Modified-release morphine or placebo for chronic breathlessness: the MABEL trial protocol

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Shareable abstract (@ERSpublications)
Guidelines support morphine for breathlessness but scarce data exist for >7 days use. This RCT will test the effectiveness (worst breathlessness in 24 h) of 10–20 mg daily oral modified-release morphine or placebo on chronic breathlessness over 28 days. https://bit.ly/3ImbSZ3

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Abstract

Chronic breathlessness, a persistent and disabling symptom despite optimal treatment of underlying causes, is a frightening symptom with serious and widespread impact on patients and their carers. Clinical guidelines support the use of morphine for the relief of chronic breathlessness in common long-term conditions, but questions remain around clinical effectiveness, safety and longer term (>7 days) administration. This trial will evaluate the effectiveness of low-dose oral modified-release morphine in chronic breathlessness.

This is a multicentre, parallel group, double-blind, randomised, placebo-controlled trial. Participants (n=158) will be opioid-naïve with chronic breathlessness due to heart or lung disease, cancer or post-coronavirus disease 2019. Participants will be randomised 1:1 to 5 mg oral modified-release morphine/placebo twice daily and docusate/placebo 100 mg twice daily for 56 days. Non-responders at Day 7 will dose escalate to 10 mg morphine/placebo twice daily at Day 15.

The primary end-point (Day 28) measure will be worst breathlessness severity (previous 24 h). Secondary outcome measures include worst cough, distress, pain, functional status, physical activity, quality of life, and early identification and management of morphine-related side-effects. At Day 56, participants may opt to take open-label, oral modified-release morphine as part of usual care and complete quarterly breathlessness and toxicity questionnaires.

The study is powered to be able to reject the null hypothesis and an embedded normalisation process theory-informed qualitative substudy will explore the adoption of morphine as a first-line pharmacological treatment for chronic breathlessness in clinical practice if effective.

Introduction

Chronic, or persistent, breathlessness, defined as persistent disabling breathlessness despite optimal treatment of the underlying pathophysiology [1], is frightening, worsens with disease progression, and is associated with poor quality of life, physical and psychosocial limitations, and high health service utilisation [2–5]. It is prevalent in chronic progressive illnesses, affecting nearly everyone with advanced lung cancer [6], non-malignant chronic lung disease [7, 8] and heart failure [9]. Non-pharmacological interventions for breathlessness form the bedrock of management, but there is an emerging evidence base for morphine [10–13].

Opioids are thought to modify breathlessness perception in brain areas rich in opioid receptors [14], reducing subjective sensation [15]. Previous meta-analyses of placebo-controlled randomised controlled trials (RCTs) showed evidence of benefit with opioid use [10–13]. The most recent demonstrated a clinically significant reduction for breathlessness (standardised mean difference −0.32, 95% CI −0.18–−0.47) [13]. However, studies were small with a maximum 7-day duration. Two subsequent phase 3 RCTs (20 mg morphine *versus* placebo) showed no benefit for breathlessness [16, 17] at 7 days, but interpretation of results was hindered in the 2020 RCT by the inclusion of less severely breathless participants (modified Medical Research Council (mMRC) breathlessness scale 2) and allowable "as-needed" immediate-release morphine in both arms [16], and in the 2022 RCT by the lack of standardised exercise testing [17, 18]. Of note, an exploratory substudy of the 2022 RCT showed a signal of benefit regarding increased level of physical activity and active calories in the morphine arms [19].

The only adequately powered phase 3 trial with a primary end-point of 4 weeks, the MORphine for DYspnea in COPD (MORDYC) RCT [20], demonstrated significant improvement in disease-specific health status in people with COPD receiving 10 mg oral sustained-release morphine twice daily for 4 weeks, with an optional dose escalation to 3 times daily. There was no difference in breathlessness, but a subgroup analysis of participants with mMRC 3 and 4 showed a 1.33-point greater improvement in worst breathlessness in the morphine group. A 3-month placebo-controlled RCT in heart failure closed early due to slow recruitment (n=45) and was underpowered to demonstrate effect [21]. However, a signal suggesting benefit was seen and morphine had an acceptable safety profile.

The safety and harm profile of low-dose morphine is well described; persisting clinician concerns appear to be unfounded. A systematic review and meta-analysis found no evidence of clinically relevant respiratory adverse effects [22]. Longer term observational studies of people with advanced COPD and advanced interstitial lung disease patients found no association between low-dose opioids and hospital admissions or mortality [23, 24]. A dose-finding and pharmacovigilance study demonstrated benefit in two-thirds of patients taking 10, 20 or 30 mg daily, with no evidence of tachyphylaxis or tolerance during up to 22 months follow-up [25]. A large Canadian population-based COPD study showed a small absolute excess in respiratory adverse events (AEs) within 30 days of opioid prescription [26]. However, causality cannot be ascribed and no details about reasons for opioid initiation, the overall point of opioid initiation on the disease trajectory or the subjects' respiratory function were given.

