medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Health Economic Evaluation of a Double-Blind, Randomised, Placebo-Controlled Trial of Low-Dose Oral Morphine (MABEL)

Authors: Atter M[1] (corresponding author, *marek.atter@ed.ac.uk*), Hall PS[1] (*p.s.hall@ed.ac.uk*), Evans RA[2] (*re66@leicester.ac.uk*), Norrie J[1] (*j.norrie@qub.ac.uk*), Cohen J[3] (*Judith.Cohen@hyms.ac.uk*), Williams B[3] (*Bronwen.Williams@hyms.ac.uk*), Chaudhuri N[4] (*n.chaudhuri@ulster.ac.uk*), Bajwah S[5] (*sabrina.bajwah@kcl.ac.uk*), Higginson IJ[5] (*irene.higginson@kcl.ac.uk*), Pearson M[3] (*Mark.Pearson@hyms.ac.uk*), Currow DC[6] (*dcurrow@uow.edu.au*), Stewart G[7] (*Gareth.Stewart@nhs.scot*), Fallon MT[1] (*Marie.Fallon@ed.ac.uk*), Johnson MJ[2] (*Miriam.Johnson@hyms.ac.uk*)

1. *Edinburgh Clinical Trials Unit, The Usher Institute, University of Edinburgh*
2. *Department of Respiratory Sciences, NIHR Leicester Biomedical Research Centre – Respiratory, University of Leicester*
3. *Hull Health Trials Unit, Hull York Medical School, University of Hull*
4. *School of Medicine, Department of Life and Health Sciences, Ulster University,*
5. *Cicely Saunders Institute, King's College London*
6. *Faculty of Health, University of Technology Sydney, Sydney, NSW, Australia*
7. *Western General Hospital, NHS Lothian*

ABSTRACT

Objectives: To compare costs and health consequences and to assess the cost-effectiveness of using low-dose oral long-acting morphine in people with chronic breathlessness.

Design: Within-trial planned cost-consequences and cost-effectiveness analysis of data from a multi-site, parallel-group, double-blind, randomised, placebo-controlled trial of low-dose, long-acting morphine.

Setting: 11 hospital outpatients across the UK.

Participants: Those eligible to participate were consenting adults with chronic breathlessness due to long-term cardiorespiratory conditions.

Intervention: 5-10mg twice-daily oral long-acting morphine with a blinded laxative for 56 days.

Primary outcome measures: Mean and standard deviation (SD) of healthcare resource use (HRU) by trial arm; mean differences and 95% confidence intervals (CI) of costs between trial arms.

Secondary outcome measures: Mean differences in 28- and 56-day quality-adjusted life years (QALYs based on EQ-5D), SF-6D scores, and ICECAP-SCM scores; cost-utility of long-acting morphine for chronic breathlessness.

Results: 143 participants (75 morphine, 67 placebo) were randomised; 140 formed the modified intention-to-treat population (90% power; males 66%; mean age 70.5 [SD 9.4]). There were more inpatient and fewer outpatient services used by the morphine group *versus* placebo. In the base case analysis at 56 days, long-acting morphine was associated with similar mean per-patient costs and QALYs: There was an increase of £24 (95% CI: -£395, £552) and 0.002 (95% CI: -0.004, 0.008) QALYs. Hospitalisations were the main driver of cost differences. The corresponding incremental cost-

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

effectiveness ratio (ICER) was £12,000/QALY, with a probability of cost-effectiveness of 54% at a £20,000 Willingness-to-Pay (WTP) threshold. In the scenario analysis that excluded costs of adverse events considered unrelated to long-acting morphine by site investigators and researchers, the probability of cost-effectiveness increased to 73%.

Conclusion: Oral morphine for chronic breathlessness is likely to be a cost-effective intervention provided adverse events are minimised but the effect on outcome is small and cautious interpretation is warranted.

ARTICLE SUMMARY

Strengths and limitations of this study

- Comprehensive collection of patient-reported health economic data in a randomised controlled trial, including three different health outcome measures relevant to people living with chronic breathlessness due to medical conditions
- The parent trial intervention dosing schedule mirrored clinical practice to give a pragmatic indication of cost impacts
- Limited interpretation of cost-effectiveness analysis due to a likely random imbalance in deaths and expensive adverse events, in a study design not primarily designed to detect differences in economic endpoints
- Technical challenges in analysing and estimating costs for concomitant medications

Keywords

Economics, Clinical Trial, Morphine, Respiration

INTRODUCTION

Chronic breathlessness is a disabling symptom common in cardio-respiratory diseases and cancer. [1,2] Breathlessness is a global problem, with population prevalence ranging from 9% in high-income countries to 40% in low-income countries such as India, mirroring countries with higher rates of causal diseases, higher smoking rates and greater levels of environmental pollution. [3,4] Despite the significant adverse impacts of chronic, or persistent, breathlessness on quality of life, physical and psychosocial functioning, and healthcare service utilisation, effective management is often neglected. [5–7]

Opioids have shown potential in reducing the perception of breathlessness by modulating central pathways, but clinical trials in ambulant populations have not consistently demonstrated benefits, partly due to short study durations and the lack of measures of exercise endurance. In addition, morphine has a well-known adverse effect profile, including complications which could plausibly increase health service costs, complications from gastrointestinal and neurocognitive side effects, and respiratory

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

depression. The health economic implications of chronic breathlessness beyond the specific context of chronic obstructive pulmonary disease (COPD) have not been comprehensively studied. The only published health economic evaluation, to our knowledge, however, found a high likelihood that four weeks of long-acting morphine was cost-effective, compared with placebo, in the management of people living with chronic breathlessness due to COPD. [7]

The Morphine And BrEathLessness (MABEL) trial aimed to assess the effectiveness, cost-consequences, cost-effectiveness and safety of long-acting low-dose, oral long-acting morphine on patient-reported worst breathlessness in people with chronic breathlessness. [8]

This paper contains the health economic analysis component of the MABEL trial. This analysis aimed to compare the costs, health outcomes (cost-consequences analysis), and cost-effectiveness of using morphine on patient-reported *worst breathlessness* in people with chronic breathlessness.

METHODS

Trial overview

Full details of the MABEL trial, its procedures (including inclusion/exclusion criteria), and clinical findings can be found in the study protocol and main results paper; this section's summary is included for context. [8]

MABEL was an 11-site, UK-based multicentre, Phase-III, parallel-group, double-blind, randomised placebo-controlled titration trial. Eligible patients were ambulant adults with moderate to severe chronic breathlessness (mMRC ≥ grade 3 or 4) due to cardio-respiratory disease or cancer, with adequate renal function, who gave informed consent. The *Active* (Morphine) intervention consisted of 5-10mg twice-daily oral long-acting morphine with a blinded laxative, for 56 days. The primary outcome was worst breathlessness in the past 24 hours (measured by a 0-10 numerical rating scale (NRS) on Day 28. Outcome measures pertinent to the health economic evaluation were the Short-form-12 (SF-12), the EuroQol-5dimension-5level score (EQ-5D-5L), ICEpop CAPability-Supportive Care Measure (ICECAP-SCM) and Health Resource Use Questionnaire measured at baseline, Day 28 and Day 56. [9–12] Attribution of serious adverse events to study drug was assigned by the recruiting site clinician, and discussed with the clinical Chief-Investigator (with over thirty years' experience of opioid prescribing).

Methods for the economic analysis

The paper follows Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidance for health economic evaluations (summarised in Supplementary Table 1). [13] The methods of calculating costs, health outcomes and cost-effectiveness metrics were stipulated in a Health Economic Analysis Plan (HEAP) approved by the lead economist and chief investigator before the data lock and unblinding (see Supplementary Materials).

In line with guidance, all costs and health outcomes were calculated from a National Health Service (NHS) & Personal Social Services perspective, which includes the costs of primary and secondary care, and community NHS activity in England. [14]

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

As per the National Institute for Health and Care Excellence (NICE) guidelines, the health outcome of interest is the quality-adjusted life years (QALY), which is an "index of survival that is adjusted to account for the patient's quality of life" best calculated using the EQ-5D-5L measure. [14,15]

In light of the evolving discussion in the scientific literature about the interpretation of the QALY in end-of-life settings, SF-6D (derived from SF-12) and the capability measure the ICECAP-SCM were selected as alternative measures in the sensitivity analyses. [9,10]

Data collection

The data needed for the health economic analysis were drawn from a combination of trial case report form (CRF) data and a modified version of the UK Cancer Costs Questionnaire collected on Day 28 and Day 56 after randomisation. [12] The time horizon used in this paper is therefore 56 days, but selected key results for Day 28 are also presented. With a time horizon of under 1 year, no discounting of costs or outcomes were applied.

Estimating outcomes

QALYs were calculated individually for each patient in the intention-to-treat population by using the following steps: First calculating Health State Utility Values (HSUVs) from EQ-5D-5L Patient-Reported Outcome Measure (PROM) questionnaire data at each time point using a validated mapping function by Hernández Alava et al. [16] subsequently calculating 56-day QALYs as a function of HSUVs and their corresponding time points using the area-under-the-curve method outlined by Manca et al. [17]

The SF-6D was converted into HSUVs using validated ProCore software provided by QualityMetric, while the ICECAP-SCM measure was converted into tariff values for its capability score, which ranges from 0 (no capability) to 1 (full capability), using its published value set. [18,19] SF-6D and ICECAP-SCM scores were not used in QALY calculation or the cost-effectiveness analysis.

