor Irene Higginson
Assistant Medical Director (Research), King's College Hospital
King's College London
Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation
King's College London
London
SE5 9PJ

Dear Professor Higginson

Study title:	**Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS)**
REC reference:	**15/LO/1774**
Amendment number:	**1**
Amendment date:	**20 June 2016**
IRAS project ID:	**159556**

- **5 Month Extension Study from 18/07/2016-19/12/2016**

Thank you for your letter of 20 June 2016, notifying the Committee of the above amendment.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Notice of Minor Amendment [Notice of Non-Substantial Amendment	1	20 June 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

15/LO/1774:	**Please quote this number on all correspondence**

Yours sincerely



Nafeesa Khanam
REC Assistant

Email: nrescommittee.london-southeast@nhs.net

Copy to: Ms Liba Stones, Senior Research Facilitator (Grants)
Professor Irene Higginson, King's College London
Mr Keith Brennan

Host site approval: St George's Hospital NHS Trust

St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

St George's Joint Research & Enterprise Office (JREO)
Ground Floor, Hunter Wing, St George's University of London,
Cranmer Terrace, Tooting, London SW17 0RE

Direct Line: 0208 725 0892
Email: dmccartn@sgul.ac.uk

30/03/2016

Dr Oliver Minton
Palliative Medicine
St George's University Hospitals NHS Foundation Trust
Blackshaw Road
London SW17 0QT

Dear Dr Minton

PROJECT TITLE	Development of a preference-based outcome measure for use in economic evaluations of palliative care services using the Patient (palliative) care Outcome Scale (POS).
REC Reference	15/LO/1774
JREO Reference	16.0047
CSP Reference (if applicable)	159556
Sponsor	King's College London
Principal Investigator (PI):	Oliver Minton

Notification of St George's University Hospitals NHS Foundation Trust host site permission

Permission for the above research has been granted on the basis described in the application form, protocol and supporting documentation. The documents reviewed and approved were those specified in the ethics approval letter dated **21/12/2015**. The protocol version approved is version **2.0** dated **21/11/2015**

Permission is granted on the understanding that the study is conducted in accordance with the Research Governance Framework, and NHS Trust policies. Permission is only granted for the activities for which a favourable opinion has been given by the REC. The permission may be invalidated in the event that the terms and conditions of any research contract or agreement change significantly and while the new contract/agreement is negotiated.

The research sponsor, the Chief Investigator, or the local Principal Investigator, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety. The JREO should be notified that such measures have been taken. The notification should also include the reasons why the measures were taken and the plan for further action. The JREO should be notified within the same time frame of notifying the REC.

All amendments to this study (including changes to the local research team) need to be submitted in accordance with the guidance on IRAS. In addition any changes to the status of a study should be notified to the JREO.

Please note that the JREO is required to monitor research to ensure compliance with the Research Governance Framework and other legal and regulatory requirements.

Any intellectual property that is identified should be discussed with the JREO prior to any disclosure of this information by publication or presentations to ensure that all rights are protected.

At study closure, the JREO together with the approving ethics committee should be notified that the study is closed. Study findings should be disseminated as identified in the original ethics application (including participants where appropriate). Study files should be appropriately archived.

Please contact the JREO if you require any further guidance or information on any matter mentioned above. We wish you every success in your research.

Yours sincerely



Dr Deborah McCartney
On behalf of SGUL/SGHT
Joint Research and Enterprise Office

Copy to: London (South) CLRN

St George's University of London

St George's University Hospitals NHS
NHS Foundation Trust

St George's Joint Research And Enterprise Office
Ground Floor, Hunter Wing, St George's University of London,
Cranmer Terrace, Tooting, London SW17 0RE

Date: 08/04/2016

Letter of access for research – Mendwas Dzingina

This letter should be presented to each participating organisation before you commence your research at that site. The participating organisation is: **St George's University Hospitals NHS Foundation Trust.**

In accepting this letter, each participating organisation confirms your right of access to conduct research through their organisation for the purpose and on the terms and conditions set out below. This right of access commences on **8th April 2016** and ends on **19th August 2018** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from **St George's University Hospitals NHS Foundation Trust.** Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving confirmation from the individual organisation of their agreement to conduct the research.

The information supplied about your role in research at the organisation has been reviewed and you do not require an honorary research contract with the organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. However the final decision rests with St George's, University of London. Evidence of checks should be available on request to the organisation.

You are considered to be a legal visitor to the organisations premises. You are not entitled to any form of payment or access to other benefits provided by the organisation or this organisation to employees and this letter does not give rise to any other relationship between you and the organisation, in particular that of an employee.

While undertaking research through the organisation(s) you will remain accountable to your substantive employer but you are required to follow the reasonable instructions of your line manager, **Dr. Ollie Minton** or those instructions given on their behalf in relation to the terms of this right of access.

Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by **St George's University Hospitals NHS Foundation Trust** in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with **St George's University Hospitals NHS Foundation Trust** policies and procedures, which are available to you upon request, and the Research Governance Framework.

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Yours sincerely



Lucy H H Parker
Head of Research Governance
JREO

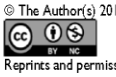
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10.5. Appendix 8 [publication 5]: Variations in the cost of formal and informal health care for patients with advanced chronic disease and refractory breathlessness: a cross-sectional secondary analysis

The publication that follows reports an analysis that was conducted by the author on separate project during the course this PhD. Although not directly related to the aims of this thesis it covers issues around measuring and valuing costs in palliative care. This analysis aimed to measure the cost of care for patients with advanced disease and refractory breathlessness and to identify factors associated with high costs. It demonstrates the significant contributions of informal carers and highlights the need for health and social care policy makers to support and acknowledge the contributions of informal carers.

Original Article

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Variations in the cost of formal and informal health care for patients with advanced chronic disease and refractory breathlessness: A cross-sectional secondary analysis

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Abstract

Background: Refractory breathlessness in advanced chronic disease leads to high levels of disability, anxiety and social isolation. These result in high health-resource use, although this is not quantified.

Aims: To measure the cost of care for patients with advanced disease and refractory breathlessness and to identify factors associated with high costs.

Design: A cross-sectional secondary analysis of data from a randomised controlled trial.

Setting/participants: Patients with advanced chronic disease and refractory breathlessness recruited from three National Health Service hospitals and via general practitioners in South London.

Results: Of 105 patients recruited, the mean cost of formal care was £3253 (standard deviation £3652) for 3 months. The largest contributions to formal-care cost were hospital admissions (>60%), and palliative care contributed <1%. When informal care was included, the total cost increased by >250% to £11,507 (standard deviation £9911). Increased patient disability resulting from breathlessness was associated with high cost (£629 per unit increase in disability score; $p = 0.006$). Increased breathlessness on exertion and the presence of an informal carer were also significantly associated with high cost. Patients with chronic obstructive pulmonary disease tended to have higher healthcare costs than other patients.

Conclusion: Informal carers contribute significantly to the care of patients with advanced disease and refractory breathlessness. Disability resulting from breathlessness is an important clinical cost driver. It is important for policy makers to support and acknowledge the contributions of informal carers. Further research is required to assess the clinical- and cost-effectiveness of palliative care interventions in reducing disability resulting from breathlessness in this patient group.

Keywords

Healthcare costs, palliative care, terminal care, end-of-life care, chronic disease, breathlessness, dyspnoea, cancer, chronic obstructive pulmonary disease, heart failure, interstitial lung diseases

What is already known about the topic?

- Refractory breathlessness in advanced chronic disease leads to high levels of disability, anxiety and social isolation.
- These result in high health-resource use, although this is not quantified.
- We also do not know what factors are associated with high cost in these patients.

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What this paper adds?

- The largest contributions to formal-care cost were hospital admissions (>60%), while palliative care contributed <1%
- The total cost of care increased by >250% when informal-care costs were included.
- Increased patient disability resulting from breathlessness was the main clinical factor associated with increased cost.

Implications for practice, theory or policy

- Our findings highlight the need for health and social care policy makers to support and acknowledge the contributions of informal carers.
- Further research is required to assess the clinical- and cost-effectiveness of palliative care interventions in reducing disability resulting from breathlessness in patients with advanced disease and refractory breathlessness.

Introduction

Breathlessness is a common and distressing symptom affecting many people with advanced chronic disease. It causes substantial disability, anxiety and social isolation and is difficult to treat.[1–4] Globally, over 75 million people have breathlessness annually, including over 58 million people with severe lung disease,[5] more than 5 million people with incurable cancer and more than 12 million people with heart failure.[6,7]

The high symptom burden and progressive nature of refractory breathlessness in advanced disease suggest that patients will require increasing help from professionals and family members. As the underlying disease progresses, breathlessness increases and is accompanied by panic.[8,9] This is terrifying for patients and their families and often results in emergency hospital admissions.[9] Despite the concerns about the large resource inputs for these patients, there is no evidence on the costs of care for them. Thus, it is important to establish the costs of caring for people with advanced disease and refractory breathlessness. Such information is vital to understand the likely 'burden' of the condition and to provide a baseline to assess the relative economic impact of different treatments. It is conceivable that costs will arise as a result of direct healthcare input and care provided by other agencies, such as social care services. Some unpaid care will also frequently be provided by family members and/or friends (informal care), and this has never been quantified.

The aims of this study were to measure the formal and informal costs of care for patients with advanced disease and refractory breathlessness and to identify patient and clinical factors associated with high costs.