Despite international clinical practice guideline recommendations and policy statements [27, 28], safety and effectiveness uncertainties remain, with variable implementation into clinical practice [15]. The current evidence base supports short-term, regular, low-dose, modified-release morphine as safe and efficacious, but there are scarce data regarding longer term use or characteristics which predict benefit. The Morphine And BrEathLessness (MABEL) study aims to evaluate clinical effectiveness, safety and long-term effects.

Methods and analysis

Study design

This is a multicentre, parallel group, randomised, double-blind, placebo-controlled trial with an embedded normalisation process theory (NPT)-based substudy and a Study Within A Trial (SWAT).

Participants will be randomised 1:1 to receive 5 mg oral modified-release morphine/placebo twice daily. Laxative (docusate)/placebo will be given as a non-investigational medicinal product (non-IMP) to manage constipation, an almost universal morphine-related side-effect.

Study objectives

The primary objective is to evaluate the effect of low-dose oral modified-release morphine on worst breathlessness over the previous 24 h at 28 days.

The secondary objectives are to: 1) assess the benefit of modified-release morphine on placebo-controlled net effects (benefit in the context of harms) in the longer term (beyond 7 days) with blinded side-effect data up to 2 months; 2) assess the net benefit in the study population, extending the study population beyond COPD; 3) ascertain the net effect on changes in physical activity; 4) determine the impact on health service use, especially hospital inpatient days; 5) examine cost-effectiveness; 6) identify influences affecting trial equipoise and to develop a clinical process for safe prescribing and monitoring of morphine in specialist and generalist settings; 7) identify informal carer burden and bereavement (if relevant); and 8) explore i) predictor characteristics of net benefit, ii) benefits on those participating in pulmonary rehabilitation, and iii) proportions of participants requiring dose escalation and those choosing ongoing open-label morphine.

Study population

Eligible patients will be consenting adults (n=158; 14 UK centres) with moderate to severe chronic breathlessness (mMRC 3 or 4) despite optimal management of underlying disease(s). Use of opioid medications >5 mg morphine-equivalent daily for >7 out of the last 14 days is not permitted. See table 1 for a list of eligibility criteria.

Study recruitment

Patients will be identified, approached and provided with study information by a usual clinical care team member. Once eligibility is confirmed, informed consent will be taken by a study doctor or sponsor-approved registered independent prescriber prior to baseline data collection. In addition to face-to-face consent at the clinic or in the patient's home, coronavirus disease 2019 adaptations to study design permit remote electronic or postal consent by phone or video. Participants will be enrolled in the web-based study database (REDCap Cloud (RCC); www.redcapcloud.com). A unique sequential subject ID number will be generated for each participant.

Randomisation

Participants will be randomised (1:1, random permuted blocks) using the RCC system to 5 mg morphine or placebo, stratified by causal disease and site. Site pharmacies will be notified of blinded randomisation allocation (Group A or B) using an access-restricted case report form (CRF).

Study IMP/non-IMP

All participants will start on 5 mg twice-daily oral modified-release morphine sulfate (MST Continus)/placebo and 100 mg twice-daily oral docusate sodium/placebo. Day 1 denotes the first day of trial IMP administration. At Day 7, a dose-escalation decision will be made.

Blinding

IMP and non-IMP, and corresponding placebo capsules, will be over-encapsulated with identical taste, smell and consistency. The 5 mg morphine/placebo, 10 mg morphine/placebo and non-IMP/placebo

TABLE 1 Eligibility criteria

Inclusion criteria
1) Ambulant people with chronic breathlessness due to cardiac disease, respiratory disease, post-coronavirus disease 2019 chronic breathlessness or cancer
2) Modified Medical Research Council breathlessness scale grade 3 or 4
3) Male or female aged ⩾18 years
4) Management of the underlying condition unchanged for the previous 7 days
5) Australia-modified Karnofsky Performance Scale ⩾40
6) Estimated glomerular filtration rate ⩾25 mL·min^{-1}·1.73 m^{-2}, unless the primary diagnosis is heart failure (⩾30 mL·min^{-1}·1.73 m^{-2}) within 21 days of consent
7) If female and of childbearing potential, must agree to use adequate contraception when taking the IMP and for 7 days following cessation
8) Able to complete questionnaires and trial assessments
9) Able to provide written informed consent
Exclusion criteria
1) Unable to provide informed consent
2) Unable to complete baseline study questionnaires even with the assistance of the study nurse
3) Have coexisting malignant disease only if this would affect the study in the investigators' opinion
4) Have used opioid medications >5 mg morphine-equivalent daily for >7 out of the last 14 days
5) Have known true morphine or docusate allergies or hypersensitivity to any of the tablet constituents as assessed by a clinician
6) Have known central hypoventilation syndrome (*e.g.* Ondine's curse post-stroke)
7) Have been involved in another clinical trial of an IMP within the past 28 days
8) Are pregnant or lactating
9) Have respiratory depression, head injury, paralytic ileus, "acute abdomen" or acute hepatic disease
10) Have concurrent administration of monoamine oxidase inhibitors or are within 14 days of discontinuation of their use
11) Are within the first 24 h post-operatively
12) Are taking >20 mg diazepam-equivalent per day or are unable to reduce dose before randomisation to <20 mg·day^{-1} for the duration of the study treatment period
13) Cannot/do not wish to take gelatine (used as a medication encapsulation ingredient)

