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

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Summary Key message:

Guidelines support morphine for breathlessness, but few data exist for >7 days use. This RCT will test the effectiveness (worst breathlessness/24 hours) of 10 to 20mg daily oral modified-release morphine or placebo on chronic breathlessness over 28 days.

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-COVID-19. Participants will be randomised 1:1 to 5mg oral modified-release morphine/placebo twice daily and docusate/placebo 100mg twice daily for 56 days. Non-responders at Day 7 will dose escalate to 10mg morphine/placebo twice daily at Day 15.

The primary endpoint (Day 28) measure will be worst breathlessness severity (past 24 hours). 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 sub-study 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[13] demonstrated a clinically significant reduction (standardised mean differences (SMD) -0.32; -0.18 to -0.47). However, studies were small with a maximum 7-day duration. Two subsequent phase III RCT (20mg morphine vs 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 Breathlessness Scale (mMRC) 2) and allowable "as needed" immediate-release morphine in both arms, and in the 2022 RCT by the lack of standardised exercise testing[17, 18]. Of note, an exploratory sub-study 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 III trial with a primary endpoint of 4 weeks, the MORphine for DYspnea in COPD (MORDYC) RCT[20] demonstrated significant improvement in disease-specific health status in people with chronic obstructive pulmonary disease (COPD) receiving 10mg 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[22] found no evidence of clinically relevant respiratory adverse effects. Longer term observational studies of people with advanced COPD and advanced interstitial lung disease (ILD) patients found no association between low-dose opioids and hospital admissions or mortality[23, 24]. A dose-finding and pharmacovigilance study[25] demonstrated benefit in two-thirds of patients taking 10, 20 or 30mg daily, with no evidence of tachyphylaxis or tolerance during up to 22 months follow-up. A large Canadian population-based COPD study[26] showed a small absolute excess in respiratory adverse events within 30 days of opioid

prescription. 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 few 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 sub-study and a Study Within A Trial (SWAT).

Participants will be randomised 1:1 to receive oral 5mg morphine modified release (MR) twice daily/ placebo. Docusate/placebo will be given as a non-Investigational Medicinal Product (nIMP) to manage constipation, an almost universal morphine-related side effect.

Study Objectives

The primary objective is to evaluate the effect of low dose oral MR morphine on worst breathlessness in the previous 24 hours at 28 days.

The secondary objectives are to:

(i) Assess the benefit of MR 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
(ii) Assess the net benefit in the study population, extending the study population beyond COPD
(iii) Ascertain the net effect on changes in physical activity
(iv) Determine the impact on health service use, especially hospital inpatient days
(v) Examine cost-effectiveness
(vi) Identify influences affecting trial equipoise and to develop a clinical process for safe prescribing and monitoring of morphine in specialist and generalist settings
(vii) Identify informal carer burden and bereavement (if relevant)
(viii) Explore: predictor characteristics of net benefit; benefits on those participating in pulmonary rehabilitation; 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 ≥ grade 3 or 4) despite optimal management of underlying disease(s). Use of opioid medications greater than 5mg morphine-equivalents daily >7 out of the last 14 days is not permitted. See Table 1 for a list of eligibility criteria. <<*Insert Table 1*>>

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 clinic or in the patient's home, COVID-19 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)). 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 5mg 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 Investigational Medicinal Product (IMP)/Non-Investigational Medicinal Product (nIMP)

All participants will start on twice daily oral 5mg Morphine Sulfate modified release (MST® CONTINUS®)/placebo, and 100mg twice daily oral Docusate Sodium/placebo. At Day 7, a dose escalation decision will be made <<*insert Figure 1 Participant Study Procedures*>>.

Blinding

IMP and nIMP, and corresponding placebo capsules will be over-encapsulated with identical taste, smell and consistency. The 5mg morphine/placebo, 10mg morphine/placebo and nIMP/placebo 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 <<*insert Figure 1*>>

The study includes two face-to-face visits [baseline and Day 28] for vital signs data collection at either 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 twice daily oral 10mg morphine/placebo in non-responders (Day 15) until the study end. Participants not achieving a clinically meaningful improvement by Day 7 (a reduction of ≥1 NRS point[29]) <u>and</u> have acceptable side-effects (see Figure 1), will dose escalate at Day 15. As the vast majority of participants will be out-patients and most assessments will be carried out in the community, a period of 7 days between dose escalation decision and start of the new dose allows time for the prescription to be issued, dispensed and new dose of IMP to be supplied ensuring a continuous IMP supply.