Materials and methods

Design

This study is a cross-sectional secondary analysis of data from a randomised controlled parallel-group, pragmatic, single-blind fast-track trial (ClinicalTrials.gov, number NCT01165034).[4] The main study, and also this study, had ethical approval from the King's College Hospital Ethics Committee (Ref. 10/H0808/17). Participants provided their written consent to participate in the main study. The data set used for this cross-sectional secondary analysis was anonymised and de-identified prior to analysis. This procedure was approved by the Ethics Committee.

Setting and sample

Study participants were included according to a standard proforma completed by the identifying clinician. Details of the trial have been published elsewhere.[4] But in summary, participants were adult patients (≥18 years) with advanced disease (e.g. cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease (ILD) and motor neuron disease) and refractory breathlessness on exertion or rest (Medical Research Council (MRC) dyspnoea scale score ≥2), despite optimum treatment of the underlying disease, as deemed by the identifying clinician. Participants were recruited from three large teaching hospitals and via general practitioners (GPs) in South London.

Procedures

In the main study, data were collected at study entry by trained interviewers, usually in participants' homes. The data set used for this cross-sectional secondary analysis was collected during the main trial. This data set was anonymised and de-identified prior to analysis and comprises demographic, clinical outcome assessments and use of healthcare services including the Chronic Respiratory Disease Questionnaire (CRQ);[10,11] Numerical Rating Scale (NRS), average, at rest and on exertion;[12] London Chest Activity of Daily Living (LCADL), a questionnaire of the level of disability induced by breathlessness;[12] EuroQol five dimensions questionnaire (EQ-5D) (three levels);[12] Palliative care Outcome Scale (POS), a 10-item measure for advanced disease widely validated in cancer and non-cancer;[13] Hospital Anxiety and Depression Scale (HADS);[14]

and the breathlessness version of the Client Services Receipt Inventory[15] (CSRI) which has been provided in Supplementary File S1. Details of other procedures conducted in the main trial have been published elsewhere.[4]

Clinical outcomes

Study outcomes included breathlessness mastery (using a sub-domain of the CRQ); severity of breathlessness on exertion in the previous 24 h, disability (LCADL); health-related quality of life (EQ-5D); palliative needs (POS); breathlessness, fatigue and emotional function (other domains of the CRQ); anxiety and depression (HADS) and lung function (spirometer).

Service use and cost

A broad costing perspective was taken with services including those provided by health and social care agencies and also informal carers. However, societal costs were not calculated as this analysis did not include lost productivity. In this analysis, formal care comprised both direct health care and social care. Service use was measured at study entry using a version of the Client Service Receipt Inventory (CSRI).[15] Patients gave details of services used during the 3 months prior to study entry.

Services included hospital care, primary health care, social care, the provision of aids and home adaptations and informal care provided by family members and/or friends. Length of hospital admission was recorded, while the number of contacts and, where relevant, the mean length of these contacts were documented for other services. Information was provided on the number of hours that family/friends spent providing personal care and help in and outside the home and in other tasks, per week.

Costs were calculated by combining resource use data with unit costs obtained from standard sources such as the National Health Service (NHS) reference cost data[16] or the Unit Costs of Health and Social Care (Personal Social Services Research Unit (PSSRU)),[17] where applicable. We assumed that in the absence of an informal carer, social services would need to provide home care, and therefore, the unit cost of a home care worker was used as proxy for informal care. Missing values for quantities of resource use were imputed using multiple imputation by chained equations (MICE) via the 'ice' command in Stata.[18,19]

Statistical analysis

We compared formal and informal health-resource use and cost across primary diagnosis using descriptive statistics. We used scatter and box plots to graphically examine variations in costs and Spearman's Rho to assess correlations.

We used generalised linear models (GLM) to determine which factors were associated with cost. The dependent variable was cost, while clinical and demographic variables were used as independent variables. Age and EQ-5D index were centred to means to enable appropriate interpretation of intercepts. Spearman's rank correlations of the independent variables were used to determine whether any variables were highly correlated and therefore not recommended for inclusion in the same regression model. A high correlation was defined as a correlation coefficient $>|0.7|$.[20] Where two or more independent variables were found to be highly correlated, we conducted univariate analysis with the dependent variable and selected the independent variable with highest adjusted R^2. Separate regression models were fitted for total cost, health service cost and informal care cost. We used the modified Park test[21] and the modified Hosmer–Lemeshow test[22] to determine the appropriate combination of link function and distributional family. The analysis was performed using STATA release 13.[23] This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cross-sectional studies.

Regression equation

$$\text{Costs} = f(\text{age}, \text{gender}, \ldots, \text{POS}) = \beta_0 + \beta_1 \text{age} + \beta_2 \text{gender} + \cdots + \beta_n \text{POS} + \varepsilon$$

where α_i is the linear predictor formed from explanatory variables and coefficients. ε_i follows gamma distribution which has an increasing variation with larger mean. $g(\mu_i) = \log(\mu_i)$, where g is the link function.