Estimating costs

Price weights used to calculate per-patient costs of hospital and community (hospice) resource use are presented in Table 1. Medication unit costs, which include morphine as the investigational medicinal product (IMP), laxatives as the non-investigational medicinal product (NIMP), and concomitant medications, were sourced from the British National Formulary (BNF). [20]

In light of an observed imbalance in hospital admissions deemed by the investigator to be unrelated to morphine, a *post hoc* costing scenario was undertaken in which hospitalisation costs were measured only by Serious Adverse Events (SAEs) using industry-standard definitions considered to be related to morphine by site clinicians and study investigators, instead of the number of self-reported inpatient days which formed the base case *a priori*. All SAE reporting (including causality) was done whilst still blinded, except one SAE that was judged as having a causal relationship *post hoc*; this increased the number of causal SAEs (all in in the morphine arm) from 2 to 3, leading to a more conservative result than the fully blinded causality. In the scenario analysis, the hospital stay data were collected from the SAE reporting in the case report forms which were verified from the clinical record by site investigators and study monitors, as opposed to inpatient stay data which were sourced from patient questionnaires.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Corresponding unit costs were sourced and approved for the three SAEs included in the scenario analysis by the Chief Investigators (reported in Table 1).

Table 1: MABEL HRU Unit Costs

Item	Cost	Ref	Notes
Hospital Health Resources			
Inpatient Stay	£401	[21]	Approximation of a bed day cost, assumed to be half the cost of a short non-elective inpatient stay, defined as 1-2 nights (index: "Non-elective inpatient - short stay"); this cost is excluded from the scenario analysis and replaced by SAE-specific costs
Emergency Assessment	£242	[21]	Index: "Emergency care"
Hospital Consultant/Doctor	£224	[21]	Weighted average for outpatient face-to-face consultant-led "Respiratory Medicine Service" entries
Specialist Nurse	£110	[21]	Index: "Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Face to face"
Physiotherapist	£100	[21]	Index: "Physiotherapy Service"
Dietician	£105	[21]	Index: "Dietetics Service"
Occupational Therapy	£106	[21]	Index: "Occupational Therapy Service"
Social Worker	£53	[22]	No information on average visit duration, so the hourly unit cost for a qualified social worker (adult services) is assumed as a reasonable approximation
Optometry	£138	[21]	Index: "Optometry Service"
Computerised Tomography	£140	[21]	Weighted average for adult CT scan entries in the "Total HRGs" tab
X-Ray	£41	[21]	Index: "Plain Film" (outpatient)
Ultrasound	£73	[21]	Weighted average for ultrasound entries in the "IMAG" tab
Osteopathy	£100	[21]	Index: "Physiotherapy Service" (no distinct osteopathy cost was identified, physiotherapy cost was assumed as an approximation)
Music Therapy	£15	[21]	Index: "Music Therapy Service"
Magnetic Resonance	£213	[21]	Weighted average for adult MRI scan entries in "Total HRGs"
Phlebotomy	£5	[21]	Index: "Phlebotomy"
Telehealth Service	£9	[22]	Nurse-led triage (cost per intervention)
Hospital Consultant/Doctor (phone call)	£49	[21]	Index: "Follow-up, Non Face to Face"
Specialist Nurse (phone call)	£70	[21]	Index: "Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Non face to face"
Administrator/Secretary (phone call)	£9	[22]	Assumed to be approximated by: nurse-led triage (cost per intervention)
Community Health Resources			
Hospice Inpatient Stay	£305	[22]	Inpatient, specialist palliative care (19 years and over), average cost per bed day (19 years and over)
Doctor	£76	[21]	Index: "Follow-up, Adult, Face to Face"
Nurse	£54	[21]	Index: "District Nurse, Adult, Face to face"
Day Hospice	£80	[21]	Index: "Community health services"
Other Professional	£253	[21]	Index: "Clinical Psychology Service"
Consultant/Doctor (phone call)	£49	[21]	Index: "Follow-up, Non Face to Face"
Specialist Nurse (phone call)	£70	[21]	Index: "Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Adult, Non face to face"
Administrator/Secretary (phone call)	£9	[22]	Assumed to be approximated by: nurse-led triage (cost per intervention)
Scenario Analysis: Causal SAEs			

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Item	Cost	Ref	Notes
Causal SAE #1	£3,966	[21]	Weighted mean reference cost for "Ureteric or Bladder Disorders, with Interventions"
Causal SAEs #2 & #3	£1,422	[21]	Weighted mean reference cost for "Non-Malignant Gastrointestinal Tract Disorders without Interventions"

SAE = Serious Adverse Event

Per-patient costs were calculated by multiplying each patient's recorded HRU units by their corresponding price weight.

All costs are reported in British Pounds (GBP) for the financial year of 2021/22, based on the most recent NHS reference costs available at the time of conducting the cost analysis. [21]

Analysis

To account for missing data and the non-normal and skewed distribution of estimates, statistical tools from the validated *bootImpute* R programming package were used to estimate cost and QALY 95% confidence intervals (CIs) for means and differences in means between trial arms. [23,24] These methods combined multiple imputation by chained equations, non-parametric bootstrapping, and generalised linear model regression with a Gamma distribution and a log link to account for estimate skewness. [23,25,26]

The regression model, consistent with the main clinical trial analysis, controlled for age, sex, study site, and disease. [8] QALYs were additionally adjusted for baseline HSUV, as recommended by Manca *et al*. [17]

Estimates of the regression analyses from the simulated bootstrapped datasets and estimates from the pooled regression model were used to complete the cost-effectiveness analysis. As per NICE guidelines, the primary cost-effectiveness metric was the ICER measured in incremental costs per QALY gained (intervention minus control). The ICER was calculated alongside measures of parameter uncertainty in the form of a Cost-Effectiveness Plane (CEP) scatterplot and a Cost-Effectiveness Acceptability Curve (CEAC). [14]

Concomitant medications

In contrast to the other patient-reported variables, concomitant medication data were collected from a CRF. Its analysis proved challenging for the following reasons:

- The concomitant medications CRF had a large number of entries (n = 1,852)
- Drug names were recorded as a free text variable, prone to erroneous and inconsistent spelling
- Many values were impossible to interpret (e.g., dose frequency recorded as "Other")
- Each entry needed to be cross-referenced with a unit cost from the BNF
- many concomitant medications were unrelated to the MABEL trial (e.g., unrelated to breathlessness or morphine-related side effects)

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

To resolve these issues, the following steps were taken: the 1,852 concomitant medication data entries were cleaned, from which 424 unique categorical drug values were extracted (including a missing/error term); then, the 424 drug names were classified into drug categories by a clinician and health economics lead on the MABEL trial team, 328 of which were classified as 'not relevant' and were therefore excluded from cost calculation. Then, the unit costs of the remaining 96 drugs were identified by a web-scraping algorithm written in R with access to the BNF database. Then, the observed medication cost was calculated for each non-excluded entry (n = 444 out of N = 1,852) by multiplying the unit cost by the units used (as recorded in the CRF). At this point, there was still too much missing data to sum up medication costs by the patient, so the remaining data were imputed and bootstrapped using *bootImpute* in parallel to the patient-level data. This allowed imputed total per-patient concomitant medication costs to be calculated separately for each iteration of the simulated dataset.

Patient and public engagement

No additional patient and public involvement was undertaken specifically for the trial's health economic evaluation, beyond that of the main trial (see main clinical trial report for details). [8]

RESULTS

Study population

140 participants formed the MABEL intention-to-treat population (see Table 2). The CONSORT (Consolidated Standards of Reporting Trials) flow diagram (reporting checklist) is provided in Supplementary Figure 1. The main clinical paper describes further details of the screening and randomisation processes. [8]

Table 2: Baseline Characteristics

	Morphine (n=73)	**Placebo (n=67)**	**Total (n=140)**
Age in years	70.6 (10.2)	70.3 (8.4)	70.5 (9.4)
Gender			
Male	48 (66%)	45 (67%)	93 (66)
Female	25 (34%)	22 (33%)	47 (34)
Ethnicity or Origin			
White	69 (95)	63 (94)	132 (66)
Asian / Asian British	2 (3)	2 (3)	4 (3)
Black / African / Caribbean / Black British	2 (3)	1 (1)	3 (2)
Other ethnic origin	0 (0)	1 (1)	1 (1)
Primary Diagnosis			
COPD	40 (52)	37 (48)	77 (55)
Other non-malignant lung disease*	30 (50)	30 (50)	60 (42.8)
Heart Disease	3 (100)	0 (0%)	3 (2.1)
Body Mass Index (kg/m^2)	27.1 (6.4)	27.4 (5.1)	27.2 (5.8)
eGRF (ml/min/1.73^2)	70.5 (16.7)	69.9 (19.1)	70.2 (17.8)
Resting BP (mm/Hg)			
Resting Systolic BP (mm/Hg)	132.2 (20.8)	131.3 (23.3)	131.8 (21.8)
Resting Diastolic (mm/Hg)	74.8 (10.4)	75.1 (12.0)	75.0 (11.1)
Resting Pulse (bpm)	80.29 (13.0)	79.39 (14.6)	79.9 (13.8)