IMP: investigational medicinal product.

capsules will be coloured differently and supplied in identical, tamper-evident, child-resistant bottles of 28 capsules with a unique kit number. Participants will be advised to swallow the capsules whole.

Study procedures

The trial procedures are outlined in figure 1.

The study includes two face-to-face visits (baseline and Day 28) for vital signs data collection at either the clinic or participants' homes. All other visits can be completed by phone or video call.

The total dosing study period is 56 days. The dose may be escalated to 10 mg twice-daily oral morphine/placebo in non-responders (Day 15) until the study end. Participants not achieving a clinically meaningful

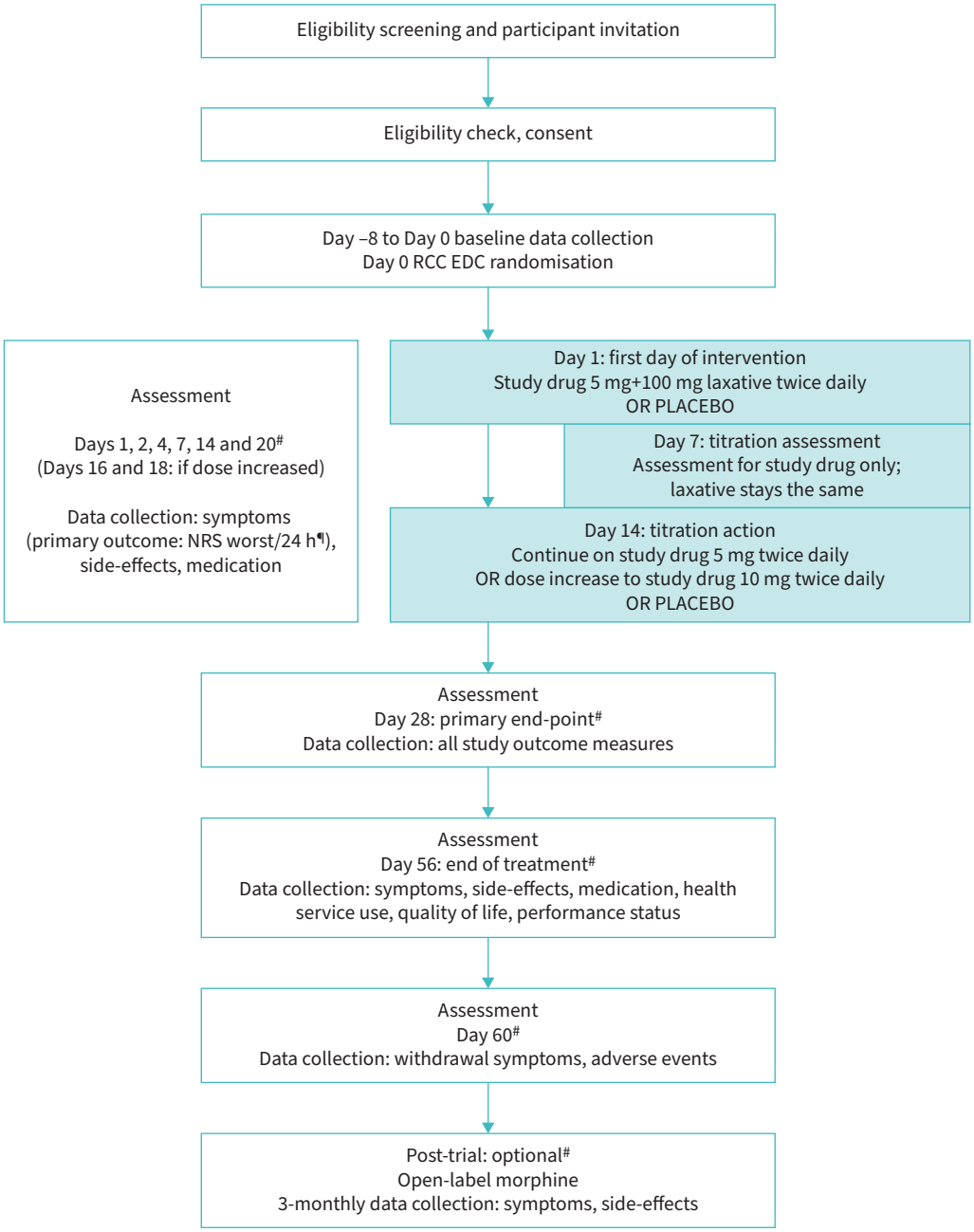

FIGURE 1 Participant study flowchart. #: for details of data collection, see study schedule of events (table 2); ¶: numerical rating scale (NRS) worst breathlessness over the previous 24 h. RCC: REDCap Cloud; EDC: electronic data capture.

TABLE 2 Schedule of events

Assessments	Baseline[#]	Day 2	Day 4	Day 7	Day 14	Day 16	Day 18	Day 20	Day 28	Day 42	Day 56	Day 60	Follow-up
Primary outcome													
Breathlessness severity: NRS worst/previous 24 h	X	X	X	X	X	X	X	X	X		X		X
Secondary outcomes													
Distress due to breathlessness: NRS/previous 24 h	X			X	X			X	X		X		X
Average pain: NRS/previous 24 h	X			X					X		X		
Severity of cough: NRS/previous 24 h	X			X					X		X		
Daytime sleepiness: Epworth Sleepiness Scale	X								X		X		
Functional status: Australia-modified Karnofsky Performance Status	X								X		X		
Physical activity: ActiGraph	X							X	X				
Quality of life questionnaires: SF-12, EQ-5D-5L	X								X		X		
Health economics questionnaires: ICECAP-SCM, Health Resource Utilisation Questionnaire	X								X		X		
IMP-related side-effects													
Gastrointestinal (constipation, nausea, vomiting) and neurocognitive (confusion, cognitive impairment, hallucinations, memory impairment)	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleepiness: Karolinska Sleepiness Scale	X	X	X	X	X	X	X	X	X		X		
Onset of vivid dreams	X	X	X	X	X	X	X	X	X	X	X		X
Cognitive function: St Louis University Mental Status Examination	X								X				
Opioid withdrawal: Subjective Opiate Withdrawal Scale												X	
Carer burden questionnaire: Zarit Burden Interview-12	X				X				X		X		
Impact on bereavement: VOICES-Short Form (for bereaved carers only)													X