Results

In all, 105 patients were recruited. The mean age was 67 years, 61 (58%) were men, over half (54%) had COPD, 20% had cancer, 18% had ILD, 5% had heart failure and 3% had other diseases. Patients had severe disease: forced expiratory volume (FEV_1) was 46% predicted, vital capacity (VC) 58% predicted, oxygen saturation at rest 93%, average breathlessness 5.9/10 and on exertion 8.3/10. Their mean EQ-5D index score was 0.35, and their average total Palliative care Outcome Score was 15/40, indicating a disabled group with poor quality of life (see Table 1).

The results show high levels of outpatient visits, GP contacts, inpatient care and accident and emergency attendance. More than 75% received care from family and friends (Table 2). The mean total cost of care per patient was £11,507 (standard deviation (SD) £9911). Informal care accounted for over 70% of this.

Over 64% of informal care cost was accounted for by the number of hours: on call (45%), providing help inside the home (9%) and providing personal care (8%). Over 60% of direct healthcare cost was accounted for by hospital admissions (inpatient care 49.3% and critical care

Table 1. Characteristics of the study participants at study entry.

	N = 105
Age (years)	67 (10)
Sex	
Women	44 (42%)
Men	61 (58%)
Diagnosis	
Chronic obstructive pulmonary disease	57 (54%)
Cancer	21 (20%)
Interstitial lung disease	19 (18%)
Heart failure	5 (5%)
Other[a]	3 (3%)
Has carer or family member	
Yes	75 (71%)
No	30 (29%)
Living situation	
Living home	97 (92%)
Living elsewhere	8 (8%)
EQ-5D index[b]	0.35 (0.33)
Clinical variables	
Saturated O_2 (%)[c]	93.6 (3.9)
POS total score (score range = 0–40)[d]	15.1 (6.5)
HADS anxiety (score range = 0–21)[d]	9.2 (2.7)
HADS depression (score range = 0–21)[d]	9.9 (3.2)
NRS breathlessness worst at rest (0–10)[d]	4.9 (2.6)
Predicted FEV_1 (% predicted)[e]	46.2 (23.3)
Predicted VC (% predicted)[e]	57.9 (25.7)
NRS breathlessness on exertion (0–10)[1]	8.3 (1.4)
NRS breathlessness average 24 h (0–10)[1]	5.9 (2.0)

SD: standard deviation; NRS: Numerical Rating Scale; FEV_1: forced expiratory volume; VC: vital capacity; HADS: Hospital Anxiety and Depression Scale; POS: Palliative care Outcome Scale; EQ-5D: EuroQol five dimensions questionnaire.
Data are absolute numbers or mean (SD) unless otherwise stated.
[a]Other diagnoses were left lower lobe collapse of unknown aetiology associated with severe symptoms; lupus, shrinking lung syndrome and rheumatoid arthritis; and severe asthma and gastro-oesophageal reflux disease.
[b]EQ-5D index scores based on the standard UK population-based preference weights with the standard scoring algorithm; 0.0 = death and 1.0 = perfect health.
[c]Measured for 13 patients (3 in breathlessness support service group and 10 in control group) while on supplemental oxygen (mean (SD) SaO_2 = 91.8 (5.1)) and the remainder on room air (mean (SD) 93.8 (3.6)).
[d]Scale interpretation: high score indicates worse.
[e]Scale interpretation: high score indicates better.

11%). Palliative care (home palliative care and hospice) accounted for less than 1% of direct healthcare cost, and rehabilitation and other therapies accounted for less than 5% (Table 2). Over 68% of social care cost was spent on providing special beds (52%) and wheel chairs (17%).

Overall, there was a high variation in cost with more variation in the cost of informal care when compared to formal care, across all diagnoses. The variability in healthcare cost was largest for COPD patients (range: £53–£22,178), whereas cancer patients had the highest variability in informal care cost (range: £0–£43,536) (Figure 1).

We found no correlation between direct healthcare and informal care costs (Figure 2).

The following independent variables were found to be highly correlated (Spearman's Rho >0.78): three variables FEV_1 percent predicted, VC percent predicted and CRQ dyspnoea and also between NRS average, NRS breathlessness at rest and NRS on exertion. FEV1 percent predicted and NRS on exertion were selected as they each had higher adjusted R^2 values in univariate analysis with cost.

The results of GLM regression showed that disability resulting from breathlessness was significantly associated with high total cost (£629 per unit increase in LCADL total score; $p = 0.006$) as well as informal and direct healthcare costs (Table 3). The presence of an informal carer was also significantly associated with high total and informal-care cost. Increased breathlessness on exertion was associated with increased healthcare cost; no other clinical variable was significantly associated with cost. Patients with COPD tended to have higher healthcare costs than patients with cancer, ILD or heart failure (Table 3).