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

	Morphine (n=73)	Placebo (n=67)	Total (n=140)
Resting Respiration Rate (RR/min)	20.59 (3.9)	20.0(4.2)	20.3 (4.0)
Pulse Oximetry	93.84 (3.4)	94.33 (2.6)	94.1 (3.0)
Transcutaneous CO_2 measurements conducted?			
Yes	4 (5%)	3 (4%)	7 (5%)
No	69 (95%)	64 (96%)	133 (95%)
Transcutaneous CO2 (mm/Hg)	42.75 (5.44)	29.67 (20.50)	37.14 (14.28)
Disease Type			
COPD GOLD Stage III - Severe	20 (31)	17 (28)	37 (30)
COPD GOLD Stage IV- Very severe	12 (19)	10 (16)	22 (18)
ILD – Mild / Moderate	19 (30)	21 (34)	40 (32)
ILD - Severe	9 (14)	5 (8)	14 (11)
Other respiratory	4 (6)	8 (13)	12 (10)
Cardiac NYHA Class III	3 (100)	1 (100)	4 (100)
Cancer	1(100)	0 (0)	1 (100)
Comorbidities			
0	3 (4)	1 (1)	4 (3)
1	15 (21)	15 (22)	30 (21)
At least 2	55 (75)	51 (76)	106 (76)
AKPS			
50 - considerable assistance, frequent medical care	4 (5.5)	5 (7.5)	
60 - occasional assistance, can care for most needs	29 (39.7)	26 (38.8)	
70 - Cares for self; cannot carry on normal activity or work	27 (37.0)	25 (37.3)	
80 - Normal activity with effort; some signs or symptoms	11 (15.1)	8 (11.9)	
90 - Normal activity; minor signs or symptoms	1 (1.4)	2 (3.0)	
100 - Normal; no complaints; no evidence of disease	1 (1.4)	1 (1.5)	
NRS worst breathlessness (SD)	6.8 (1.5)	6.8 (1.9)	6.8 (1.7)
NRS distress due to breathlessness (SD)	5.3 (2.6)	5.1 (2.8)	5.2 (2.7)
NRS most severe cough (SD)	4.5 (2.9)	3.9 (2.7)	4.2 (2.8)
NRS pain (SD)	3.0 (2.8)	2.7 (2.8)	2.8 (2.8)
SF-12			
Physical component	31.4 (6.5)	31.2(6.3)	31.3 (6.4)
Mental component	49.3 (10.1)	44.4 (10.8)	46.9 (10.7)
EQ-5D-5L mean (SD)	0.60 (0.19)	0.56 (0.23)	0.58 (0.21)
EQ-VAS mean (SD)	55 (16)	48 (21)	52.0 (19.0)
Epworth Sleep Scale mean (SD)	6.5 (4.9)	7.4 (5.4)	7.0 (5.2)
Karolinska sleepiness scale mean (SD)	6.5 (4.9)	7.4 (5.4)	7.0 (5.2)
SLUMS questionnaire mean (SD)	24.9 (4.1)	25.1 (3.2)	25.0 (3.7)
Average daily step count mean (SD)	6824 (2562)	7189 (3454)	6998 (3014)
Zarit Burden Interview (carers) mean (SD)	13.3 (9.9)	22.6(13.2)	18.6 (12.6)

Data are median (IQR), n (%), or mean (SD). COPD = chronic obstructive pulmonary disease. ILD = interstitial lung disease. mMRC = Modified Medical Research Council. eGRF = estimated glomerular filtration rate. GOLD = Global initiative for chronic obstructive lung disease. NYHA = New York Heart Association

Deaths over time by study group are presented in Figure 1 and, in conjunction with EQ-5D-5L data, were used to calculate QALYs.

Data quality

The percentage of patients in each arm with missing values is categorised by each patient-reported health economic variable and presented in Supplementary Table 2. In these variables, missingness was below 20%. Unsurprisingly, missingness was highest for variables collected on Day 56 since randomisation, followed by those gathered on Day 28, and 0% for baseline measures. For both health

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

outcomes and resources/costs, missingness is consistently slightly higher in the morphine arm (by up to 9% points).

Concomitant medication data is summarised separately in Supplementary Table 3. The table shows the number of entries in the CRF and the number and percentage of receiving patients by concomitant medication category.

Health resource use

Table 3 shows the sums of patient-reported health resources used by each study group, which were used to calculate hospital and community costs.

Table 3: Health Resource Use by Study Group - n (summed total by study group), mean ± SD

Variable	Placebo (n=67)		Morphine (n=73)	
	n	*mean ± SD*	*n*	*mean ± SD*
28 days				
Inpatient Stay (nights)	5	0.1 ± 0.5	36	0.6 ± 2.3
Emergency Assessment (attendances)	2	0.0 ± 0.2	1	0.0 ± 0.1
Hospital Consultant/Doctor (attendances)	10	0.2 ± 0.4	4	0.1 ± 0.2
Specialist Nurse (attendances)	20	0.3 ± 1.2	6	0.1 ± 0.3
Physiotherapist (attendances)	17	0.3 ± 1.2	11	0.2 ± 1.0
Dietician (attendances)	0	0	0	0
Occupational Therapy (attendances)	2	0.0 ± 0.3	1	0.0 ± 0.1
Social Worker (attendances)	0	0	0	0
Other Outpatient (attendances)	6	0.1 ± 0.3	5	0.1 ± 0.3
Hospital Consultant/Doctor (phone calls)	3	0.0 ± 0.3	7	0.1 ± 0.4
Specialist Nurse (phone calls)	23	0.4 ± 1.7	4	0.1 ± 0.2
Administrator/Secretary (phone calls)	1	0.0 ± 0.1	1	0.0 ± 0.1
Hospice Inpatient Stay (nights)	7	0.1 ± 0.9	0	0
Hospice Doctor (attendances)	0	0	0	0
Hospice Nurse (attendances)	0	0	0	0
Day Hospice (attendances)	2	0.0 ± 0.3	0	0
Hospice Consultant/Doctor (phone calls)	0	0	0	0
Hospice Specialist Nurse (phone calls)	0	0	1	0.0 ± 0.1
Hospice Administrator/Secretary (phone calls)	0	0	0	0
Other Professional (attendances)	0	0	0	0
56 days				
Inpatient Stay (nights)	17	0.3 ± 1.5	54	0.9 ± 3.6
Emergency Assessment (attendances)	2	0.0 ± 0.2	3	0.0 ± 0.2
Hospital Consultant/Doctor (attendances)	18	0.3 ± 0.6	13	0.2 ± 0.5
Specialist Nurse (attendances)	30	0.5 ± 1.5	6	0.1 ± 0.3
Physiotherapist (attendances)	18	0.3 ± 1.3	12	0.2 ± 1.1
Dietician (attendances)	0	0	0	0
Occupational Therapy (attendances)	2	0.0 ± 0.3	1	0.0 ± 0.1
Social Worker (attendances)	0	0	0	0
Other Outpatient (attendances)	22	0.4 ± 1.0	9	0.1 ± 0.4
Hospital Consultant/Doctor (phone calls)	3	0.1 ± 0.2	15	0.2 ± 0.6
Specialist Nurse (phone calls)	41	0.7 ± 2.8	17	0.3 ± 0.6
Administrator/Secretary (phone calls)	6	0.1 ± 0.4	4	0.1 ± 0.3
Hospice Inpatient Stay (nights)	7	0.1 ± 0.9	0	0
Hospice Doctor (attendances)	0	0	0	0
Hospice Nurse (attendances)	0	0	0	0

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Variable	Placebo (n=67)		Morphine (n=73)	
Day Hospice (attendances)	3	0.1 ± 0.4	0	0
Hospice Consultant/Doctor (phone calls)	0	0	0	0
Hospice Specialist Nurse (phone calls)	0	0	1	0.0 ± 0.1
Hospice Administrator/Secretary (phone calls)	0	0	0	0
Other Professional (attendances)	0	0	0	0

Table 3 shows a disparity in resource use patterns; patients in the Morphine arm spent more inpatient nights than Placebo (54 vs 17 by day 56), while the Placebo arm used more outpatient and community services. While this could be explained by random variation, it is also possible that due to small numbers, an imbalance in unrelated non-intervention-related SAEs has led to a spuriously high admission rate in the intervention arm. Therefore, we conducted a *post hoc* scenario analysis, wherein the self-reported inpatient stay nights were replaced with SAE hospitalisations recorded in the CRFs that were likely related to the intervention; three such SAEs were identified amongst three patients in the Morphine arm (one due to urinary retention, and two due to constipation) and 0/3 SAEs in Placebo.

Regression analysis results

The summary statistics of the main MABEL economic variables are reported in Table 4. The *Placebo* and *Morphine* arms present mean per-patient values and 95% CIs estimated via non-parametric bootstrapping. The *Difference* column presents regression estimates and 95% CIs of the mean effects of the IMP on each variable, adjusted by the regression controls.

