A pragmatic, phase III, multisite, double-blind, placebo-controlled, parallel-arm, dose increment randomised trial of regular, low-dose extended-release morphine for chronic breathlessness: Breathlessness, Exertion And Morphine Sulfate (BEAMS) study protocol

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Introduction

Chronic breathlessness is highly prevalent and distressing to patients and families. No medication is registered for its symptomatic reduction. The strongest evidence is for regular, low-dose, extended-release (ER) oral morphine. A recent large phase III study suggests the subgroup most likely to benefit have chronic obstructive pulmonary disease (COPD) and modified Medical Research Council breathlessness scores of 3 or 4. This protocol is for an adequately powered, parallel-arm, placebo-controlled, multisite, factorial, block-randomised study evaluating regular ER morphine for chronic breathlessness in people with COPD.

Methods and analysis

The primary question is what effect regular ER morphine has on worst breathlessness, measured daily on a 0–10 numerical rating scale. Uniquely, the coprimary outcome will use a FitBit to measure habitual physical activity. Secondary questions include safety and, whether upward titration after initial benefit delivers greater net symptom reduction. Substudies include longitudinal driving simulation, sleep, caregiver, health economic and pharmacogenetic studies. Seventeen centres will recruit 171 participants from respiratory and palliative care. The study has five phases including three randomisation phases to increasing doses of ER morphine. All participants will receive placebo or active laxatives as appropriate. Appropriate statistical analysis of primary and secondary outcomes will be used.

Ethics and dissemination

Ethics approval has been obtained. Results of the study will be submitted for publication in peer-reviewed journals, findings presented at relevant conferences and potentially used to inform registration of ER morphine for chronic breathlessness.

Strengths and limitations

► This study is adequately powered to provide clinically meaningful outcomes.
► To optimise the generalisability of the findings, this multisite study will capture people from across a spectrum of care settings.
► This study builds on the experience of several double-blind randomised controlled trials investigating the role of extended release morphine in breathlessness.
► This study includes objectives which assess changes in habitual function as well as symptom control outcomes.
► This is a relatively long study for participants from palliative care which may potentially influence completion rates independently of the intervention.

INTRODUCTION

There is a growing understanding of the complex pathological, neurophysiological, emotional and psychospiritual components of breathlessness.1 2 The burden of this distressing symptom however remains...
devastatingly high for people who experience it and their caregivers. It is not only a highly feared symptom in those approaching end of life but unlike many other symptoms, breathlessness typically worsens, despite treatment, as death approaches.

Defined as ‘a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity’ breathlessness can be described as chronic when it persists despite the maximal treatment of reversible causes. Chronic breathlessness is a distinct syndrome with implications for patients, caregivers, health services, funders and researchers. The subjective experience of chronic breathlessness cannot be accurately predicted by diagnosis or by standard physiological respiratory measures such as spirometry, oxygen saturations and respiratory rate. However, despite the lack of investigative predictors, chronic breathlessness is severely debilitating both physically and psychologically. Over half of people with lung cancer report physical limitations due to breathlessness and around a quarter describe negative effects on their psychological well-being. Anxiety can both aggravate chronic breathlessness as well as arise from it. Depression and overall reduced quality of life are also prevalent. Worsening chronic breathlessness is associated with worsening and physical and mental components of quality of life at a population level.

Chronic breathlessness has a prevalence of 9%–11% in the general community. As the incidence of chronic obstructive pulmonary disease (COPD), heart failure and other causes of breathlessness continue to rise globally, the problem of chronic breathlessness will continue to rise in parallel.

Despite the magnitude of the problem, internationally there is no medication currently registered for the symptomatic management of chronic breathlessness. Treatment of the underlying cause remains the mainstay of therapy although there is increasingly robust evidence for various non-pharmacological and pharmacological interventions. Systematic reviews support the use of walking aids and pulmonary rehabilitation, and there is randomised trial evidence for multidisciplinary breathlessness support services and for nurse-led clinic support. Phase III clinical trial data and a meta-analyses support the use of oxygen therapy for symptomatic relief of chronic breathlessness in people with evidence of hypoxaemia. In an adequately powered, randomised trial in patients with COPD and chronic breathlessness without resting hypoxaemia, oxygen provided no greater relief than placebo air. Other studies have produced conflicting results and data in daily life settings are limited.

The beneficial clinical role for morphine in chronic breathlessness is becoming increasingly established. In vivo laboratory-controlled trials demonstrate opioids modulate the work of breathing during exercise and resistive load breathing in both healthy volunteers and those with COPD. Clinically, low-dose regular extended release (ER) morphine reduces the intensity of chronic breathlessness without compromising gas exchange in people with moderate to severe COPD. These data are further validated in two recent systematic reviews and meta-analyses specifically exploring opioids for the relief of breathlessness in COPD. Although systemic morphine improves breathlessness in COPD, there is no evidence to date that it improves exercise capacity measured by 6min walk test or duration on treadmill.

Pharmacovigilance data show no evidence of tachyphylaxis or tolerance during up to 22 months of follow-up of people using ER morphine for chronic breathlessness with dose titrated to benefit. The patients’ and caregivers’ experience of use of morphine for chronic breathlessness is also positive with minimal adverse effects reported when used specifically at low doses for chronic breathlessness although the benefits can be easily negated by any side effects from the ER morphine. In broader post-marketing studies of opioid use in people with COPD where clinical indications are predominantly for musculoskeletal pain, findings in two separate population-based studies are conflicting. Additionally, there is some evidence demonstrating increased sleep quality when using opioids for breathlessness.