Potential side-effects (constipation, nausea with or without vomiting, sedation, cognitive disturbance) are expected to arise within the first week of any dose level and be mild and settle either spontaneously or with simple management (such as anti-emetics). Constipation needs proactive and continued management with laxative. Careful monitoring of side effect National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE) grading at Day 2, 4 and Day 16, 18 (if dose escalated) will capture the emergence of unacceptable side effects.

Participants with unacceptable side-effects defined as those that when compared to baseline either appear or worsen that are grade 4 (life-threatening/urgent intervention needed) or 5 (death), or grade 3 events which do not improve despite clinical management (see Figure 1) will stay on 5mg morphine/placebo or withdraw from study medication. IMP/placebo and nIMP/placebo "holidays"

are permitted, for side-effects, but should be reinstated when/if clinically indicated. See Box 1 for acceptable side effects. <<*insert Box 1*>>

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 for 18 months or until the last participant has completed the Day 56 visit, whichever is earliest. 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 Adverse Event Reporting

Adverse event (AE) reporting focuses on early recognition of known morphine-related side-effects or treatment emergent adverse events (TEAEs), with thresholds for triggering AE reporting. Neurocognitive disturbance (cognition, memory, hallucinations 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 IMP.

Other opioids are not permitted during the trial. If a participant requires strong opioid for clinical care, they will be withdrawn from IMP and nIMP, but may continue providing data. Where this commenced **before** the primary endpoint, their data will be omitted from the final analysis dataset for the primary outcome. Where this is commenced **after** the primary endpoint they will be included in the intention-to-treat analysis.

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 <<*insert Table 2*>>

Primary outcome:

The primary outcome is patient-rated intensity of worst breathlessness over the previous 24 hours, at Days 2, 4, 7, 14, (Days 16 and 18 where appropriate), 20 and 28 using a validated 11-point (0-10) numerical rating scale (NRS), where 0 = no breathlessness and 10 = worst imaginable breathlessness[30]; more likely than "average breathlessness" or 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 endpoint is Day 28, consistent with longer-term morphine trials[20, 21], to allow treatment-emergent harms to resolve[34], physical activity benefits to emerge, 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 – see Table 2 <<*insert Table 2*>>.

Distress due to breathlessness[36], pain intensity and severity of cough will be measured as an average over the previous 24 hours using an 11 point (0-10) NRS. The Epworth Sleep Questionnaire will assess daytime sleepiness[37], and screen for sleep-disordered breathing. Functional status will be measured using the Australia-modified Karnofsky Performance Scale (AKPS)[38] and an ActiGraph activity monitor

will measure average step count/7 days and intensity of physical activity at baseline (Day -8 to Day 0) and the primary endpoint (Day 20 to Day 28). The 12-Item Short Form Health Survey (SF-12) will measure generic health-related quality-of-life (QoL)[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 to derive the Short-Form 6 dimension health index (SF-6) and EuroQoL 5 dimension 5 level health status questionnaire (EQ-5D-5L) to generate health utility scores to estimate Quality Adjusted Life Years (QALYs). The 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 (HRUQ), based on an adaptation of the UK Cancer Costs questionnaire (blogs.ed.ac.uk/ukcc/), will measure health service use.

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

We will explore the perspectives and burden experienced by carers using the Zarit Burden Interview (ZBI)-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 examinations conducted at baseline and Day 28 will record resting pulse rate and blood pressure, respiratory rate, pulse oximetry and transcutaneous CO_2 (if available). Study medication compliance will be recorded at study visits and IMP and nIMP accountability at each dispensing visit.

Additional Baseline Measures:

Demographic characteristics (age, sex, ethnicity), disease stage, mMRC Breathlessness score, BMI, previous medical history and recent eGFR 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/past 24 hours 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 NRS, assuming a standard deviation of around 2.5. NRS-worst breathlessness will be measured weekly at baseline, Day 7, 14, 20 and 28. 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 analysis of covariance 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 pre-specified 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 (MAR) or missing not at random (MNAR) 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, i) to explore predictors of breathlessness response (as ≥1 reduction in breathlessness worst scores from baseline at the primary endpoint) including age, worse baseline breathlessness, primary causal disease[47] as well as the impact of toxicities on response; ii) 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 endpoints consequences. We will assess potential re-distribution of resource consumption between provider organisations between trial arms. Cost-effectiveness analysis will present Incremental Cost-Effectiveness Ratio (ICER) in terms of cost per quality-adjusted life year (QALY).

Data Management

The main study RCC database will be developed and managed by Hull Health Trials Unit (HHTU). 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 (ECTU) for analysis or Data Management and Ethics Committee (DMEC) reporting in compliance with General Data Protection Regulation Act (2018).