Table 4: Summary Statistics, mean estimate (95% CI)

Variable	Placebo (n=67)	Morphine (n=73)	Difference	P
Health Outcomes				
EQ-5D-5L Health Utility (baseline)	0.48 (0.42, 0.53)	0.51 (0.46, 0.56)	-	-
EQ-5D-5L Health Utility (day 28)	0.49 (0.41, 0.56)	0.55 (0.47, 0.62)	0.05 (-0.02, 0.13)	0.16
EQ-5D-5L Health Utility (day 56)	0.53 (0.47, 0.58)	0.55 (0.46, 0.62)	0.01 (-0.06, 0.08)	0.74
ICECAP (baseline)	0.67 (0.64, 0.70)	0.64 (0.61, 0.67)	-	-
ICECAP (day 28)	0.67 (0.63, 0.71)	0.63 (0.59, 0.68)	-0.03 (-0.07, 0.00)	0.08
ICECAP (day 56)	0.66 (0.61, 0.70)	0.63 (0.56, 0.67)	-0.04 (-0.08, 0.01)	0.12
SF12 6D (baseline)	0.58 (0.56, 0.61)	0.63 (0.60, 0.65)	-	-
SF12 6D (day 28)	0.62 (0.59, 0.66)	0.64 (0.60, 0.69)	0.02 (-0.02, 0.06)	0.28
SF12 6D (day 56)	0.61 (0.58, 0.64)	0.63 (0.59, 0.68)	0.02 (-0.02, 0.06)	0.30
QALYs				
QALYs (28 days)	0.055 (0.047, 0.063)	0.062 (0.053, 0.069)	0.005 (-0.003, 0.013)	0.21
QALYs (56 days)	0.075 (0.065, 0.084)	0.081 (0.071, 0.090)	0.002 (-0.004, 0.008)	0.51
Intervention Costs (28 days)				
Morphine Costs	£0	£2 (£2, £2)	£2 (£2, £2)	0.00
Laxative Costs	£0	£4 (£4, £4)	£4 (£4, £4)	0.00

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Variable	Placebo (n=67)	Morphine (n=73)	Difference	P
Hospital Costs (28 days)				
Inpatient Stay (nights)	£84 (£0, £336)	£283 (£49, £786)	£148 (-£32, £359)	0.11
Emergency Assessment (attendances)	£11 (£0, £33)	£7 (£0, £32)	-£1 (-£15, £12)	0.85
Hospital Consultant/Doctor (attendances)	£45 (£22, £70)	£23 (£6, £48)	-£17 (-£39, £5)	0.14
Specialist Nurse (attendances)	£40 (£15, £103)	£19 (£5, £65)	-£19 (-£46, £9)	0.18
Physiotherapist (attendances)	£38 (£5, £101)	£28 (£1, £95)	-£9 (-£40, £24)	0.59
Dietician (attendances)	£0	£0	£0	0.99
Occupational Therapy (attendances)	£4 (£0, £18)	£3 (£0, £15)	-£1 (-£7, £6)	0.84
Social Worker (attendances)	£0	£0	£0	0.99
Other Outpatient (attendances)	£15 (£6, £28)	£11 (£3, £26)	-£2 (-£15, £10)	0.71
Hospital Consultant/Doctor (phone calls)	£5 (£0, £12)	£8 (£2, £18)	£3 (-£2, £9)	0.25
Specialist Nurse (phone calls)	£31 (£5, £92)	£11 (£2, £59)	-£11 (-£33, £11)	0.32
Administrator/Secretary (phone calls)	£0 (£0, £1)	£0 (£0, £1)	£0 (£0, £1)	0.83
Community Costs (28 days)				
Hospice Inpatient Stay (nights)	£31 (£0, £167)	£0 (£0, £88)	-£22 (-£61, £19)	0.28
Hospice Doctor (attendances)	£0	£0	£0	0.99
Hospice Nurse (attendances)	£0	£0	£0	0.99
day Hospice (attendances)	£3 (£0, £13)	£0 (£0, £11)	-£2 (-£6, £2)	0.30
Other Professional (attendances)	£0	£0	£0	0.95
Hospice Consultant/Doctor (phone calls)	£0	£0	£0	0.99
Hospice Specialist Nurse (phone calls)	£0 (£0, £2)	£1 (£0, £6)	£1 (-£2, £4)	0.38
Hospice Administrator/Secretary (phone calls)	£0	£0	£0	0.99
Intervention Costs (56 days)				
Morphine Costs	£0	£4 (£3, £4)	£3 (£3, £4)	0.00
Laxative Costs	£0	£7 (£7, £8)	£7 (£7, £8)	0.00
Hospital Costs (56 days)				
Inpatient Stay (nights)	£190 (£13, £790)	£431 (£75, £1,471)	£260 (-£131, £733)	0.21
Emergency Assessment (attendances)	£17 (£0, £48)	£23 (£0, £58)	£6 (-£13, £24)	0.55
Hospital Consultant/Doctor (attendances)	£87 (£47, £153)	£73 (£31, £140)	-£10 (-£44, £26)	0.58
Specialist Nurse (attendances)	£67 (£26, £160)	£31 (£7, £122)	-£28 (-£61, £6)	0.10
Physiotherapist (attendances)	£44 (£9, £128)	£37 (£3, £144)	-£9 (-£45, £30)	0.65
Dietician (attendances)	£0	£0	£0	0.98
Occupational Therapy (attendances)	£4 (£0, £12)	£2 (£0, £7)	-£1 (-£8, £7)	0.85
Social Worker (attendances)	£0	£0	£0	0.98
Other Outpatient (attendances)	£46 (£19, £93)	£29 (£10, £79)	-£14 (-£39, £12)	0.30
Hospital Consultant/Doctor (phone calls)	£7 (£1, £19)	£16 (£7, £34)	£9 (£1, £17)	0.03
Specialist Nurse (phone calls)	£61 (£17, £193)	£40 (£14, £143)	-£9 (-£42, £25)	0.58
Administrator/Secretary (phone calls)	£2 (£0, £4)	£1 (£0, £4)	£0 (-£2, £1)	0.80
Community Costs (56 days)				
Hospice Inpatient Stay (nights)	£35 (£0, £126)	£0	-£27 (-£78, £26)	0.30
Hospice Doctor (attendances)	£0	£0	£0	0.98
Hospice Nurse (attendances)	£0	£0	£0	0.98

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Variable	Placebo (n=67)	Morphine (n=73)	Difference	P
Day Hospice (attendances)	£4 (£0, £14)	£0	-£5 (-£16, £5)	0.30
Other Professional (attendances)	£0	£0	£0	0.98
Hospice Consultant/Doctor (phone calls)	£0	£0	£0	0.98
Hospice Specialist Nurse (phone calls)	£0	£1 (£0, £4)	£1 (-£1, £4)	0.35
Hospice Administrator/Secretary (phone calls)	£0	£0	£0	0.98
Concomitant Medications				
Concomitant Medications (28 days)	£20 (£0, £127)	£18 (£1, £116)	-£5 (-£64, £58)	0.88
Concomitant Medications (56 days)	£65 (£10, £338)	£44 (£8, £309)	-£19 (-£84, £49)	0.57
Causal SAEs (Scenario Analysis)				
Causal SAE Costs (28 days)	£0	£0	£0	-
Causal SAE Costs (56 days)	£0	£82 (£0, £234)	£73 (-£14, £169)	0.10
Total Costs				
Total Costs (28 days, base case)	£350 (£133, £669)	£464 (£151, £1,280)	£102 (-£216, £517)	0.57
Total Costs (28 days, scenario)	£256 (£113, £486)	£144 (£52, £405)	-£58 (-£154, £50)	0.28
Total Costs (56 days, base case)	£520 (£286, £833)	£572 (£243, £1,082)	£24 (-£395, £552)	0.92
Total Costs (56 days, scenario)	£384 (£234, £660)	£261 (£144, £535)	-£48 (-£173, £98)	0.50

Difference: Morphine – Placebo, regression-adjusted for stratification factors (age, sex, centre, and disease type); QALYs are additionally adjusted for baseline utility [17]

Overall, Table 4 presents no statistically significant differences in health outcome measures or costs between trial arms, with only two exceptions:

1. IMP and NIMP costs, which are set to £0 in the Placebo arm but are £4 (95% CI: £3, £4) and £7 (95% CI: £7, £8) in the morphine arm, respectively;
2. Hospital Consultant/Doctor phone calls have a small but statistically significant (P = 0.03) difference, being £9 (95% CI: £1, £17) higher in the Morphine arm relative to Placebo.

Cost-effectiveness analysis results

The 56-day ICER for the MABEL intervention was estimated as a function of the adjusted difference in QALYs and total costs, resulting in $\frac{\Delta Costs}{\Delta QALYs} = \frac{£24}{0.002} = £12{,}000$ per QALY gained in the base case. In the sensitivity analysis, Morphine lowers costs by -£48 (95% CI: -£173, £98), therefore the ICER cannot be calculated and the intervention dominates standard care.

Uncertainty around the ICER results is presented in the Cost-Effectiveness Plane (CEP) in Figure 2, which shows the percentage of simulated datasets found within an area of the graph. For comparison, the base case and sensitivity analysis results were plotted together, therefore the standard CEP scatterplot was not used to improve readability and instead replaced with data ellipses plotted using the *dataEllipse* function from the *car* library in R. [27] The distribution of simulated results is presented in Table 5 as a percentage of simulated results in each quadrant of the CEP.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Table 5: Summary of Cost-Effectiveness Results

Outcome	Base Case	Scenario	
Probability morphine is cost-effective:			**WTP**
by day 28	66%	87%	£20,000
	69%	86%	£30,000
by day 56	54%	73%	£20,000
	55%	72%	£30,000
Probability morphine leads to:			**CEP Quadrant**
higher costs, better health	34%	20%	Northeast
higher costs, worse health	18%	12%	Northwest
lower costs, better health	34%	48%	Southeast
lower costs, worse health	14%	20%	Southwest

WTP = Willingness-to-Pay threshold; CEP = Cost-Effectiveness Plane

The Cost-Effectiveness Acceptability Curve (CEAC), which plots the probability of morphine's cost-effectiveness compared to standard care against a WTP threshold, is presented in Figure 3. The probabilities of cost-effectiveness using NICE WTP thresholds of £20,000 and £30,000 are present in Table 5. A Value of Information (VoI) analysis was conducted alongside the CEAC calculations. The VoI results are presented in Supplementary Figure *2*, which shows the Expected Value of Perfect Information (EVPI) plotted against the WTP threshold.