Despite recent recommendations in several international clinical guidelines including recommendations in the most recent Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 and its associated peer-reviewed executive summary which state that ‘palliation efforts should be focused on the relief of dyspnoea and that opiates can relieve dyspnoea, some physicians remain reluctant to prescribe morphine and other opioids for breathlessness. A recent cohort study has also questioned the safety of initiating opioid use in older adults but this was based on dispensing data rather than observed adverse effects and from other population data of opioid prescribing, it is highly unlikely that very many of these prescriptions were for chronic breathlessness. Opioid-related adverse effects (transient drowsiness, nausea, itch, constipation, anticholinergic effects and physical tolerance) are well documented; however, prospective data to date have failed to demonstrate any episodes of respiratory depression or morphine-related hospitalisations when morphine is used at low dose and in steady state conditions. Additionally, all relevant systematic reviews comment on the low incidence of morphine-related serious adverse effects.

ER morphine preparations may be useful in improving safety and reducing the potential for side effects when used for chronic breathlessness when compared with immediate release oral morphine solution. Although data are extrapolated from studies investigating pain management, pharmacokinetic data suggest there is less variability between maximum and minimum dose concentrations with ER opioid preparations. Adherence is improved with the use of once daily preparations, an approach which is also preferred by patients. Further, randomised
double-blind studies show more rapid pain control and fewer side effects when ER opioid preparations are used compared with immediate release preparations even when initiating opioids for pain.60 61

This paper presents the protocol for an Australian national multisite study that aims to improve the current evidence base for the role of ER morphine in the management of chronic breathlessness. Parts of this study design are exploratory, parts will definitively answer new questions and several exploratory substudies are included. A list of the key questions that this study protocol will address are summarised in box 1 with features unique to this study highlighted. This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials recommendations for protocol reporting62 63 and the study will report against Consolidated Standards of Reporting Trials guidelines.64 65

### METHODS AND ANALYSIS

#### Study design

The Breathlessness, Exertion And Morphine Sulfate (BEAMS) study is a phase III multisite, double-blind, parallel-arm, block-randomised, factorial, placebo-controlled, dose increment study of ER morphine for chronic breathlessness in participants with COPD. The study has five stages which will incorporate three randomisations for each participant to titrate dose of ER morphine. The study protocol also incorporates nine substudies. Participants may elect to participate in one or more of these substudies.

#### Recruiting centres

The BEAMS study is coordinated by the Australian national Palliative Care Clinical Studies Collaborative (PaCCSC) and is sponsored by Flinders University, Adelaide, Australia. Box 2 details a list of sites involved in study participant recruitment, noting additional sites may become involved as study recruitment progresses.

#### Study objectives

The BEAMS study has two coprimary objectives: to compare the effect of ER morphine at two different doses and placebo on mean worst breathlessness on the last 3 days of 1 week of treatment and to compare the mean change in number of steps taken by participants per day in the last 3 days of week one compared with baseline in both ER morphine and placebo arms as measured by a FitBit Charge HR (FitBit, USA).

The secondary objectives of the study are to determine:

- The safety of ER morphine, including the effect of upward dose titration in a participant population of people with COPD with chronic breathlessness;
- The additional symptomatic benefit of increasing dose in participants whose breathlessness is benefited by low-dose ER morphine;
- Over what period of time does benefit continue to increase if a beneficial dose level is achieved66;
- The percentage of participants that derive benefit at each dose above placebo;
- Any existence of end-of-dose failure;
- If response, benefit and side effects to ER morphine can be predicted from collected baseline demographic data;
- The impact on general health status and quality of life of both participant and caregiver;

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**Box 1 Key questions addressed by this study protocol**

**Key questions:**

- In steady state, what effect does extended release (ER) morphine have on worst breathlessness in patients with chronic obstructive pulmonary disease (COPD) and chronic breathlessness?
- In the same patients, what effect does ER morphine have on physical activity assessed by accelerometer steps per day?*
- If there is benefit, what is the optimal dose and is there a dose-related response to upward titration, especially after initial symptomatic benefit?*
- What is the net effect of morphine for up to 6 months in its effect on chronic breathlessness and harms associated with its use?*
- What is the harm profile of ER morphine for chronic breathlessness over time?
- Does low-dose ER morphine used for chronic breathlessness impact quality of life, driving simulation performance and sleep quality?
- Through pharmacokinetic and genetic analysis, can we begin to identify which patients may benefit from, have no effect or experience harm from ER morphine for chronic breathlessness?*
- What is the economic impact of ER morphine on this population for this indication?

*Not studied before in this population for this indication.

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**Box 2 List of recruiting centres**

<table>
<thead>
<tr>
<th>State</th>
<th>Recruiting centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>New South Wales</td>
<td>Sacred Heart Health Service, Darlinghurst</td>
</tr>
<tr>
<td></td>
<td>Calvary Mater, Newcastle</td>
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<tr>
<td></td>
<td>Calvary Healthcare, Kogarah</td>
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<tr>
<td></td>
<td>Liverpool Hospital, Liverpool</td>
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<tr>
<td></td>
<td>Concord Repatriation Hospital, Concord</td>
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<tr>
<td></td>
<td>Greenwich Hospital, Greenwich</td>
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<tr>
<td>Queensland</td>
<td>Mater Health Service, Brisbane</td>
</tr>
<tr>
<td></td>
<td>The Prince Charles Hospital, Chermside</td>
</tr>
<tr>
<td></td>
<td>Nambour Hospital, Nambour</td>
</tr>
<tr>
<td></td>
<td>St Vincents Private Hospital, Brisbane</td>
</tr>
<tr>
<td>South Australia</td>
<td>Southern Adelaide Palliative Services, Daw Park</td>
</tr>
<tr>
<td></td>
<td>Repatriation General Hospital, Daw Park</td>
</tr>
<tr>
<td>Victoria</td>
<td>Barwon Health, Geelong</td>
</tr>
<tr>
<td></td>
<td>Royal Melbourne Hospital, Melbourne</td>
</tr>
<tr>
<td></td>
<td>St Vincent’s Hospital, Melbourne</td>
</tr>
<tr>
<td></td>
<td>Austin Hospital, Heidelberg</td>
</tr>
<tr>
<td>Western Australia</td>
<td>Sir Charles Gairdner Hospital, Nedlands</td>
</tr>
</tbody>
</table>

Differences in activities of daily living (ADLs) between those treated with ER morphine and placebo;

The effect of ER morphine and placebo on anxiety and depression;

The longer term benefits and side effects of ER morphine;

Blinded patient preference of intervention and dose;

If participants experience opioid withdrawal as study medicines cease.