Qualitative Sub-Study

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

After a short learning needs analysis survey, all clinicians prescribing 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[49], to detect changes in perceptions over time. Semi-structured interviews will be conducted with a purposive sample of clinicians, patients and carers to explore perspectives surrounding safe morphine use. Main trial and implementation sub-study analysis findings will be reported jointly.

Study Within A Trial (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 reference: 19/NE/0284; EudraCT 2019-002479-33) and by the Medicines and Healthcare products Regulatory Agency (MHRA). 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 HTA 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 10-30mg 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 ≥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.

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Author Contributions

MJ, DC developed the study concept. MJ, MF, DC, JC, SB, JN, CK, MP, IH, PH, developed the study design. MJ, MF, DC, JC, MP, IH, PH, SB, JN, supported the acquisition of funding. KD, developed the first draft of the manuscript. All authors contributed to the revisions and approval of final manuscript

Conflicts of Interest: KD had nothing to disclose. BW had nothing to disclose; JC had nothing to disclose; NC had nothing to disclose; CK had nothing to disclose; SB had nothing to disclose; MP had nothing to disclose; IH had nothing to disclose; JN had nothing to disclose; PH had nothing to disclose; DC had nothing to disclose. MF had nothing to disclose; MJ reports that she is the clinical advisor to Mayne Pharma and an observer in the Open [blinded] DMEC for this study

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Table 1 – Eligibility Criteria

Inclusion Criteria:	**Exclusion Criteria:**
1. Ambulant people with chronic breathlessness due to cardiac disease, respiratory disease, post Covid-19 chronic breathlessness or cancer 2. Modified Medical Research Council (mMRC) breathlessness scale grade 3 or 4 3. Male or female aged ≥18 years old 4. Management of the underlying condition unchanged for the previous 7 days 5. Australia-modified Karnofsky Performance Scale (AKPS)[38] ≥40 6. eGFR of 25mL/min/1.73m^2 or more, unless the primary diagnosis is heart failure (≥30mL/min/1.73m^2) within 21 days of consent 7. If female and of child-bearing potential, must agree to use adequate contraception when taking IMP and for 7 days following cessation 8. Able to complete questionnaires and trial assessments 9. Able to provide written informed consent	1. Unable to provide informed consent 2. Unable to complete baseline study questionnaires even with the assistance of the study nurse 3. Have co-existing malignant disease only if this would affect the study in the investigators' opinion 4. Have used opioid medications >5mg morphine-equivalents daily for >7 out of 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 CTIMP 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 hours post-operatively

	12. Are taking >20mg diazepam or equivalent/day, or are unable to reduce dose before randomisation to <20mg/day of the duration of the study treatment period 13. Cannot/do not wish to take gelatin (used as a medication encapsulation ingredient)