Other outcome measures													
Blood pressure, pulse, respiratory rate, pulse oximetry, transcutaneous carbon dioxide	X								X				
Concomitant medications (including oxygen)	X			X	X			X	X		X		
Morphine (IMP)/docusate (non-IMP) compliance		X	X	X	X	X	X	X	X	X	X		
Morphine (IMP)/docusate (non-IMP) accountability					X					X	X		
Additional baseline measures													
Demographics (age, sex, ethnicity)	X												
Medical history: comorbidity checklist	X												
BMI	X												
Disease stage	X												
eGFR	X												
Breathlessness impact: mMRC breathlessness scale	X												

[#]: Day −8 to Day 0. NRS: numerical rating scale; SF-12: 12-item Short-Form Health Survey; ICECAP-SCM: ICECAP Supportive Care Measure; IMP: investigational medicinal product; BMI: body mass index; eGFR: estimated glomerular filtration rate; mMRC: modified Medical Research Council.

improvement by Day 7 (a reduction of ⩾1 numerical rating scale (NRS) points [29]) and with acceptable side-effects will dose escalate. Participants with unacceptable side-effects despite clinical management will stay on 5 mg morphine/placebo or withdraw from study medication. IMP/placebo and non-IMP/placebo "holidays" are permitted, for side-effect management, but dosing should be reinstated when/if clinically indicated. See table 3 for acceptable side-effects.

After Day 56, participants will be offered open-label morphine and laxative under the responsibility of their routine clinical care team or general practitioner. They can also opt to provide longer term quarterly follow-up data focusing on minimum benefit and harm data until the last participant has completed the Day 56 visit. Provision of data and open-label morphine are irrespective of each other. Those who opt to do both should start this within 14 days of Day 56.

Safety considerations and AE reporting

AE reporting focuses on early recognition of known morphine-related side-effects or treatment-emergent AEs, with thresholds for triggering AE reporting. Neurocognitive disturbance (cognition, memory, hallucinations, Common Terminology Criteria for Adverse Events (CTCAE) grade ⩾1; vivid dreams new or worse since baseline; somnolence ⩾8 on the Karolinska Sleepiness Scale (KSS)) or gastrointestinal effects (constipation, nausea, vomiting) with CTCAE grade ⩾2 will be reported as AEs. Grade 3 events not improving with management, or grade 4 events, will necessitate withdrawal of the IMP.