The aims of the substudies are detailed in the relevant section below.

Study population
The study population for BEAMS is people with COPD and chronic breathlessness graded as modified Medical Research Council grade 3 or 4 and whose worst breathlessness intensity in the 24 hours prior to recruitment is greater or equal to 3/10 on a 0–10 numerical rating scale (NRS). In addition to being 18 years of age or older and able to complete the assessments in English, the study’s inclusion criteria are:

1. Physician-diagnosed COPD with spirometry confirmation, defined as a postbronchodilator forced expiratory volume in 1 s over forced expiratory volume of <0.7 consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria;67

2. Clinician confirmed optimisation of COPD treatment;

3. Stable medication for management of COPD-related breathlessness for 1 week, except ‘as needed’ medications;

4. Assessed as competent to be able to provide informed consent with a mental state examination as defined by the St Louis University Mental State Examination68 23/30 and at the discretion of the principal investigator.

A number of exclusion criteria will be applied detailed in box 3.

Recruitment and consent
The BEAMS study will be promoted to patients with COPD that interferes with ADLs through LungNet (Lung Foundation Australia) and the Primary Health Networks in each recruitment catchment area. Potentially eligible participants will be identified and approached by both primary and secondary care clinicians at participating sites across Australia who will then refer them to the research team. Research team attendance at relevant clinics and study advertisements will help to remind clinical staff of study recruitment and encourage patients to self-refer. Permission will be sought from consultants in charge of the care of potential participants for research staff to approach them directly. Case identification in both inpatient units and outpatient clinics will also occur following case-note review.

No participant will be recruited without full, written informed consent being first obtained. A process of information exchange between potential participants and research staff including the use of participant information sheets and open discussion will occur to ensure full disclosure and to comply with Good Clinical Practice (GCP) guidelines.69

Eligibility to participate will be determined initially by the research team study nurse and site investigators at each site involved. They will be responsible for completion of the medical assessment and to check eligibility criteria. Eligibility data will be entered on a secure online database and eligibility will be monitored centrally before confirmation of study participation and baseline assessments made.

Randomisation
At each participating site, consenting participants will be sequentially allocated a unique identifying number (ID number) according to PaCCSC standard operating procedures. Randomisation requests will take the form of receipt of a prescription for study medicines by site pharmacists. Randomisation will occur through the development of randomisation tables using random number tables generated by an independent provider. Site pharmacists will receive the next randomisation number available through telephone contact with the central registry.

As noted, the study has five stages (0–4: table 1). The first randomisation (stage 1) will occur by a block randomisation schedule held by the independent provider’s central registry in a 1:1:1 ratio to either 8 mg ER morphine, 16 mg ER morphine or placebo (table 1). Block randomisation will ensure relatively even allocation to each of the three arms at each site. Similar block randomisation will occur at second (stage 2) and third randomisations (stage 3) in a ratio of 1:1 to either an additional 8 mg ER morphine or placebo at each stage progression.

By the end of the third randomisation, participants will have a 1/12 chance of being on placebo, a 3/12 chance of being on 8 mg ER morphine, 4/12 chance of 16 mg ER morphine, 3/12 chance of 24 mg ER morphine and 1/12 chance of 32 mg ER morphine, thus allowing assessment of potential benefit of low-dose ER morphine and the effects of incremental dose escalation up to 32 mg ER morphine for chronic breathlessness.

Randomisation number and allocation will be provided to the site pharmacist verbally and confirmed by email. Participant ID number, randomisation allocation code, date of request, preparation and dispensing data will be recorded in a log maintained by the site pharmacist. All research staff, treating clinicians and patients will remain blinded to the treatment allocation. Unblinding will only occur in emergency situations following consultation with the principal investigator and at the conclusion of collecting the last data point for the last participant in the entire study.

Concomitant interventions
All study participants will receive written advice detailing standard therapeutic strategies for managing obstructive lung disease (GOLD) criteria67; St Louis University Mental State Examination68 23/30 and at the discretion of the principal investigator.

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breathlessness. They will also be provided with a battery-operated, handheld fan and instructions for use throughout the study period as standard breathlessness management strategies. All other medications and therapies will continue throughout the study period for each participant.

**Blinding**

All medicines used in the study will appear identical to ensure true blinding to the intervention. ER morphine capsules will contain either 8 mg or 16 mg of a currently licensed once daily ER morphine preparation within a gelatine capsule to be taken orally. Placebo capsules contain appropriately dyed sugar seed cores within an identical gelatine capsule. The creation of identical appearing capsules with differing contents will also ensure that all study participants take two capsules of study drug each morning orally for the entire duration of the study. The capsule contents will change according to the arm and randomisation stage. In addition, participants will take two capsules containing either active laxative (docusate 50 mg with sennosides 8 mg) or identical appearing placebo each morning. The participant will swallow each capsule whole.

All study medicines will be supplied as a once-daily dose in a weekly blister (Webster) pack, blinded and dispensed by site pharmacists. Dispensing pharmacists will log the participant name and ID number and the pack dispensed to that participant. Storage, delivery, dispensing and destruction of opioid medications will adhere to federal and local regulations. Empty packs will be collected for reconciliation.