DISCUSSION

The analysis suggests that long-acting morphine may be cost-effective for chronic breathlessness, at a probability consistent with the previous health economic evaluation in the context of COPD. [7] In the scenario-based *post hoc* analysis, the probability of cost-effectiveness becomes greater. However, the adjusted results of MABEL's health economic analysis show no overall statistically significant difference in costs or health outcomes between the placebo and long-acting arms and the cost-effectiveness estimates are highly uncertain. This is consistent with its main clinical results, which show that long-acting low-dose, oral morphine had no statistically significant effect on patient-reported worst breathlessness in people with chronic breathlessness. [8] The ICER is difficult to interpret when taken in isolation due to the small sample size and effect of a likely random imbalance in deaths, therefore we suggest that interpretation should focus on cost consequences analysis as this allows us to unpick possible relationships between adverse events, morphine, costs and patterns of health service use.

Despite the lack of statistical significance in the cost analysis, an interesting divergence in patient-reported HRU patterns was observed between trial arms. More outpatient services were used in the placebo arm, while the Morphine arm patients used more inpatient services. These inpatient admissions appeared to be imbalanced and unexplained by adverse events plausibly related to morphine. The scenario analysis proved a useful tool to rebalance this in case the trial's sample size exacerbated the imbalance. However, a limitation of the scenario analysis stems from it being conducted *post hoc* and judging one of the SAEs as causal only after unblinding, unlike the fully double-blinded base case analysis. However, observational studies of cohorts of people with advanced COPD and interstitial lung diseases (conditions that 55% and ~40% of the MABEL trial population had respectively) demonstrated no excess hospital admissions or deaths in people taking opioids at less than 30mg morphine-equivalent

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

doses per day. [28,29] This is despite having very severe respiratory disease; all participants in these cohorts being on long-term oxygen therapy. Of note in the MABEL trial, where hospital admission was attributed to morphine, two of the three admissions were related to constipation. This emphasises the importance of close attention to bowel care in anyone taking morphine – this is a potentially avoidable situation, and in retrospect, the blinded laxative in the MABEL trial should have included a stimulant as well as a softener. Further, we need to consider whether some infective adverse related events might be related to morphine. There is a theoretical concern about the impact of opioids on the immune system, although the effect on clinical outcomes is unknown. However, we found no evidence that participants in the morphine arm experienced more infective events than the placebo arm, making it unlikely that relatedness was misclassified with this regard. [8]

The MABEL analysis of health outcomes produced some unexpected results. Adjusted point estimates for morphine's impact on EQ-5D and SF12 scores on day 56 are positive, while those for ICECAP are negative. While not statistically significant, this is still the opposite trend to what we expected before data analysis, as it suggests that participants taking morphine are *less* capable. However, this result could be consistent with the HRU analysis, wherein morphine arm participants used more inpatient services (e.g., hospitalisation) and fewer outpatient services relative to placebo. Hospital in-patient stays would be expected to impair capability, although this is not connected to and does not suggest morphine-related cognitive bluntness. The conflict with EQ-5D and SF12 scores might stem from the pain reduction morphine provides, but the clinically and statistically significant improvement in pain in the morphine arm at Day 7 (mean difference -0.92; 95% CI: -1.70, -0.13; $p = 0.2$) was not sustained throughout the 56 days of the MABEL trial other than a small and insignificant improvement. [8] Undoubtedly the contrasts between these health outcomes highlight the importance of future research to find the most appropriate measures of health outcomes in the context of advanced illness. It is also interesting to note the cost implications of out-patient and community care. People with moderate to severe breathlessness due to chronic medical conditions are high users of all aspects of healthcare (community, emergency, hospital) with costs also driven by community care health service needs. [6]

We highlight several strengths and weaknesses. While the robustness of patient-reported data collection was a significant strength of the analysis, the difficulties in analysing data from concomitant medications CRF proved to be a non-trivial study limitation. Future trials based in the UK could avoid these issues by ensuring drug names are not entered as free text and instead selected or searched from a pre-specified list corresponding to entries in the BNF; this would minimise errors created by spelling or data entry mistakes and ensure observed drugs can be matched with the price weights needed to estimate medication costs. Furthermore, CRF design could ensure a more consistent way of recording the dosage to let researchers easily identify how many units of a given drug each patient has taken over the study time horizon. The challenge in this patient population (nearly all had at least one co-morbidity), is that most are taking multiple medications.

There are significant limitations in the ICER analysis as described above. There are also challenges when health economics are applied within a palliative context. It is likely that if morphine was a new drug developed for the management of breathlessness, a licence would not be granted based on efficacy, making cost-effectiveness irrelevant. However, in the post-marketing context of morphine being *re-purposed* for use in chronic breathlessness, we estimate that if morphine was implemented for this indication, then, on balance, the use of morphine would improve net health gain from our current NHS budget. However, this does not necessarily mean it is the correct thing to do from a clinical point of view

In conclusion, while the MABEL health economic analysis does not show statistically significant effects of morphine on costs or health outcomes in people with chronic breathlessness, the scenario analysis

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

shows a high probability of cost-effectiveness stemming from small non-statistically significant improvements in health outcomes and cost savings due to lower outpatient and community health resource usage. However, the ICER is difficult to interpret due to the small sample size and effect of a likely random imbalance in deaths, and interpretation should focus on cost consequences analysis. Despite these limitations, this study presents high-quality clinical trial results, contributes to the health-economic literature on morphine and breathlessness, and provides robust estimates that can be used in future economic modelling.

STUDY DETAILS

List of tables and figures

- Table 1: MABEL HRU Unit Costs
- Table 2: Baseline Characteristics
- Table 3: Health Resource Use by Study Group
- Table 4: Summary Statistics
- Table 5: Summary of Cost-Effectiveness Results
- Figure 1: Mortality over Time by Study Group
- Figure 2: Cost-Effectiveness Plane
- Figure 3: Probability of Cost-Effectiveness
- Supplementary Table 1: CHEERS (2022) Checklist
- Supplementary Table 2: Percentage of Patients with Missing Data (Excl. Concomitant Medications)
- Supplementary Table 3: Unique Concomitant Medication Entries by Category
- Supplementary Figure 1: MABEL CONSORT Diagram
- Supplementary Figure 2: Value of Information Analysis: Expected Value of Perfect Information

Word count

Word count (excluding the Title, Abstract, Article Summary, Study Details, References, tables, and figures): 3402

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Trial details

Trial registration ID: ISRCTN87329095

EudraCT number: 2019-002479-33

Recruitment dates: 01/03/2021 (start) - 31/10/2023 (end)

Sources of funding

This study is funded by the NIHR [HTA Project: 17/34/01]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Author contributions

Atter M (MA): conceptualisation, methodology, validation, formal analysis, data curation, data verification, data interpretation, writing (original draft), writing (review, critical input and editing), visualisation, software

Hall PS (PSH): conceptualisation, methodology, validation, funding acquisition, data curation, data verification, data interpretation, writing (review, critical input and editing), supervision; PSH acted as guarantor

Evans RA (RAE): contributions to clinical paper needed for the health economic analysis (data interpretation, writing, visualisation)

Norrie J (JN): funding acquisition, supervision

Cohen J (JC): funding acquisition, supervision, project administration

Williams B (BW): data curation, supervision, project administration

Chaudhuri N (CN): funding acquisition, data interpretation, writing (review, critical input, and editing)

Bajwah S (SB): funding acquisition, data interpretation

Higginson IJ (IJH): funding acquisition, data interpretation

Pearson M (PM): funding acquisition, data interpretation

Currow DC (DCC): funding acquisition, data interpretation, writing (review, critical input, and editing)

Stewart G (GS): patient recruitment

Fallon MT (MTF): conceptualisation, methodology, validation, funding acquisition, data interpretation, writing (review, critical input and editing), supervision, project administration

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Johnson MJ (MJJ): conceptualisation, methodology, validation, funding acquisition, data curation, data verification, data interpretation, writing (review, critical input, and editing), supervision, project administration

Data sharing

Data supporting this work are available upon reasonable request. Relevant stakeholders will review all requests based on the principles of a controlled access approach. Requests to access anonymised data should be made to *hhtuenquiries@hyms.ac.uk*.

Acknowledgements

We thank the NIHR Research Delivery Network for their support of the study. Our thanks go to many individuals and organisations who contributed to this research (full list is included in the clinical paper's supplementary material). [8]

Conflicts of interest

MA declares no conflict of interest. MJJ reports grants from National Institute for Health and Care Research (NIHR). MTF reports grants from NIHR and is on the Pfizer Steering Committee and Ananda Advisory Board. IJH reports grants from the European Union, Marie Curie Cancer Care, and NIHR, and is Scientific Director of Cicely Saunders International, NIHR Emeritus Senior Investigator, and is an Honorary Clinical Consultant in Palliative Medicine for hospitals under Kings College Hospital National Health Service Foundation Trust outside of the submitted work. DCC reports personal fees from Mayne Pharma International. JN is the Chair of the NIHR EME Funding Panel. PSH reports Institutional research funding from Lilly, Eisai, Novartis, Gilead, Sanofi, Roche, AstraZeneca, Novartis, DxCover, Abbvie, MSD and SeaGen unrelated to the work. RAE reports grants from IHR, UKRI, Wolfson Foundation, and Genentec/Roche, consulting fees from AstraZeneca/Evidera for long COVID, speaker fees from Moderna, and is the European Respiratory Society Group 01.02 Pulmonary Rehabilitation and Chronic Care Chair and ATS Pulmonary Rehabilitation Assembly Chair.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

REFERENCES

1. Kochovska S, Ferreira D, Chang S, Brunelli V, Morgan D, Similowski T, et al. Disability and long-term breathlessness: a cross-sectional, population study. BMJ Open Respir Res. 2024 Jul 22;11(1):e002029.