Discussion

This is the first study that examines the cost of care in patients with advanced disease and refractory breathlessness. Over a period of 3 months, hospital admissions (inpatient and critical-care stays) had the largest contribution to direct healthcare cost (>60%), whereas palliative care and rehabilitation accounted for less than 1% and 5%, respectively. High healthcare cost was associated with increasing disability resulting from breathlessness, breathlessness on exertion and a diagnosis of COPD. When informal care was included, the total cost of care increased by >250%. We also found wide variations in cost.

In these 105 patients with advanced disease and refractory breathlessness, we found that the cost of formal care was £3253 (equivalent to US$4593.70: using 2014 Organisation for Economic Co-operation and Development (OECD) purchasing power parities (PPP) conversion rate) over a period of 3 months. This was mainly accounted for by inpatient care, critical-care and outpatient clinics. It is difficult to compare our estimates with other studies (or patients) because no other studies have examined the cost of care in patients with advanced disease and refractory breathlessness. Nevertheless, the cost estimates we observed appear to be higher than the costs observed in studies in people with COPD. In the 2011 systematic review by Bustacchini et al.,[24] which explored the economic burden of COPD in those aged 60 years or older, mean healthcare costs at 3 months ranged from £540.98 (US$763.94) in the United States to £2535.69 (US$3580.75) in Australia (inflated for the purpose of this

Table 2. Cost of breathlessness for 3 months prior to recruitment into the study.

	Contacts (users)				Costs[a]			
	N	%	Mean	SD	Min	Max	Mean	SD
Health care								
Inpatient care	43	41	10.5[b]	7.44	0	11,352	1294	2131
Critical care	6	6	4.2[b]	3.13	0	11,890	286	1420
A&E	39	38	1.7	1.14	0	649	67	115
Outpatient	75	72	2.8	2.47	0	1330	236	271
Outpatient other[c]	33	32	3.4	4.18	0	1781.25	89	234
Other doctor	4	4	1.5	1.00	0	222	4	26
Day hospital	7	7	4.4	2.44	0	1120	42	177
Hospice	1	1	1.0	0.00	0	132	1	13
District nurse	28	27	12.0	35.41	0	9450	168	959
GP	84	81	3.2	3.22	0	1039	130	165
Practice nurse	15	14	2.0	1.51	0	61	3	9
Physiotherapist	15	14	7.9	7.26	0	396	19	64
Occupational therapist	8	8	1.6	1.04	0	132	4	16
Psychologist	11	11	8.7	17.33	0	8160	126	821
Other therapies	5	5	2.8	1.92	0	150	4	23
Rehab (pulmonary)	12	12	6.2	4.92	0	1890	78	300
Rehab (other)	7	7	4.6	3.82	0	895	23	110
Home palliative care	16	16	3.6	4.70	0	504	15	62
Dietician	11	11	1.7	0.71	0	68	3	11
Other services[d]	13	13	15.6	27.40	0	1500	35	167
Total healthcare cost (A)					53	22,178	2624	3456
Social care								
Social worker	7	7	1.4	0.79	0	222	8	32
Home help	15	15	24.8	29.44	0	4860	94	504
Walking aid	43	43	1	N/A			3	8
Wheelchair	26	25	1	N/A			104	238
Commode	12	12	1	N/A			3	7
Special bed	14	13	1	N/A			327	863
Bathroom/toilet adaptations	45	43	1	N/A			15	73
Other equipment	51	49	1.7	1.79	0	1000	75	240
Total social care cost (B)					0	5793	628	1132
Total formal service cost (A + B)					139	22,573	3253	3652
Informal care[e]								
Hours on call	51	49	149	48.32	0	12,479	5427	6096
Help outside home[f]	78	75	6.6	5.55	0	2228	366	415
Help with medical procedures	32	31	3.5	3.04	0	4200	326	696
Help inside the home[g]	81	78	18	36.46	0	20,798	1027	2438
Personal care[h]	36	35	13	25.81	0	30,240	966	3400
Other help	6	6	33	66.17	0	12,479	141	1226
Total informal care cost (C)					0	43,536	8254	8777
Total costs (A + B + C)					154	45,818	11,507	9911

SD: standard deviation; GP: general practitioner; A&E: accident and emergency.
[a]2014 GBP.
[b]Number of days on admission.
[c]Outpatient visits are not directly related with breathlessness or main disease.
[d]Services such as bereavement service, meals, exercise and Red Cross.
[e]Average number of hours used by friends or family members.
[f]For example, shopping or going to the appointments.
[g]For example, cooking or cleaning.
[h]For example, bathing or dressing.