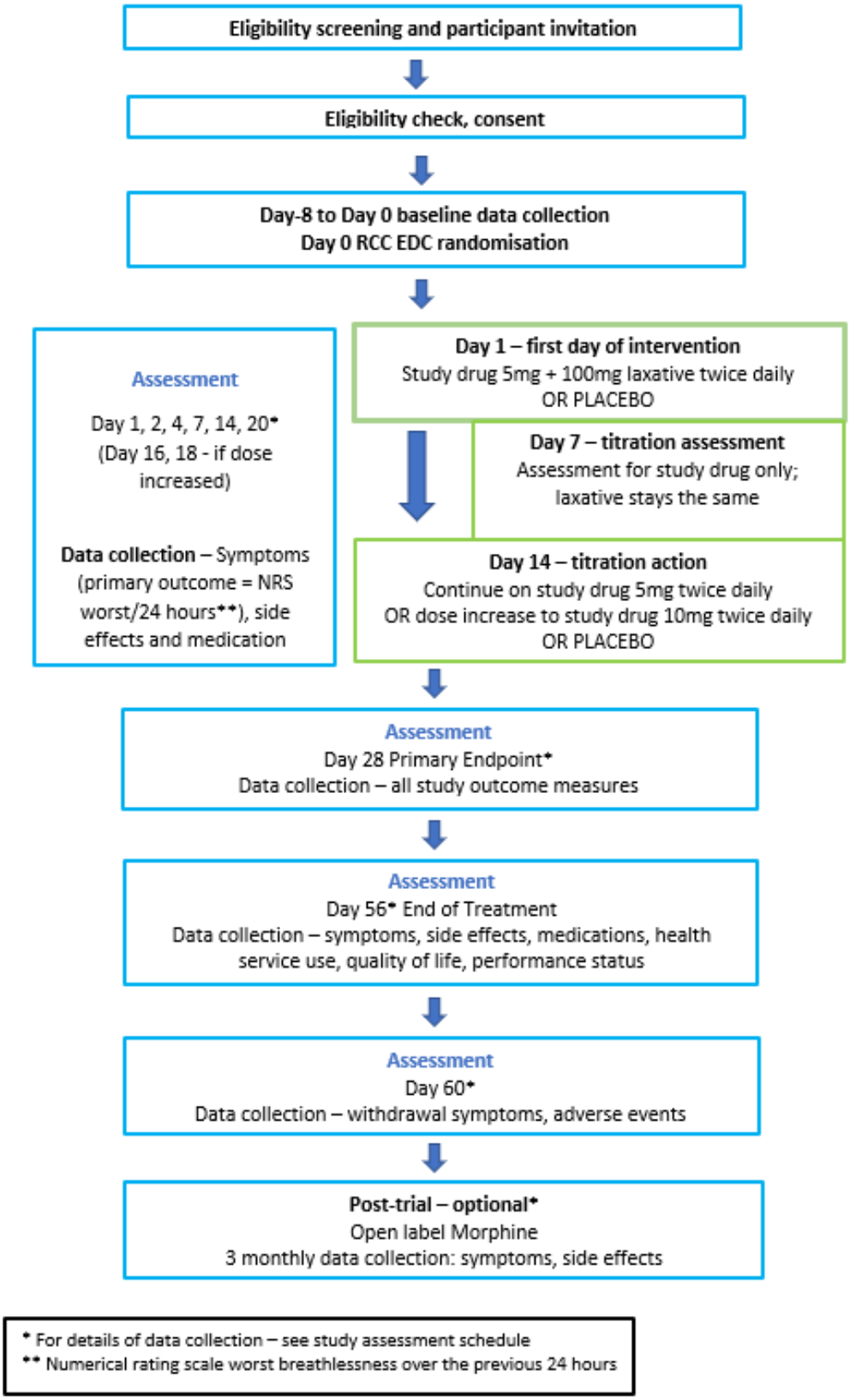

Figure 1: Participant Study Flow Chart

Box 1: Acceptable side effects

For the purposes of the MABEL trial, acceptable side effects are defined as:

1. No side-effects (all CTCAE* grade 0) OR
2.
    i. New or worse-than-baseline gastro-intestinal effects acceptable (nausea, vomiting, constipation CTCAE grades ≤2 AND neurocognitive effects acceptable (cognition, memory, hallucinations grade 0 AND no vivid dreams [grade 1 symptoms acceptable if present at same grade at baseline); AND
    ii. Ongoing side-effect management and monitoring; AND
    iii. Both clinician and participant happy to continue or increase IMP as appropriate.

**CTCAE: Common Terminology Criteria for Adverse Events*

Table 2 – schedule of events

Assessments	Baseline D-8 - D0	D2	D4	D7	D14	D16	D18	D20	D28	D42	D56	D60	Follow-Up
PRIMARY OUTCOME													
Breathlessness severity: NRS* worst/previous 24 hours	X	X	X	X	X	X	X	X	X		X		X
SECONDARY OUTCOMES													
Distress due to breathlessness: NRS* /previous 24 hours	X			X	X			X	X		X		X
Average pain: NRS* /previous 24 hours	X			X					X		X		
Severity of cough: NRS* /previous 24 hours	X			X					X		X		
Daytime sleepiness: Epworth Sleep Questionnaire	X								X		X		
Functional status: Australia Karnofsky Performance Status	X								X		X		
Physical activity: ActiGraph	XX							X	X				
Quality of Life questionnaires: SF-12, EQ-5D-5L	X								X		X		
Health economics questionnaires: ICECAP-SCM, Health Resource Utilisation	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
- 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	X				X				X		X		
Impact on bereavement: VOICES (for bereaved carers only)													X
OTHER OUTCOME MEASURES													
Blood Pressure, pulse, respiratory rate, pulse oximetry, transcutaneous Carbon dioxide (CO_2)	X								X				
Concomitant medications (including oxygen)	X			X	X			X	X		X		
Morphine (IMP**) / Docusate (nIMP***) Compliance		X	X	X	X	X	X	X	X	X	X		
Morphine (IMP) / Docusate (nIMP) Accountability					X					X	X		
ADDITIONAL BASELINE MEASURES													
Demographics (age, sex, ethnicity)	X												
Medical history: Comorbidity checklist	X												
Body Mass Index	X												
Disease stage	X												
eGFR (estimated Glomerular Filtration Rate)	X												
Breathlessness impact: modified Medical Research Council Breathlessness Scale	X												

*NRS (Numerical Rating Scale); ** IMP (Investigational Medicinal Product); *** nIMP (non-Investigational Medicinal Product)