Carers

Participants will be invited to nominate an informal carer (family member/friend) to participate. Consenting carers will complete questionnaires on carer burden.

Study outcomes and additional baseline measures

The schedule of events is detailed in table 2.

Primary outcome

The primary outcome is patient-rated intensity of worst breathlessness over the previous 24 h, at Days 2, 4, 7, 14, (Days 16 and 18 where appropriate), 20 and 28 using a validated 11-point (0–10) NRS, where 0=no breathlessness and 10=worst imaginable breathlessness [30]; more likely than "average breathlessness" on the Chronic Respiratory Questionnaire Dyspnoea domain to demonstrate change [31] and avoiding concerns about "peak-end" bias observed in average estimates of breathlessness [32, 33]. The primary end-point is Day 28, consistent with longer term morphine trials [20, 21], to allow treatment-emergent harms to resolve [34], physical activity benefits to emerge and maximum benefit from any dose escalation on Day 14 to be observed [35].

Secondary outcomes

Secondary outcomes will be measured using validated measures at various study time-points (table 2).

Distress due to breathlessness [36], pain intensity and severity of cough will be measured as an average over the previous 24 h using an 11-point (0–10) NRS. The Epworth Sleepiness Scale will assess daytime sleepiness [37] and screen for sleep disordered breathing. Functional status will be measured using the Australia-modified Karnofsky Performance Scale [38] at baseline (Day −8 to Day 0), primary end-point (Day 28) and end of treatment (Day 56); and an ActiGraph activity monitor will measure average step count per 7 days and intensity of physical activity at baseline (Day −8 to Day 0) and the primary end-point

TABLE 3 Acceptable side-effects for the purposes of the MABEL trial

No side-effects (all CTCAE grade 0)
Or all of the following are met:
New or worse-than-baseline gastrointestinal effects are acceptable (nausea, vomiting, constipation, CTCAE grade <2)
Neurocognitive effects are acceptable (cognitive, memory, hallucinations, CTCAE grade 0) and no vivid dreams (CTCAE grade 1 symptoms acceptable if present at same grade at baseline)
Ongoing side-effect management and monitoring
Clinician and participant happy to continue or increase the investigational medicinal product as appropriate

CTCAE: Common Terminology Criteria for Adverse Events.

(Day 20 to Day 28). The 12-item Short-Form Health Survey (SF-12) will measure generic health-related quality of life [39] and EuroQol EQ-5D-5L will measure health status [40].

The economic evaluation will take the form of a cost-consequence analysis and include data from the SF-12 (SF-6D) and EQ-5D-5L to generate health utility scores to estimate quality-adjusted life years (QALYs). The ICECAP Supportive Care Measure (ICECAP-SCM), specifically developed to aid economic evaluation in supportive and palliative care settings [41], will be used to estimate alternative weights based on a capability framework, subject to the availability of a valuation study. The Health Resource Utilisation Questionnaire, based on an adaptation of the UK Cancer Costs questionnaire (https://blogs.ed.ac.uk/ukcc), will measure health service use.

Participants will be monitored for opioid-related symptoms using a graded toxicity assessment (National Cancer Institute CTCAE version 5.0). Subjective sleepiness will be measured using the KSS [42] and cognitive function assessed using the St Louis University Mental Status Examination [43]. Onset or worsening of vivid dreams since the previous visit will be recorded. Participants will complete the Subjective Opioid Withdrawal Scale 3 days after stopping study treatment [44].

We will explore the perspectives and burden experienced by carers using the Zarit Burden Interview-12 [45]. If a carer is bereaved during the study, they will be asked to complete a VOICES-Short Form questionnaire [46], to explore their views on the quality of care.

Other outcome measures

Concomitant medications will be recorded from medical records and updated at regular intervals throughout the study. Vital signs examination will record resting pulse rate and blood pressure, respiratory rate, pulse oximetry and transcutaneous carbon dioxide (if available). Study medication compliance will be recorded at study visits, and IMP and non-IMP accountability at each dispensing visit.

Additional baseline measures

Demographic characteristics (age, sex, ethnicity), disease stage, mMRC breathlessness score, body mass index, previous medical history and recent estimated glomerular filtration rate result will be recorded from medical records.

Sample size

For 90% power and a 5% level of significance to detect an effect size of 0.4 in the primary outcome of NRS worst breathlessness in the previous 24 h at Day 28, a sample size of 264 participants (132 per group) is required. This effect size denotes a moderate effect and equates to a 1-point change in the NRS, assuming a standard deviation of around 2.5. NRS worst breathlessness will be measured at baseline, Day 2, 4, 7, 14, (16, 18), 20, 28 (primary end-point) and 56. Assuming a correlation of 0.5 between post-randomisation measures, the estimated sample size reduces to 168. Further adjustment for baseline covariates (assuming a correlation with outcome of 0.5) reduces the sample size to 126. Allowing for 20% attrition requires an increase to 158 participants (79 per group).