2. Moens K, Higginson IJ, Harding R, EURO IMPACT. Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. J Pain Symptom Manage. 2014 Oct;48(4):660–77.

3. Currow DC, Plummer JL, Crockett A, Abernethy AP. A community population survey of prevalence and severity of dyspnea in adults. J Pain Symptom Manage. 2009 Oct;38(4):533–45.

4. Kochovska S, Iyer R, Chang S, Ferreira D, Brunelli VN, Kinchin I, et al. Prevalence, severity and impacts of breathlessness in Indian adults: An exploratory, nationally representative, cross-sectional online survey. PLOS Glob Public Health. 2024;4(5):e0002655.

5. Currow DC, Dal Grande E, Ferreira D, Johnson MJ, McCaffrey N, Ekström M. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. Thorax. 2017 Dec;72(12):1151–3.

6. Currow DC, Chang S, Ekström M, Hutchinson A, Luckett T, Kochovska S, et al. Health service utilisation associated with chronic breathlessness: random population sample. ERJ Open Res. 2021 Oct 11;7(4):00415–2021.

7. Verberkt CA, van den Beuken-van Everdingen MHJ, Dirksen CD, Schols JMGA, Wouters EFM, Janssen DJA. Cost-effectiveness of sustained-release morphine for refractory breathlessness in COPD: A randomized clinical trial. Respir Med. 2021 Apr;179:106330.

8. Johnson M, Evans R, Keerie C, Tuck S, Norrie J, Cohen J, et al. Effectiveness and cost effectiveness of low dose oral modified release morphine versus placebo on patient-reported worst breathlessness in people with chronic breathlessness: a multi-site, parallel group, double-blind, randomised, placebo-controlled trial (MABEL) [Unpublished Manuscript] 2024.

9. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002 Mar 1;21(2):271–92.

10. Canaway A, Al-Janabi H, Kinghorn P, Bailey C, Coast J. Development of a measure (ICECAP-Close Person Measure) through qualitative methods to capture the benefits of end-of-life care to those close to the dying for use in economic evaluation. Palliat Med. 2017 Jan;31(1):53–62.

11. EuroQoL. EQ-5D-5L [Internet]. EuroQol. [cited 2024 Dec 3]. Available from: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/

12. The University of Edinburgh. UK Cancer Costs Questionnaire [Internet]. [cited 2024 Aug 23]. Available from: https://blogs.ed.ac.uk/ukcc/

13. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement:

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Updated Reporting Guidance for Health Economic Evaluations. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2022 Jan;25(1):3–9.

14. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [Internet]. London; 2022 [cited 2024 Apr 4]. (NICE process and methods [PMG36]). Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

15. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England [Internet]. NICE. NICE; [cited 2024 Jan 3]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l

16. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Policy Res Unit Econ Eval Health Care Interv [Internet]. 2020 [cited 2024 Feb 21]; Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/estimating-the-relationship-betweenE-Q-5D-5L-and-EQ-5D-3L.pdf

17. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005 May;14(5):487–96.

18. Huynh E, Coast J, Rose J, Kinghorn P, Flynn T. Values for the ICECAP-Supportive Care Measure (ICECAP-SCM) for use in economic evaluation at end of life. Soc Sci Med. 2017 Sep 1;189:114–28.

19. QualityMetric. Health Surveys [Internet]. We Measure Health. [cited 2024 Jan 24]. Available from: https://www.qualitymetric.com/health-surveys/

20. British National Formulary (BNF) [Internet]. 2024 [cited 2024 Aug 26]. Available from: https://bnf.nice.org.uk/

21. National Health Service (UK). National Cost Collection: National schedule of NHS costs - Year 2021/22 - NHS trusts and NHS foundation trusts [Internet]. [cited 2023 Dec 12]. Available from: https://www.england.nhs.uk/wp-content/uploads/2023/04/2_National_schedule_of_NHS_costs_FY21-22_v3.xlsx

22. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2023 Manual [Internet]. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2024 [cited 2024 May 14]. Available from: https://doi.org/10.22024/UniKent/01.02.105685

23. Hippel PT von, Bartlett JW. Maximum Likelihood Multiple Imputation: Faster Imputations and Consistent Standard Errors Without Posterior Draws. Stat Sci. 2021 Aug;36(3):400–20.

24. The R Foundation. R: The R Project for Statistical Computing [Internet]. [cited 2024 Jan 4]. Available from: https://www.r-project.org/

25. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? J Health Econ. 2001 Jul;20(4):461–94.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011 Feb 20;30(4):377–99.

27. Fox J, Weisberg S, Price B, Adler D, Bates D, Baud-Bovy G, et al. car: Companion to Applied Regression [Internet]. 2024 [cited 2025 Jan 14]. Available from: https://cran.r-project.org/web/packages/car/index.html

28. Bajwah S, Davies JM, Tanash H, Currow DC, Oluyase AO, Ekström M. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. Eur Respir J. 2018 Dec;52(6):1801278.

29. Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. BMJ. 2014 Jan 30;348:g445.

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

SUPPLEMENTARY MATERIALS

Supplementary Table 1: CHEERS (2022) Checklist

Item	Topic	Page	Section
	Title		
1	Title	1	[Title]
	Abstract		
2	Abstract	1	Abstract
	Introduction		
3	Background and objectives	2	Introduction
	Methods		
4	Health economic analysis plan	3	Methods for the economic
5	Study population	3	Trial overview
6	Setting and location	3	Trial overview
7	Comparators	3	Trial overview
8	Perspective	3	Methods for the economic
9	Time horizon	4	Data collection
10	Discount rate	4	Data collection
11	Selection of outcomes	4	Estimating outcomes
12	Measurement of outcomes	4	Estimating outcomes
13	Valuation of outcomes	4	Estimating outcomes
14	Measurement and valuation of resources and costs	4	Estimating costs
15	Currency, price date, and conversion	4	Estimating costs
16	Rationale and description of model	6	Analysis
17	Analytics and assumptions	6	Analysis
18	Characterizing heterogeneity	6	Analysis
19	Characterizing distributional effects	6	Analysis
20	Characterizing uncertainty	6	Analysis
21	Approach to engagement with patients and others affected by the study	7	Patient and public engagement
	Results		
22	Study parameters	10	Regression analysis results
23	Summary of main results	10	Regression analysis results
24	Effect of uncertainty	10	Regression analysis results
25	Effect of engagement with patients and others affected by the study	7	Patient and public engagement
	Discussion		
26	Study findings, limitations, generalizability, and current knowledge	13	Discussion
	Other relevant information		
27	Source of funding	16	Sources of funding
28	Conflicts of interest	17	Conflicts of interest

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Supplementary Table 2: Percentage of Patients with Missing Data (Excl. Concomitant Medications)

Variable	Placebo	Morphine
Health Outcomes		
EQ-5D-5L Health Utility (baseline)	0%	0%
EQ-5D-5L Health Utility (day 28)	9%	12%
EQ-5D-5L Health Utility (day 56)	10%	18%
ICECAP (baseline)	0%	0%
ICECAP (day 28)	9%	12%
ICECAP (day 56)	10%	18%
SF12 6D (baseline)	0%	0%
SF12 6D (day 28)	9%	15%
SF12 6D (day 56)	10%	19%
Change in EQ-5D-5L Utility	10%	18%
Change in SF12-6D Score	10%	19%
Change in ICECAP Score	10%	18%
QALYs	12%	15%
Costs (56 days)		
Morphine Costs	1%	1%
Laxative Costs	1%	1%
Causal SAE Costs	0%	0%
Inpatient Stay (nights)	13%	18%
Emergency Assessment (attendances)	13%	18%
Hospital Consultant/Doctor (attendances)	13%	18%
Specialist Nurse (attendances)	13%	18%
Physiotherapist (attendances)	13%	18%
Dietician (attendances)	13%	18%
Occupational Therapy (attendances)	13%	18%
Social Worker (attendances)	13%	18%
Other Outpatient (attendances)	13%	18%
Hospital Consultant/Doctor (phone calls)	13%	18%
Specialist Nurse (phone calls)	13%	18%
Administrator/Secretary (phone calls)	13%	18%
Hospice Inpatient Stay (nights)	13%	18%
Hospice Doctor (attendances)	13%	18%
Hospice Nurse (attendances)	13%	18%
Day Hospice (attendances)	13%	18%
Other Professional (attendances)	15%	18%
Hospice Consultant/Doctor (phone calls)	13%	18%
Hospice Specialist Nurse (phone calls)	13%	18%
Hospice Administrator/Secretary (phone calls)	13%	18%
Total Hospital Costs	13%	18%

medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Variable	Placebo	Morphine
Total Community Costs	15%	18%
Total Medication Costs (IMP + NIMP)	1%	1%
Concomitant Medications	0%	0%
Total Costs	15%	18%
Total Costs (non-causal SAE admissions removed)	15%	18%