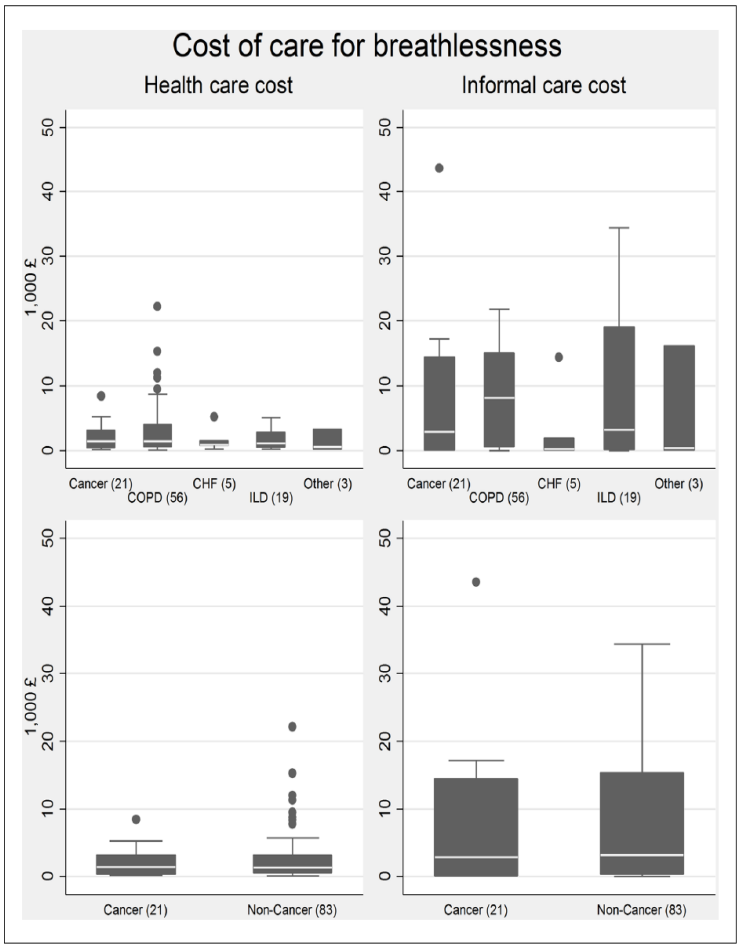


Figure 1. Box plots showing medians and 25th and 75th percentiles of healthcare versus informal care cost by diagnosis (number of observations in brackets).

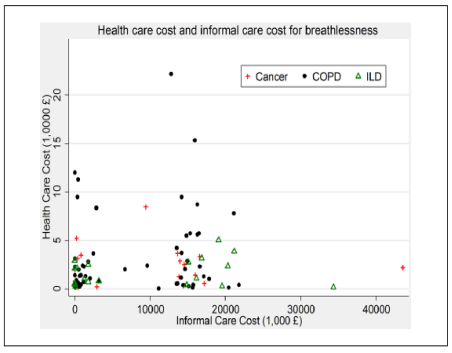


Figure 2. Relationship between healthcare cost and informal care cost.

comparison from 2010 US$ to 2014 GBP using standard conversion formulae). Inpatient care was the main driver of healthcare cost in the Bustacchini et al.[24] review.

Our study suggests that the cost of formal care for people with advanced disease and refractory breathlessness is very high (more expensive than the cost of COPD). This perhaps is a reflection of the high cost of care in the last year of life; 25% of annual Medicare hospital costs are spent on people in the last year of life in the United States, while in the United Kingdom, up to 29% of NHS hospital expenditures are for people who are in the last year of life.[25]

This is the first study to quantify the informal care cost of advanced disease and refractory breathlessness. We found that the cost of informal care in our study was high. Including informal care increased the total cost per patient

Table 3. Factors associated with costs of breathlessness (results from generalised linear model regression).

$N = 105$	Total cost (£)[a]			Informal care cost (£)[a]			Healthcare cost (£)[a]		
	β	CI_{LL}	CI_{UL}	β	CI_{LL}	CI_{UL}	β	CI_{LL}	CI_{UL}
EQ-5D index (centred at mean)	5923	−8647	20,493	−6118	−13,171	935	−3070	−6951	811
HADS depression (=1 if high)	578	−8971	10,127	−3741	−14,085	6604	−1417	−3821	988
HADS anxiety (=1 if high)	−1910	−12,194	8373	−3788	−11,859	4283	−1823	−3703	56
LCADL total score	**629****	180	1079	**411***	61	760	**635***	85	1186
POS total score	−366	−1467	736	−24	−817	769	−82	−232	68
CRQ mastery	−5713	−11,833	407	−2569	−5525	388	−226	−963	511
CRQ fatigue	−2062	−6785	2661	−2148	−5429	1133	−118	−751	515
Has carer (=1 if yes)	**13,650****	6793	20,507	**12,345****	8512	16,178	−492	−2427	1442
FEV_1 (% predicted)	−40	−217	136	22	−91	135	−21	−48	5
NRS breathless on exertion	700	−2296	3696	944	−2029	3917	**699***	243	1155
Age (centred at mean)	−165	−477	147	−76	−236	85	−36	−87	16
Female (=1 if yes)	−2602	−11,376	6172	−1915	−8627	4798	496	−693	1685
Living situation (ref: lives at home)	45,980	−42,090	134,049	16,844	−9906	43,595	10,771	−13,911	35,452
Cohabitee (ref.: wife/husband)									
Partner	−12,376	−24,846	93	**-8340****	−14,842	−1837	−587	−3205	2031
Son/daughter	−2271	−14,876	10,334	−2287	−10,334	5760	−223	−2132	1687
Other	−2851	−11,257	5554	1260	−7708	10,227	−689	−2373	994
Diagnosis (ref: COPD)									
Cancer	−3098	−8845	2648	−1224	−4848	2401	**−1474****	−2397	−551
Interstitial lung disease	−5508	−11,221	205	−2480	−8895	3935	**−2256***	−3862	−650
Heart failure	37,077	−1984	76,138	41,871	−1352	85,094	**−2297****	−3452	−1143
Other	19,145	−3706	41,997	13,659	−3734	31,051	−831	−2731	1069
Constant	**1057****	81	13,837	**1****	0	4076	**217,597****	10,523	4,499,493
Link function	Log			Log			Log		
Family	Gamma			Gaussian			Poisson		
Prob. H.L.[b]	0.49			0.082				0.397	