Participants will be reviewed at baseline and a FitBit Charge HR will be fitted to record accelerometer data including steps per day, activity and basic sleep data in weeks one and three of the study.

**Data collection and outcome measures**

Table 2 provides an overview of the data collection tools used in this study and table 3 describes the tools and data collected at each study time point.

The first coprimary objective will be assessed by the mean change in worst breathlessness intensity measured each morning on the last three mornings of week 1 compared between arms and adjusted for rates measured at baseline. Both the intensity and the unpleasantness of breathlessness will be rated by patients each morning based on breathlessness in the preceding 24 hours on an 11-point
(0–10) NRS with 0 representing ‘no breathlessness’ or ‘breathing is not unpleasant’ and 10 ‘worst possible breathlessness’ or ‘most unpleasant breathlessness possible’. Scores will be recorded in a patient diary. Primary comparisons at the completion of stage 1 will be between 8 mg ER morphine and placebo and 16 mg ER morphine and placebo. A difference of one point on NRS will be considered a clinically meaningful difference; consistent with consensus statements and empirical studies.

The choice of worst breathlessness is based on data from a recent large randomised controlled trial comparing regular, low-dose, ER morphine with placebo for chronic breathlessness. The most responsive measure from unpleasantness and intensity (now, average, best and worst) was worst breathlessness in the previous 24 hours. This directly reflects previous work that compared the performance of NRS measures of breathlessness with a modified Borg scale in 1048 participants. Worst breathlessness has the widest distribution of responses, whereas average breathlessness appeared to have a ceiling effect and breathlessness now had a much smaller range of responses.

There are potential parallels with pain when considering average, worst and current pain in people treated with radiotherapy for painful bony metastases: worst pain had the strongest correlation with functional interference at baseline and larger decreases in functional interference scores as pain was relieved. Of all the measures in the Brief Pain Inventory, ‘pain at its worst in the previous 24 hours’ satisfied more of the key Food and Drug Administration recommendations for patient reported measures than any other.

The second coprimary objective will be assessed by comparison of number of steps taken per day as recorded using a Fitbit Charge HR on the last 3 days of stage 1 and with baseline. Comparisons will be made between 8 mg ER morphine and placebo and 16 mg ER morphine and placebo. A secondary endpoint will also occur at the end of stage 3. A clinically meaningful difference has been calculated to be 940 steps per day, which is one half of an SD in people with GOLD grade IV COPD in previous studies comparing exercise training in participants with varying levels of COPD. Accelerometers measure habitual physical activity with a 3–5 day period of recording considered sufficient to have stable data. By contrast, a 6 min walk test measures functional exercise capacity, with the measures complementing each other. It is more likely that any improvement in symptoms will be reflected in great mobility across each day, rather than in functional exercise capacity, especially given the evidence to date on the effect of opioids on exercise capacity.

Secondary outcomes will be assessed by completion of a number of validated participant and research team-mediated measures at various time points throughout the study period (table 2). These measures will provide quantitative and qualitative assessments of participants’ symptom severity and ensure measurement of quality of life (QoL) for both participants and caregivers in line with the Australian national Palliative Care Strategy’s aims.

The participant diary will remain the most important source of data collection. Diary completion by participants throughout stages 1, 2 and 3 will document daily NRS recording of both the intensity (worst, now, average) and unpleasantness of breathlessness. It will also allow documentation of Likert-scale grading of sleep quality, clarity of thought, daytime drowsiness, constipation, nausea, vomiting, itch, difficulty with micturition and any other patient-identified symptoms. During stage 4, participants will complete diary entries for a 24-hour period each week and will have additional questions on additional adverse events such as falls and Australia-modified Karnofsky Performance Status (AKPS). Particular emphasis will also be placed on data collection of health service utilisation rates and quality of life data to inform the economic analysis substudy. Participants will be contacted regularly by telephone during each week of intervention to ensure safety and compliance.

Additional information at the end of stage 3 will be recorded including blinded participant preference for treatment at study conclusion, medication compliance and differential rates of withdrawal from the study. All participants will be asked to complete the Subjective Opioid Withdrawal Scale assessment for three consecutive days after completion or withdrawal from the study.