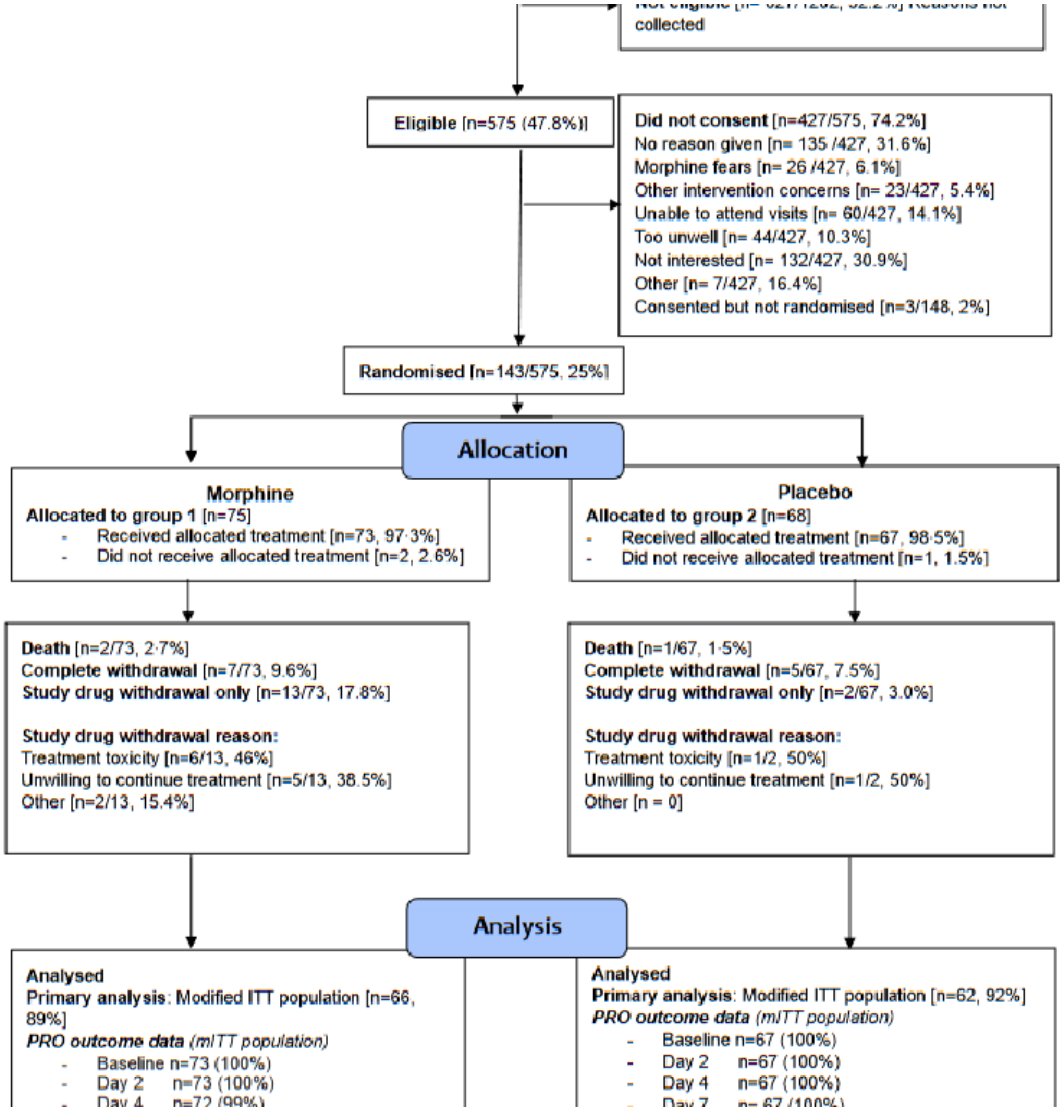
Supplementary Table 3: Unique Concomitant Medication Entries by Category

Category	Total Entries		Receiving Patients, n (%)	
	Placebo (n=67)	Morphine (n=73)	Placebo (n=67)	Morphine (n=73)
analgesic	64	78	38 (57%)	43 (59%)
antidepressant	9	9	9 (13%)	9 (12%)
antiemetic	3	5	3 (4%)	5 (7%)
anxiolytic	9	6	8 (12%)	6 (8%)
corticosteroid	44	50	24 (36%)	31 (42%)
inhaler	44	52	33 (49%)	37 (51%)
laxative	12	30	8 (12%)	22 (30%)
other (excluded)	640	709	67 (100%)	73 (100%)

'other' consists of concomitant medication categories judged as not relevant to the trial intervention and excluded from cost-effectiveness analysis; 'total entries' refers to the number of times a drug within a given category has been recorded in the concomitant medications data; 'receiving patients' refers to the number (and share) of patients who have received a given a drug within a given category during the study period.

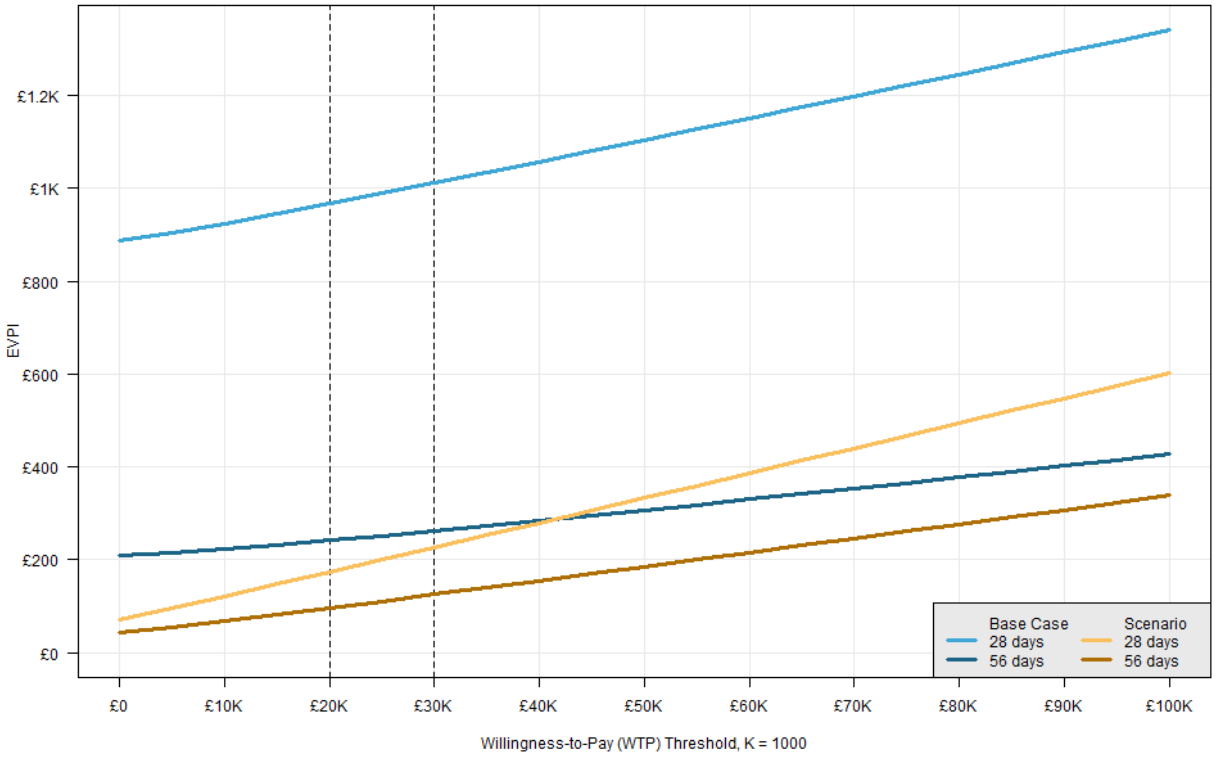
medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