EQ-5D: EuroQol five dimensions questionnaire; HADS: Hospital Anxiety and Depression Scale; POS: Palliative care Outcome Scale; FEV_1: forced expiratory volume; NRS: Numerical Rating Scale; LCADL: London Chest Activity of Daily Living; CRQ: Chronic Respiratory Disease Questionnaire; COPD: chronic obstructive pulmonary disease; CI_{LL}: lower limit of confidence interval; CI_{UL}: upper limit of confidence interval.

[a]2014 GBP.

[b]The *p* value for the modified Hosmer–Lemeshow test.

*$p < 0.05$; **$p < 0.005$.

by over 250% from £3253 (US$4593.70) to £11,507 (US$16,249.52). Informal care was mainly accounted for by the time spent supervising a patient (hours on call), and to a lesser extent, bathing, dressing, cooking and cleaning. This highlights the importance of informal care particular in advanced disease. It is essential to account for informal care cost because in the absence of informal carers, possibly the same amount of care would need to be provided by formal carers via health or social care services. For example, certain patients (e.g. patients on medical equipment like tracheostomies or non-invasive ventilation or at risk of falls) will require 24-h supervision. In the United Kingdom, if such patients do not have informal carers, then often they are cared for in care-homes where they are supervised by formal carers, and the health service bears the cost. However, it is conceivable that the time spent on supervision reported in this study for some patients may have been more than what would have been required had such supervision been provided by formal carers. Nevertheless, if the cost of supervising patients was completely excluded from our analysis, informal care would still account for more than 50% of the total cost of care. Conversely, it is possible that informal carers may have underestimated how much time they spent supervising. If cost of supervision was assumed to be at the maximum for all carers (£12,479), then informal care cost would account for more than 82% of the total cost of care per patient.

High healthcare cost was associated with increasing disability resulting from breathlessness and breathlessness on exertion. Also, the healthcare cost for COPD was significantly more than lung cancer, ILD. Our results are supported by evidence from several studies on COPD patients which suggest that increased disability and poor physical performance are both independently associated with increased healthcare utilisation, particularly the risk of hospital re-admission.[26–32] Further research is required to

assess the effectiveness and cost-effectiveness of palliative care interventions in reducing disability resulting from breathlessness in patients with advanced disease and refractory breathlessness.

The presence of a career was found to be associated with high cost (both total and informal-care costs) as is to be expected. Also, we found a high variation in cost with more variation in the cost of informal care when compared to formal care. We cannot explain this high variation based on our data. However, it is conceivable that such variation is either due to random variation or, more likely, due to specific factors that we have not measured. We believe palliative care may reduce some of this variation. Palliative care has been shown to decrease rates of emergency department attendance[33] and length of hospital stay and to increase home-death rates, quality of life and possibly survival in patients with advanced illness.[4]

Our study has limitations. First, we did not account for drugs in our estimates but assumed that these are included in the cost of care, and so, we may have underestimated the full cost of care. Studies in elderly patients with COPD suggest that pharmaceutical agents may have a moderate to high impact on costs.[24] Second, we did not obtain resource use estimates from medical records but rather relied on self-report which may have introduced recall bias. However, self-report of service use has been shown to be reliable.[15,34] Third, we had to assume a proxy cost for informal care. In the absence of informal carers, it is unlikely that all patients would have received help from social services, but the cost of a home care worker should nevertheless indicate the value of this informal care. Fourth, the regression model only included data recorded as part of the study. It is likely that other unmeasured patient characteristics could have had some impact on cost. Fifth, our study was also limited by a small sample size which made it difficult to conduct more extensive analyses, particularly for some disease groups (such as cardiac failure where we had only five patients). Finally, the data in our study were highly skewed and there were a number of 'zero' resource use data (i.e. instances where costs were '£0' because patients did not use any resources), which both reduce the power to detect a significant difference. It is conceivable that a larger study would highlight other cost drivers in this group.