Blood sampling will occur at baseline to record haemoglobin level, hepatic function and to calculate creatinine clearance unless a sample is available from the preceding 4 weeks without any change in clinical condition. This will ensure absence of reversible causes of breathlessness such as anaemia and organ dysfunction that may impact...
<table>
<thead>
<tr>
<th>Assessments</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of worst</td>
<td>► NRS</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>► 0–10 (11-point) scale</td>
</tr>
<tr>
<td>assessments</td>
<td>► 0 = ‘no breathlessness’ to 10 = ‘worst possible breathlessness’</td>
</tr>
<tr>
<td>Unpleasantness of worst</td>
<td>► NRS</td>
</tr>
<tr>
<td>breathlessness over the</td>
<td>► 0–10 (11-point) scale</td>
</tr>
<tr>
<td>previous 24 hours</td>
<td>► 0 = ‘breathing is not unpleasant’ to 10 = ‘most unpleasant breathlessness possible’</td>
</tr>
<tr>
<td>mMRC</td>
<td>► Five-point (0–4) categorical breathlessness scale</td>
</tr>
<tr>
<td></td>
<td>► Descriptive measure of functional impairment due to breathlessness; lower scores indicate less breathlessness.</td>
</tr>
<tr>
<td>CRQ-DS</td>
<td>► Total of 20 questions covering social and emotional symptoms and perceptions of breathlessness in relation to five activities over the preceding 2 weeks</td>
</tr>
<tr>
<td></td>
<td>► Higher scores indicate better respiratory function.</td>
</tr>
<tr>
<td>CRQ-M</td>
<td>► Assessment of perceived change in patient mastery over their breathlessness</td>
</tr>
<tr>
<td></td>
<td>► Higher scores indicate better mastery.</td>
</tr>
<tr>
<td>CCMI</td>
<td>► Severity and number of comorbid conditions incorporated into a single score.</td>
</tr>
<tr>
<td>Baseline assessments</td>
<td>► Score will be unweighted and not include participants life-limiting illness.</td>
</tr>
<tr>
<td></td>
<td>► Independent predictor of long-term survival</td>
</tr>
<tr>
<td>SLUMS</td>
<td>► 11-item questionnaire scored out of 30; testing memory, orientation, attention and executive functions</td>
</tr>
<tr>
<td></td>
<td>► Score adjusted for school education.</td>
</tr>
<tr>
<td>ESAS</td>
<td>► Rating of severity of coexisting symptoms on a numeric rating scale from 0 to 10</td>
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<tr>
<td></td>
<td>► Sum of scores is termed symptom distress score. Higher scores equate higher levels of distress.</td>
</tr>
<tr>
<td>Activity monitoring</td>
<td>► Daily step count measured by Fitbit Charge HR wearable step count technology device</td>
</tr>
<tr>
<td>Performance and</td>
<td>► Provides data and insight into overall physical activity including steps per day, sleep minutes and sleep activity, activity and sedentary levels and total energy expenditure</td>
</tr>
<tr>
<td>activity assessors</td>
<td>► Motion sensors provide an objective, reliable, valid and responsive measure</td>
</tr>
<tr>
<td>AKPS</td>
<td>► Validated variant of Karnofsky Performance Status</td>
</tr>
<tr>
<td></td>
<td>► Scored 0–100 in increments of 10 assigned to participants based on ability to perform activities of daily living; higher scores imply better level of function.</td>
</tr>
<tr>
<td>Barthel Index (clinician</td>
<td>► Assess impairment of ADLs through assessment of 10 variables</td>
</tr>
<tr>
<td>rated)</td>
<td>► Higher scores indicate associated with increased independence with ADLs.</td>
</tr>
<tr>
<td>Mood</td>
<td>► 14-item questionnaire consisting of two seven-item subscales looking at depression and anxiety, respectively</td>
</tr>
<tr>
<td></td>
<td>► Higher scores are associated with greater morbidity.</td>
</tr>
</tbody>
</table>
on study medication pharmacology. This sample will also be used for the pharmacogenetic study. Bloods in steady state will also be taken at the end of weeks 1 and 3 to understand any relationship between blood levels and symptomatic response. Baseline testosterone levels will be measured for all participants at baseline and again at 6 months for those who enter the testosterone level substudy.

To assess for the risk of opioid-induced respiratory failure from low-dose ER morphine, end-tidal carbon dioxide (CO₂) and pulse oximetry will be recorded using a portable unit at baseline and at the three, weekly randomisation stages. Recent spirometry from any source will be recorded to confirm the COPD diagnosis.

In addition to age and gender, demographic data including domestic situation, educational and marital status, availability of primary caregiver, ethnicity and Aboriginal or Torres Strait Islander status will be recorded. Smoking history and use of long-term oxygen therapy will also be recorded at baseline. A full baseline physical examination will also be conducted. First randomised treatment will commence the day following completion of the baseline 2-day assessment period.

Participant safety will remain of paramount importance throughout the study period. Rescue medication will therefore be available for participants for treatment of common opioid side effects including nausea and constipation. Opioid toxicity is defined by physician assessment of respiratory depression (≤10 breaths per minute), drowsiness, myoclonus, myosis or National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAEv4) grade ≥3 for cognitive

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### Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
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</table>
| Quality of life assessments | Quality of Life EQ-5D-5L<sup>124</sup>  
  - Standardised instrument for use as a measure of health outcome in both clinical and economic evaluation of healthcare  
  - Five descriptive questions rated on a 5-point Likert scale and a single VAS rating overall health.  
  - CAT<sup>125</sup>  
  - Validated measure of health-status in COPD and is responsive to quality of life changes after an exacerbation and pulmonary rehabilitation.  
  - Eight questions specific to COPD-related symptoms each rated on a 6-point scale.  
  - GIC<sup>126</sup>  
  - Seven-point scale regarding participant perception of change since study commencement; graded from ‘very much worse’ to ‘very much improved’  
  - Adapted for measurement of breathlessness from original<sup>127</sup>  
  - Higher scores imply better global quality of life. |
| Sleep assessments    | ESS<sup>128</sup>  
  - Validated tool for characterising daytime sleepiness  
  - Eight questions rated on a four-point scale  
  - LSEQ<sup>129</sup>  
  - Validated tool for measuring changes in sleep such as going to sleep, perceived quality of sleep and morning alertness  
  - Ten questions self-rated on 0–100 millimetre (mm) line  
  - KSS<sup>130 131</sup>  
  - Validated single question on a nine-point scale evaluating subjective sleepiness  
  - Higher scores indicate higher perceived sleepiness at the time of scoring. |
| Caregiver           | Zarit Burden Interview<sup>132</sup>  
  - Caregiver well-being assessment 12-item short form questionnaire<sup>133</sup>  
  - Commonly used questionnaire assessing level of subjective caregiver burden rated on a five-point Likert scale |
| Adverse effects     | SOWS<sup>84</sup>  
  - 16-point questionnaire rating presence of signs and symptoms of opioid withdrawal on a five-point Likert scale  
  - Higher scores indicate increasing severity of opioid withdrawal. |