Statistical analyses

The null hypothesis is that there is no difference in the relief of chronic breathlessness provided by morphine or placebo. Statistical analysis will be performed under the intention-to-treat principle using a 5% two-sided significance level.

The primary analysis uses a repeated measures ANCOVA including terms for treatment and breathlessness measurements. The randomisation stratification variables (site and causal disease) will be included and the model will adjust for baseline NRS worst breathlessness. The model will also include a treatment-by-time interaction. The repeated measures analysis will enable the estimation of a treatment effect at Day 28 (the primary outcome) and also an overall assessment of the treatment effect over the whole 28-day outcome period, taking into consideration NRS worst breathlessness measured across all prespecified time-points.

Secondary outcomes measured at multiple time-points will be analysed using the repeated measures approach described for the primary outcome. Where outcomes are not measured repeatedly, analyses will be undertaken using the appropriate version of the generalised linear model suitable for the distribution of that specific secondary outcome (*e.g.* linear, logistic or count). Outcome definitions will align in the statistical and health economic analyses.

A sensitivity analysis will be conducted in which missing primary outcome data are imputed. The imputation method will be determined at time of analysis, taking into consideration assumptions such as missing at random or missing not at random depending on reasons for loss to follow-up. The imputation method will be model based and shall make use of the stratification variables as part of the imputation model.

Exploratory analyses will be conducted: 1) to explore predictors of breathlessness response (as $\geqslant$1 reduction in breathlessness worst scores from baseline at the primary end-point) including age, worse baseline breathlessness, primary causal disease [47] as well as the impact of toxicities on response; and 2) breathlessness and activity outcomes in participants recruited through pulmonary rehabilitation clinics.

Economic evaluation

Health economic analysis will focus on cost-consequence analysis, describing service utilisation frequencies and mean costs adjusted to a common base-year, alongside primary and secondary end-point consequences. We will assess potential redistribution of resource consumption between provider organisations between trial arms. Cost-effectiveness analysis will present the incremental cost-effectiveness ratio in terms of cost per QALY.

Data management

The main study RCC database will be developed and managed by Hull Health Trials Unit (HHTU; University of Hull, Hull, UK). Paper questionnaire and CRF source data will be entered at site onto RCC. HHTU Data Management will validate and verify checks to monitor data quality and completeness according to a sponsor-approved monitoring plan. RCC data will be exported and transferred to the study statistician at Edinburgh Clinical Trials Unit (University of Edinburgh, Edinburgh, UK) for analysis or Data Management and Ethics Committee (DMEC) reporting in compliance with the General Data Protection Regulation Act (2018).

Qualitative substudy

An embedded mixed-methods substudy will use NPT to understand clinician, patient and carer perspectives of morphine prescription for chronic breathlessness, and explore barriers and enablers of clinical practice implementation [48].

After a short learning needs analysis survey, all clinicians prescribing the study IMP, as well as wider members of site teams, will be invited to undertake online, narrated clinical training on morphine prescribing and side-effect management. After training and at 4 months, they will complete a modified normalisation measurement instrument (NoMAD) survey, to detect changes in perceptions over time [49]. Semistructured interviews will be conducted with a purposive sample of clinicians, patients and carers to explore perspectives surrounding safe morphine use. Main trial and implementation substudy analysis findings will be reported jointly.

SWAT

The SWAT will evaluate the effect of a visual infographic sheet on participant recruitment. Sites will be cluster randomised 1:1 to use the infographic sheet plus standard patient information leaflet (PIL) *versus* a standard PIL only. The primary outcome will be recruitment rate, with secondary outcomes focusing on the proportions of participants screened but not consented and cost-effectiveness of the intervention. Results will contribute to a future meta-analysis with other similar SWAT studies.

Ethics and dissemination

Regulatory approvals and trial oversight

The trial protocol and amendments were approved by the North East – Tyne and Wear South Research Ethics Committee (REC: 19/NE/0284; EudraCT: 2019-002479-33) and by the Medicines and Healthcare Products Regulatory Agency. The sponsor is Hull University Teaching Hospitals NHS Trust (HUTH). HHTU is responsible for study implementation.

A Trial Management Group has been convened to oversee trial delivery and operations. An independent Trial Steering Committee will provide overall trial supervision. A DMEC will monitor progress, review safety and efficacy data, and make recommendations on study conduct, where necessary.

Dissemination

Results will be disseminated in peer-reviewed journals, through local relevant clinical networks, and at national and international meetings in accordance with the MABEL Dissemination and Publications Plan.

The final study report will also be available as a peer-reviewed published manuscript for the *Health Technology Assessment* journal.