This study provides the first evidence on the costs of caring for people with advanced disease and refractory breathlessness; it highlights the likely 'burden' of the condition and provides a baseline for assessing the relative economic impact of different treatments in future studies. Further research is required to assess the effectiveness and cost-effectiveness of palliative care interventions in reducing disability resulting from breathlessness in patients with advanced disease and refractory breathlessness.

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Supplementary Material

King's College Hospital NHS
NHS Foundation Trust

"An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial"

LREC protocol number XXX

Patient ID _____	Assessment date _____
Care setting _____	Assessment no. _____

SAMPLE
For Peer Review

CLIENT SERVICE RECEIPT INVENTORY
Breathlessness version

1. Please provide details of **hospital and residential services** you have used over the last three months.

Service	**HAVE YOU HAD CONTACT?** **NO 0** **YES 1**	**Amount of use in the last 3 months**	**Any other information?**
1-Specialist medicine outpatient visit (e.g. respiratory, cardiac, oncology) (specify)	☐ ☐	... attendances	
2-Other hospital outpatient visit (specify)	☐ ☐	... attendances	
3-Day hospital department (e.g. respiratory, cardiac, oncology) (specify)	☐ ☐	... attendances	
4-Rehabilitation (e.g. pulmonary, cardiac) (specify)	☐ ☐	... attendances	
5-A&E department	☐ ☐	... attendances	
6-Nursing or residential home	☐ ☐	... days	
7-Hospice	☐ ☐	... days	
8-Inpatient ward (specify)	☐ ☐	...days	
9-Critical care unit (intensive care or high dependency unit)	☐ ☐	...days	
10-Other inpatient ward (specify)	☐ ☐	... days	

SAMPLE For Peer Review

2. Please provide details of **primary and community care services** you have used over the last three months.

Service	HAVE YOU HAD CONTACT? No 0	Yes 1	No. of contacts in last 3 months	Average duration (minutes)	Any other information?
1-General practitioner (GP)	□	□			
2-Other doctor, not including those in section 1 (specify) _____	□	□			
3-Physiotherapist	□	□			
4-Social worker	□	□			
5-District nurse	□	□			
6-Practice nurse	□	□			
7-Rehabilitation (e.g. pulmonary, cardiac), not including rehabilitation included in section 1; (specify)	□	□	... attendances		
8-Psychologist	□	□			
9-Home help	□	□			
10-Occupational therapist	□	□			
11-Dietician	□	□			
12-Home palliative care/ hospice service	□	□			
13-Other therapists (e.g. speech)	□	□			
14-Other service (specify)	□	□			

SAMPLE For Peer Review

3. Please list any **investigations / diagnostic tests** you have received over the last three months.

Service	HAVE YOU HAD THIS TEST? No 0	Yes 1	No. in the last 3 months	Any other information?
1-Respiratory function test	□	□		
2-Chest x-ray	□	□		
3-Echocardiogram	□	□		
4-ECG	□	□		
5-Blood gas test	□	□		
6-Magnetic Resonance Image (MRI)	□	□		
7-CT/ CAT scan	□	□		
8-Blood test	□	□		
9-Other investigations/ tests	□	□		

SAMPLE
For Peer Review

4. Please give details of any help you have received from **friends of family** members in the last three months **as a result of your illness**.

Type of help	HAVE YOU HAD HELP? No 0	Yes 1	Average no. of hours per week	Any other information?
1-Personal care (e.g. bathing, dressing)	□	□		
2-Help with medical procedures	□	□		
3-Help inside the home (e.g. cooking, cleaning)	□	□		
4-Help outside the home (e.g. shopping)	□	□		
5-Time spent 'on-call' i.e. you need someone to stay with you if even they don't do specific jobs	□	□		
6-Other (specify)	□	□		

SAMPLE For Peer Review

4. Please list below any **additional equipment** you have been using over the last three months.

Type of help	HAVE YOU HAD HELP? No 0	Yes 1	Average no. of hours per day	Any other information?
1- Ambulatory oxygen (oxygen cylinders)	□	□		
2-Long-term oxygen therapy (oxygen concentrator)	□	□		
3- Non-invasive ventilation (or CPAP)	□	□		□ overnight □ also during the day
4-Walking stick, rollator	□	□		
5-Wheelchair	□	□		
6-Feeding pump	□	□		
7-Commode	□	□		
8-Special bed	□	□		
9-Bathroom or toilet adapted	□	□		
10-Other equipment (specify)	□	□		

For Peer Review
SAMPLE

- Thank-you –