ADLs, activities of daily living; AKPS, Australian-modified Karnofsky Performance Status; BEAMS, Breathlessness, Exertion And Morphine Sulfate; CCMI, Charlson Co-Morbidity Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CRQ-DS, Chronic Respiratory Questionnaire—Dyspnoea Subscale; CRQ-M, Chronic Respiratory Questionnaire—Mastery Subscale; ESAS, Edmonton Symptom Assessment System; ESS, Epworth Sleepiness Scale; GIC, Global Impression of Change; EQ-5D-5L, Five-Level EuroQol five dimensions questionnaire; HADS, Hospital Anxiety and Depression Scale; KSS, Karolinska Sleepiness Scale; LSEQ, Leeds Sleep Questionnaire; mMRC, modified Medical Research Council; NRS, Numerical Rating Scale; SOWS, Subjective Opioid Withdrawal Scale; SLUMS, St Louis University Mental Status Examination; VAS, Visual Analogue Scale.
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<th>Time point</th>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
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### Research team mediated

- AKPS ✓ ✓ ✓ ✓ ✓
- mMRC ✓ ✓ ✓ ✓ ✓
- GIC ✓ ✓ ✓ ✓ ✓
- Barthel Index ✓ ✓ ✓ ✓ ✓
- Blinded preference ✓ ✓ ✓ ✓ ✓
- Side effects ✓ ✓ ✓ ✓ ✓ ✓
- CCI ✓ ✓ ✓ ✓ ✓
- SLUMS ✓ ✓ ✓ ✓ ✓
- Compliance ✓ ✓ ✓ ✓ ✓

### Economic

- Inpatient stay days ✓ ✓ ✓ ✓ ✓
- ED visits ✓ ✓ ✓ ✓ ✓
- Med/health visits ✓ ✓ ✓ ✓ ✓
- Date of death ✓ ✓ ✓ ✓ ✓

### Substudies

- ZCBS ✓ ✓ ✓ ✓ ✓ ✓
  - PG blood sample ✓ ✓ ✓ ✓ ✓ ✓
  - PK and PD blood sample ✓ ✓ ✓ ✓ ✓ ✓
  - Home sleep study ✓ ✓ ✓ ✓ ✓ ✓
  - Laboratory sleep study ✓ ✓ ✓ ✓ ✓ ✓
  - Driving simulation ✓ ✓ ✓ ✓ ✓ ✓
  - Qualitative interview ✓ ✓ ✓ ✓ ✓ ✓
  - Serum testosterone ✓ ✓ ✓ ✓ ✓ ✓

*Primary endpoint.

AKPS, Australian-modified Karnofsky Performance Status; CAT, COPD Assessment Test; CC, creatinine clearance; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CO2, carbon dioxide; CRQ-DS, Chronic Respiratory Questionnaire—Dyspnoea Subscale; CRQ-M, Chronic Respiratory Questionnaire—Mastery; ED, emergency department; Elec, electrolytes; Epworth SS, Epworth Sleepiness Scale; ESAS, Edmonton Symptom Assessment Scale; EQ-5D-5L, Five-Level EuroQol five dimensions questionnaire; FEV1/FVC, forced expiratory volume in 1s over forced expiratory volume; FBC, full blood count; GIC, Global Impression of Change; HADS, Hospital Anxiety and Depression Scale; Hx, history; KSS, Karolinska Sleepiness Scale; LFT, Liver Function Tests; LSQ, Leeds Sleep Questionnaire; LTOT, long-term oxygen therapy; Med, medical; mMRC, Modified Medical Research Council Dyspnoea Scale; PD, pharmacodynamic; PG, pharmacogenetic; PK, pharmacokinetic; SLUMS, St Louis University Mental State Examination; SOWS, Subjective Opioid Withdrawal Scale; ZCBS, Zarit Caregiver Burden Scale (short form).
impaired breathlessness. Signs suggestive of opioid toxicity will result in urgent physician assessment, investigation of contributing factors and treated with either opioid dose reduction or naloxone according to the severity of the toxicity and degree of respiratory compromise.

Reasons for cessation of study drug or withdrawal from the study include treatment failure as defined by unacceptable side effects of NCI CTCAEv4 grade 3 that do not settle with symptomatic intervention or grade 4 or 5 harms. Participants may also be withdrawn if treatment is deemed ineffective by treating clinician, increasing breathlessness scores despite study treatment or withdrawal of participant consent.

Substudies

As previously mentioned, the BEAMS study protocol also incorporates nine substudies (table 4). Participants may elect to participate in one or more of these to enrich the study data collection. The timing of the substudy assessments are also detailed in table 3.

Morphine/metabolite levels substudy

Participants who consent to be included in this substudy will have one blood taken at baseline and then trough levels on 1 day at the end of the first and third weeks of the study. Levels for morphine and its active metabolites (morphine, morphine-3-glucuronid and morphine-6-glucuronide) will be analysed and response to chronic breathlessness parameters explored. This will be particularly important in terms of symptomatic response to the two morphine dose levels for the primary outcome and to adverse effects for the secondary outcomes.

Pharmacogenetic substudy

Changes in the binding capacity of the mu-opioid receptor (MOR) or in the pathways of morphine metabolism are thought to account for observed variation in the responses to opioids.87 Although such variations are being increasingly described in the context of response of pain to opioids, they have yet to be tested prospectively in the response of breathlessness.88 Participants who consent to inclusion in the pharmacogenetic substudy will have a single baseline blood test taken for laboratory analysis. Blood samples will be assessed for the presence of single-nucleotide polymorphisms (SNPs) known to modify MOR activity including A118G, UGT2B7*2 and 828 polymorphisms. P-glycoprotein (ABCB1 5SNPs in a haplotype block) and interleukins (IL), IL-1B and IL-6, and other innate immune pathway gene variants as well as variants associated with opioid responses (such as catechol-O-methyltransferase) will also be measured given their association with morphine requirements in acute pain.88 Previous work by the investigators has shown that different doses of morphine may be required by different people to manage chronic breathlessness.89 It has also been shown in a hypothesis generating study of 112 SNPs from 25 genes that people on morphine with 5-hydroxytryptamine type 3B gene rs7103572 SNP were three times more likely to have more intense breathlessness while on morphine.88

Baseline blood samples will be stored frozen then transferred to Adelaide for genetic analysis. Genetic analysis will be correlated with responses to randomised study interventions.