Discussion

Existing recommendations, clinical practice guidelines and moderate-level evidence support the use of opioids as a first-line pharmacological treatment for the palliation of chronic breathlessness [13, 27, 28]. The best evidence is for 10–30 mg daily low-dose oral sustained-release morphine in opioid-naïve patients [15], but longer term follow-up data are scarce especially in advanced diseases other than COPD.

The MABEL trial is designed to extend the evidence base in this field, specifically addressing methodological issues in previous trials. A patient population spanning respiratory, cardiology and oncology will provide a broader view of effectiveness in the clinically relevant population (mMRC $\geqslant$3) [16, 20]. Physical activity monitoring is measured and immediate-release morphine use is not permitted. The rigorous side-effect monitoring schedule is key to aiding participant retention, and the inclusion of the online clinical training programme for clinicians may help dispel risk perceptions for both themselves and participants.

Provenance: Submitted article, peer reviewed.

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This study is registered at EudraCT with identifier number 2019-002479-33. It is intended that individual participant data that underlie the results reported in final results papers will be made available for sharing for research purposes after de-identification. Data will not be shared until after completion of the final study report to the funder but will then be available with no end date. Final anonymised clinical trial datasets and metadata will be produced in accordance with participant consent, and stored in an appropriate format to enable discoverability and sharing in the University of Hull's data repository HYDRA. Publications will include data availability statements.

Protocol version: Based on protocol version 1.8, 18 February 2022.

Author contributions: M. Johnson and D. Currow developed the study concept. M. Johnson, M. Fallon, D. Currow, J. Cohen, S. Bajwah, J. Norrie, C. Keerie, M. Pearson, I. Higginson and P. Hall developed the study design. M. Johnson, M. Fallon, D. Currow, J. Cohen, M. Pearson, I. Higginson, P. Hall, S. Bajwah and J. Norrie supported the acquisition of funding. K. Date developed the first draft of the manuscript. All authors contributed to the revisions and approval of the final manuscript.

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References

1 Johnson MJ, Yorke J, Hansen-Flaschen J, *et al.* Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. *Eur Respir J* 2017; 49: 1602277.
2 Currow DC, Dal Grande E, Ferreira D, *et al.* Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. *Thorax* 2017; 72: 1151–1153.
3 Clark J, Chang S, Kinchin I, *et al.* Lower workforce participation is associated with more severe persisting breathlessness. *BMC Pulm Med* 2022; 22: 93.
4 Currow DC, Chang S, Ekström M, *et al.* Health service utilisation associated with chronic breathlessness: random population sample. *ERJ Open Res* 2021; 7: 00415-2021.
5 Hutchinson A, Barclay-Klingle N, Galvin K, *et al.* Living with breathlessness: a systematic literature review and qualitative synthesis. *Eur Respir J* 2018; 51: 1701477.
6 Muers MF, Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax* 1993; 48: 339–343.
7 Moens K, Higginson IJ, Harding R, *et al.* 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; 48: 660–677.
8 Bajwah S, Higginson IJ, Ross JR, *et al.* Specialist palliative care is more than drugs: a retrospective study of ILD patients. *Lung* 2012; 190: 215–220.
9 Nordgren L, Sörensen S. Symptoms experienced in the last six months of life in patients with end-stage heart failure. *Eur J Cardiovasc Nurs* 2003; 2: 213–217.
10 Jennings A-L, Davies AN, Higgins JP, *et al.* A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002; 57: 939–944.
11 Barnes H, McDonald J, Smallwood N, *et al.* Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016; 3: CD011008.
12 Ekström M, Nilsson F, Abernethy AA, *et al.* Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc* 2015; 12: 1079–1092.
13 Ekström M, Bajwah S, Bland JM, *et al.* One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax* 2018; 73: 88–90.
14 Mahler DA, Gifford AH, Waterman LA, *et al.* Effect of increased blood levels of β-endorphin on perception of breathlessness. *Chest* 2013; 143: 1378–1385.
15 Johnson MJ, Currow DC. Opioids for breathlessness: a narrative review. *BMJ Support Palliat Care* 2020; 10: 287–295.
16 Currow D, Louw S, McCloud P, *et al.* Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. *Thorax* 2020; 75: 50–56.
17 Ekström M, Ferreira D, Chang S, *et al.* Effect of regular, low-dose, extended-release morphine on chronic breathlessness in chronic obstructive pulmonary disease: the BEAMS randomized clinical trial. *JAMA* 2022; 328: 2022–2032.
18 Schwartzstein RM. Dyspnea – when a sensation becomes a symptom. *JAMA* 2022; 328: 2014–2015.
19 Ferreira DH, Johnson MJ, Janssen D, *et al.* The effect of regular, low-dose, sustained-release morphine on routine physical activity in people with persistent breathlessness: a hypothesis-generating study. *Eur Respir J* 2022; 60: 2201484.
20 Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, *et al.* Effect of sustained-release morphine for refractory breathlessness in chronic obstructive pulmonary disease on health status: a randomized clinical trial. *JAMA Intern Med* 2020; 180: 1306–1314.
21 Johnson MJ, Cockayne S, Currow DC, *et al.* Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial. *ESC Heart Fail* 2019; 6: 1149–1160.
22 Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, *et al.* Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J* 2017; 50: 1701153.
23 Ekström MP, Bornefalk-Hermansson A, Abernethy AP, *et al.* Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 348: g445.
24 Bajwah S, Davies JM, Tanash H, *et al.* Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur Respir J* 2018; 52: 1801278.
25 Currow DC, McDonald C, Oaten S, *et al.* Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage* 2011; 42: 388–399.
26 Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. *Eur Respir J* 2016; 48: 683–693.