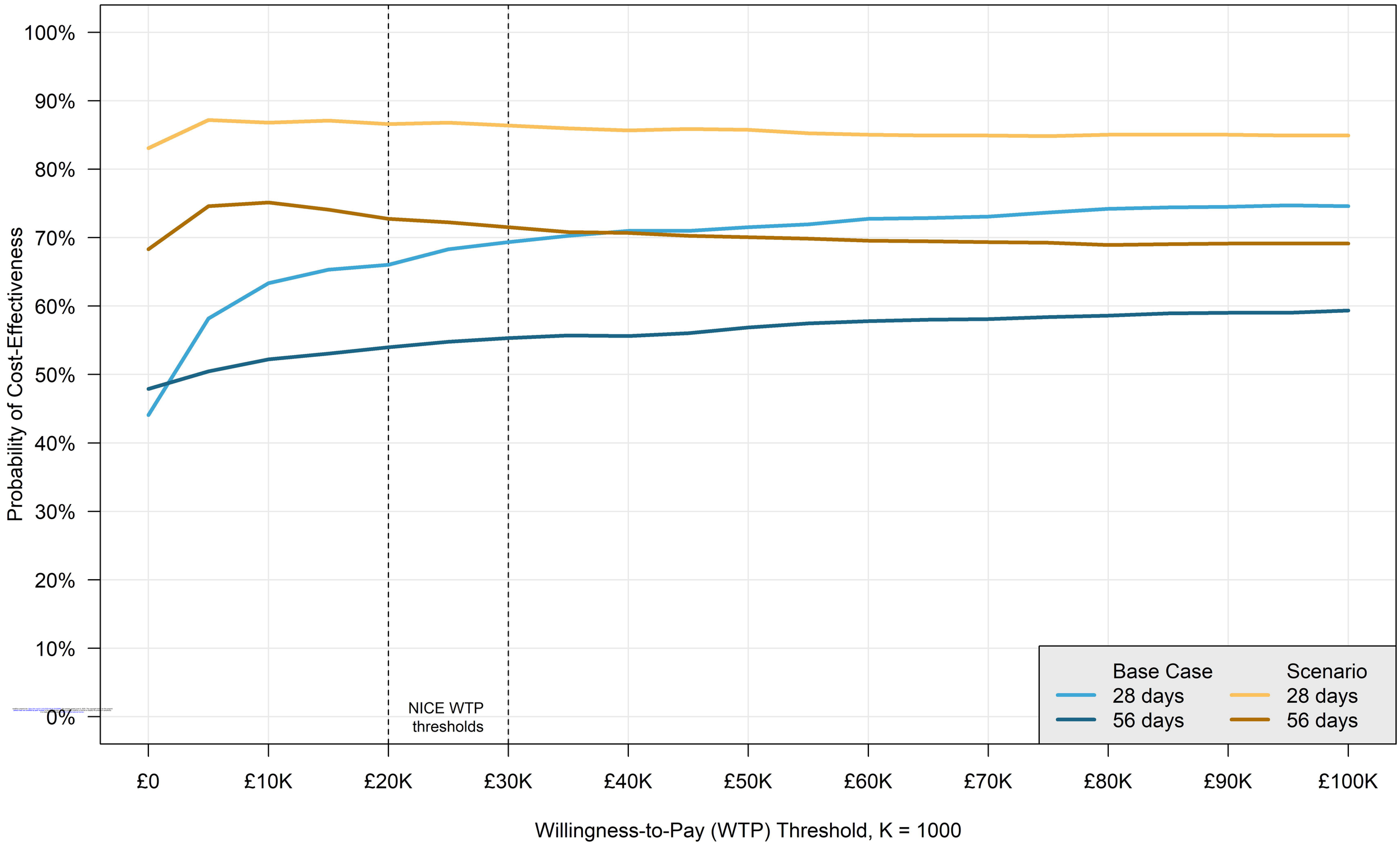
Supplementary Figure 1: MABEL CONSORT Diagram

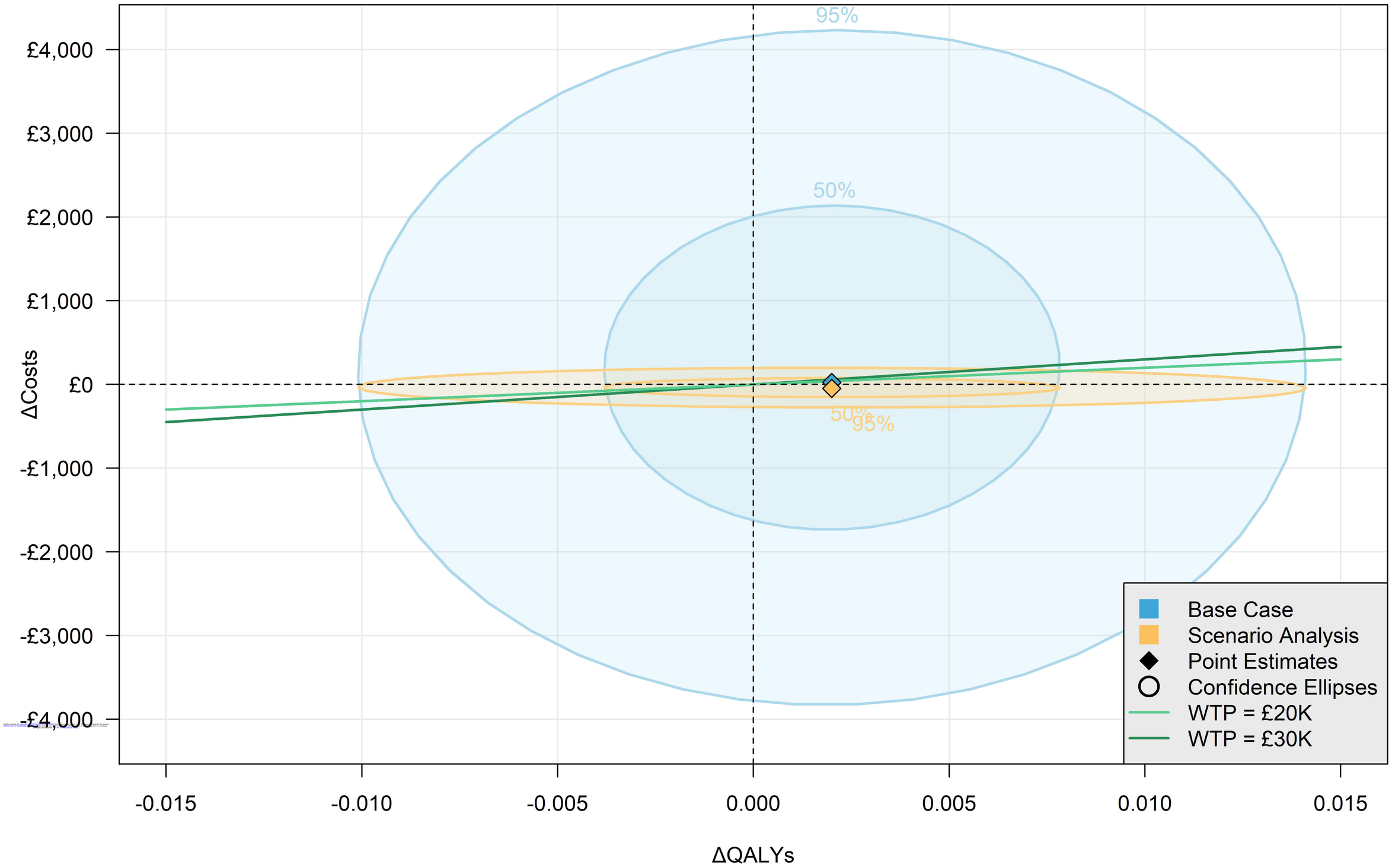


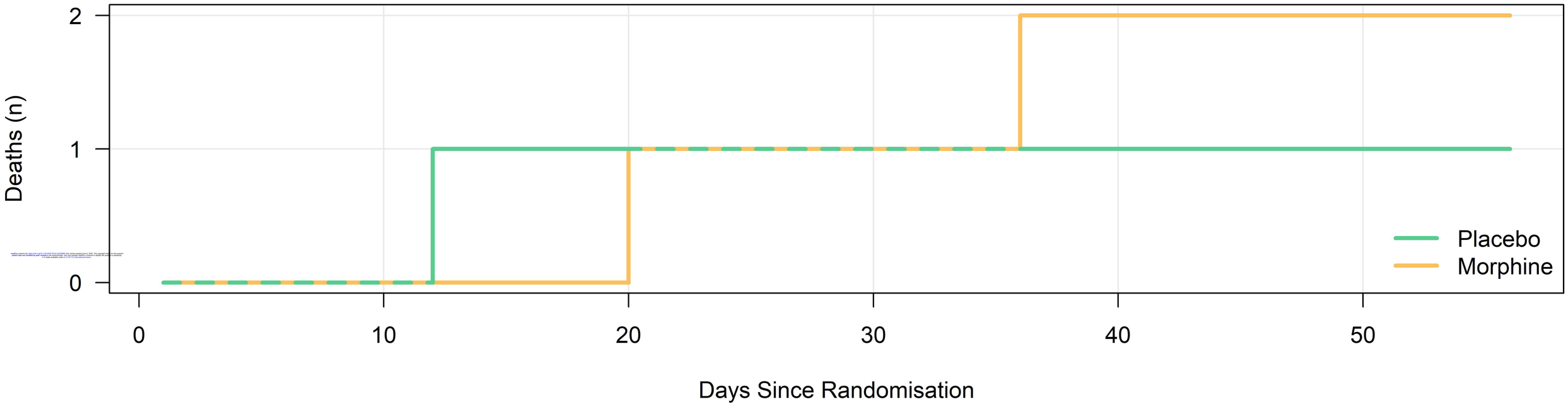
medRxiv preprint doi: https://doi.org/10.1101/2025.06.04.25328980; this version posted June 5, 2025. The copyright holder for this preprint **(which was not certified by peer review)** is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY 4.0 International license .

Supplementary Figure 2: Value of Information Analysis: Expected Value of Perfect Information




100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Probability of Cost-Effectiveness
NICE WTP
thresholds
Base Case
28 days
56 days
Scenario
28 days
56 days
£0
£10K
£20K
£30K
£40K
£50K
£60K
£70K
£80K
£90K
£100K
Willingness-to-Pay (WTP) Threshold, K = 1000


95%
50%
50%
95%
£4,000
£3,000
£2,000
£1,000
£0
-£1,000
-£2,000
-£3,000
-£4,000
ΔCosts
-0.015
-0.010
-0.005
0.000
0.005
0.010
0.015
ΔQALYs
Base Case
Scenario Analysis
Point Estimates
Confidence Ellipses
WTP = £20K
WTP = £30K



medRxiv preprint doi: https://doi.org/10.1101/2020.06.04.20120840; this version posted June 5, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-4.0 International license.