Sleep substudy

Thirty participants will be invited to undertake a home sleep study at baseline and during the last 3 days of stage 3 (post third randomisation in steady state). This will allow data collection on overnight measures of breathing and oxygenation to compare with more subjective sleep assessments and questionnaires. Following a demonstration of use, participants will be asked to wear an ApneaLink Plus (ResMed, San Diego, California, USA) home sleep diagnostic device for one night at baseline and one night during stage 3. The device will measure oximetry, nasal airflow pressures and chest movements and has a high sensitivity and specificity in defining breathing disturbances.89 90

Up to 20 participants will also be invited to undergo two laboratory polysomnography overnight sleep studies to objectively quantify sleep quality according to the GOLD standard.91 92

Driving substudy

A driving simulation task will be performed in 30 consenting participants to assess data on steering, crash incidence and reaction time using the AusEd (Woolcock Institute for Medical Research, Sydney, Australia) computer-based driving simulation programme.93 Participants will be asked to complete a baseline assessment questionnaire to capture driving history as well as a baseline simulation. Results will be compared with driving simulation assessments performed at day 2 and day 7 after the first randomisation and will be compared with data obtained on sleep quality94 and study medicines.

Patients’ and caregivers’ qualitative substudy

Previous qualitative studies have examined the experiences of patients and their caregivers living with chronic breathlessness as a result of COPD and their attitudes to use of opioids.95 Patients and caregivers will be approached at baseline to consent to be included in this substudy. They will be asked to participate in an individual qualitative interview exploring perceptions surrounding these issues in greater detail. As this substudy will also recruit participants who are unable to participate in BEAMS, it may capture data from people not willing to take morphine for symptomatic reduction of chronic breathlessness.

Economic evaluation substudy

The main objective of this substudy is to determine the incremental costs and consequences of ER morphine use for symptomatic management of chronic breathlessness in people with COPD. The primary outcome measure
<table>
<thead>
<tr>
<th>Substudy title</th>
<th>Participants</th>
<th>Substudy details</th>
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</table>
| Morphine/morphine metabolite sub-study     | 55           | ▶ Aim: to determine the relationship between the steady-state plasma concentrations of M3G and M6G along with the effects of renal function with change in breathlessness intensity  
▶ Blood samples collected at baseline and steady state at trough levels end of week 1 and week 3  |
| Pharmacogenetic substudy                   | All consenting | ▶ Aim: identification and assessment of genetic variations in opioid receptor, neuronal, immune, metabolic or signalling pathways that may influence clinical responsiveness to ER morphine for symptomatic treatment of chronic breathlessness  
▶ Blood sample collection at baseline  |
| Sleep substudy                             | 30 20        | ▶ Aim: to investigate the effect that study interventions have on sleep quality  
▶ Data obtained from Fitbit Charge HR for all participants  
▶ Thirty participants recruited to non-invasive, home-based sleep studies at baseline and at the end of stage 3  
▶ Up to 20 participants from two centres (Sydney and Adelaide) will participate in two formal overnight laboratory sleep studies at baseline and at the end of stage 3.  |
| Driving substudy                           | 20           | ▶ Aim: assess effects of introducing and steady-state ER morphine use on driving simulator performance in subgroup of participants  
▶ Short questionnaire to assess driving history  
▶ Participants from two centres (Sydney and Adelaide) will complete three 30 min office-based driving simulations. One at baseline, one on day 2 and again on day 7 of stage 1.  |
| Caregiver well-being substudy              | All consenting | ▶ Aim: to compare the impact on caregiver well-being between study interventions when compared with baseline  
▶ Caregivers asked to provide basic demographic data and complete the Zarit burden interview 12-item short-form questionnaire  
▶ Assess level of subjective burden at baseline and the end of stages 1, 2, 3 and 4 (or study withdrawal)  |
| Patient and caregiver qualitative substudy | All consenting | ▶ Aim: to understand the experience of living with chronic breathlessness and the attitudes towards ER morphine use for its symptomatic treatment  
▶ Limited to participants from Adelaide  
▶ Separate patient and caregiver qualitative interviews  
▶ People who decline to participate in the BEAMS study but who fulfil the inclusion criteria will also be offered participation in this substudy.  |
| Economic analysis substudy                 | All consenting | ▶ Aim: to compare within trial incremental costs and cost effectiveness of regular low-dose ER morphine using prospectively collected data  
▶ Data collected will include hospitalisations, presentations to emergency departments, use of primary care, allied health practitioners and palliative care services throughout the study and for 4 weeks after last study medication is given.  |
| Testosterone level substudy                | All consenting from stage 4 | ▶ Aim: to further evaluate changes in total testosterone levels given concerns in previous studies that suggest morphine may reduce testosterone levels  
▶ Prospectively obtained blood samples at baseline and on completion of stage 4  |
| Cortisol substudy                          | All consenting (who have not been on glucocorticoids in the preceding 4 weeks) | ▶ Aim: to understand if hypothalamic–pituitary–adrenal axis dysregulation of chronic disease is influenced by reduction in chronic breathlessness as a stressor, with some return of normal diurnal variation.  
▶ Saliva tests three times each of 8 days across the study.  |

BEAMS, Breathlessness, Exertion And Morphine Sulfate; ER, extended release; M3G, morphine, morphine-3-glucuronid; M6G, morphine-6-glucuronide.
of this study will be cost per responder as recommended by the Pharmaceutical Benefits Advisory Committee. Data will be collected from first randomisation to 28 days post treatment (or death, if shorter) for each patient regarding:

- Efficacy of study medicines;
- Days of survival;
- Days of survival with breathlessness rated as mild or absent;
- Five-Level EuroQol Five Dimensions Questionnaire scores of health-related quality of life;
- Number of inpatient admissions and presentations to emergency departments;
- Outpatient, general practitioner, palliative care team visits;
- Concomitant medicines.