27 Mahler DA, Selecky PA, Harrod CG, *et al.* American College of Chest Physicians consensus statement on the management of dyspnea in patients with advanced lung or heart disease. *Chest* 2010; 137: 674–691.
28 Hui D, Maddocks M, Johnson MJ, *et al.* Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines. *ESMO Open* 2020; 5: e001038.
29 Johnson MJ, Bland JM, Oxberry SG, *et al.* Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage* 2013; 46: 957–963.
30 Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. *Am J Crit Care* 1998; 7: 200–204.
31 Lovell N, Etkind SN, Bajwah S, *et al.* To what extent do the NRS and CRQ capture change in patients' experience of breathlessness in advanced disease? Findings from a mixed-methods double-blind randomized feasibility trial. *J Pain Symptom Manage* 2019; 58: 369–381.
32 Wade J, Mendonca S, Booth S, *et al.* Are within-person Numerical Rating Scale (NRS) ratings of breathlessness 'on average' valid in advanced disease for patients and for patients' informal carers? *BMJ Open Respir Res* 2017; 4: e000235.
33 Sandberg J, Sundh J, Anderberg P, *et al.* Comparing recalled versus experienced symptoms of breathlessness ratings: an ecological assessment study using mobile phone technology. *Respirology* 2022; 27: 874–881.
34 Johnson MJ, Sbizzera I, Fairhurst C, *et al.* No excess harms from sustained-release morphine: a randomised placebo-controlled trial in chronic breathlessness. *BMJ Support Palliat Care* 2020; 10: 421–428.
35 Currow DC, Quinn S, Greene A, *et al.* The longitudinal pattern of response when morphine is used to treat chronic refractory dyspnea. *J Palliat Med* 2013; 16: 881–886.
36 Banzett RB, O'Donnell CR, Guilfoyle TE, *et al.* Multidimensional dyspnea profile: an instrument for clinical and laboratory research. *Eur Respir J* 2015; 45: 1681–1691.
37 Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991; 14: 540–545.
38 Abernethy AP, Shelby-James T, Fazekas BS, *et al.* The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care* 2005; 4: 7.
39 Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34: 220–233.
40 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; 20: 1727–1736.
41 Bailey C, Orlando R, Kinghorn P, *et al.* Measuring the quality of end of life using ICECAP SCM: feasibility and acceptability. *BMJ Support Palliat Care* 2014; 4: 112.
42 Kaida K, Takahashi M, Akerstedt T, *et al.* Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol* 2006; 117: 1574–1581.
43 Tariq SH, Tumosa N, Chibnall JT, *et al.* Comparison of the Saint Louis University Mental Status Examination and the Mini-Mental State Examination for detecting dementia and mild neurocognitive disorder – a pilot study. *Am J Geriatr Psychiatry* 2006; 14: 900–910.
44 Handelsman L, Cochrane KJ, Aronson MJ, *et al.* Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987; 13: 293–308.
45 Bédard M, Molloy DW, Squire L, *et al.* The Zarit Burden Interview: a new short version and screening version. *Gerontologist* 2001; 41: 652–657.
46 Hunt KJ, Richardson A, Darlington AE, *et al.* Developing the methods and questionnaire (VOICES-SF) for a national retrospective mortality follow-back survey of palliative and end-of-life care in England. *BMJ Support Palliat Care* 2019; 9: e5.
47 Johnson MJ, Bland JM, Oxberry SG, *et al.* Opioids for chronic refractory breathlessness: patient predictors of beneficial response. *Eur Respir J* 2013; 42: 758–766.
48 May CR, Mair F, Finch T, *et al.* Development of a theory of implementation and integration: normalization process theory. *Implement Sci* 2009; 4: 29.
49 Finch TL, Girling M, May CR, *et al.* Improving the normalization of complex interventions: part 2 – validation of the NoMAD instrument for assessing implementation work based on normalization process theory (NPT). *BMC Med Res Methodol* 2018; 18: 135.