These data will allow within-trial modelling using bootstrapping methods of replicates for costs and consequences of alternative strategies, allowing for covariance between costs and effects. Incremental net monetary benefit and cost-effectiveness acceptability curves will be estimated at potential threshold values for an additional responder. Quality-adjusted life years will be estimated if differences in QoL assessments are found between active treatment and placebo.

Testosterone substudy
All participants who consent to be included in the optional stage 4 study extension will be approached to participate in an additional substudy looking at prospective analysis of testosterone levels in patients on morphine. Participants who consent will have a blood sample taken at baseline for total testosterone levels and again at the end of the 6-month stage 4 extension.

Cortisol substudy
Evidence suggests that patients with moderate-to-severe breathlessness have dysregulation of the normal circadian rhythm of cortisol production characterised by flatter mean diurnal cortisol slopes compared with people with mild or no breathlessness. Importantly, flatter cortisol slopes have been shown to predict a decrease in function, worse physical performance and mortality in patients with chronic conditions. Morphine has been shown to relieve the sensation of breathlessness in people with chronic diseases which may decrease physiological stress and thus modify the hypothalamic–pituitary–adrenal axis’ response over time.

All willing participants will be included in this substudy unless they were treated with systemic corticosteroids in the previous 4 weeks or suffer from insulin-dependent diabetes. The salivary cortisol profile will be analysed with respect to two summary parameters recommended for cortisol assessment in randomised controlled trials:

1. diurnal cortisol slope
2. cortisol area under the curve.

Each participant will be required to collect three saliva samples per day across 8 days: 2 days at baseline, 2 days in stage 1, 2 days in stage 3 and 2 days at the end of the third month of the extension phase. Samples will be collected at 3, 6 and 12 hours after awakening using Salivette Cortisol devices (SARSTEDT, Australia). Within and between-group changes will be analysed from baseline through the follow-up period. Multilevel modelling will be used to conduct the statistical analysis.

Sample size calculation
All calculations assume a type I family-wise error rate (FWER) of 5% and type II error rate of 20% (power of 80%). The primary analysis comprises two comparisons made at the end of stage 1 (placebo compared with 8mg ER morphine and placebo compared with 16mg ER morphine), each assessed at alpha=0.025 (two sided) to protect the overall type 1 error rate. Using variance–covariance matrices from previous studies by PaCCSC that have investigated worst breathlessness in the previous 24 hours, it is calculated that a total sample size of 171 subjects will be required to provide over 80% power and allow for a 20% rate of attrition. To ensure a sample size sufficient to provide an adequately powered study, a blinded review of the SD of the difference will occur at one-third and two-thirds of the way through recruitment.

Statistical analysis
The first coprimary null hypothesis for the BEAMS study is that in people with COPD and chronic breathlessness, there is no difference in mean change from baseline to days 5-7 worst breathlessness intensity with the addition of regular, low-dose oral ER morphine when compared with placebo. The second coprimary null hypothesis is that in the same population, there is no difference in the mean change from baseline to days 5 to 7 in number of steps taken each day with the addition of regular, low-dose ER morphine when compared with placebo.

Appropriate statistical analysis will be performed to assess the validity of these null hypotheses on an intention to treat basis. Missing data will be imputed using multiple imputation with 50 resamples drawn.

The primary comparisons occur on the last 3 days of week 1; days 5 to 7 days post first randomisation. Primary comparisons are between:

1. Placebo MP342 compared with 8mg ER morphine daily;
2. Placebo MP342 compared with 16mg ER morphine daily.

To control the FWER for each coprimary endpoint at 5%, each pairwise treatment comparison described above will be tested at the two-sided 2.5% significance level. The comparison will be deemed to be statistically significant if the associated p value is less than 0.025. To control the family-wise error rate at 5% across both coprimary endpoints, a hierarchical testing procedure will be used where the second coprimary endpoint for a particular pairwise treatment comparison will only be tested if
the first coprimary endpoint for that pairwise treatment comparison is statistically significant.

Change in worst breathlessness in the previous 24 hours between these groups will be evaluated using a linear random effects mixed-model adjusting for baseline score and using days 5–7 scores as outcomes, clustering over site and individual to account for correlated readings. The dependent variable is worst breathlessness in the previous 24 hours, and the independent variables are group, day (and the interaction term of group and day), age, gender, baseline breathlessness, Charlson Comorbidity Index score, baseline end-tidal CO₂, baseline oxygen saturation and AKPS. The effect of the interventions will be assessed as the difference between groups in mean change from baseline over days 5–7 at the end of week 1 (stage 1).

The difference in groups of who respond will also be explored using 2×2 tables of the proportion of people who achieve ≥1 point reduction in intensity of worse breathlessness in both primary comparison groups and tested using χ². Baseline clinical and demographic predictors of response to opioids will also be explored in a secondary regression model to identify any participant subgroups who may be more likely to respond or indeed those who experience harm from study interventions. Standard sensitivity analyses will be undertaken with other prognostic factors entered into the model. For all secondary endpoints where the two pairwise treatment comparisons are tested (placebo compared with 8 mg morphine; and placebo compared with 16 mg morphine), the FWER for that endpoint will be controlled at 5% by testing each pairwise treatment comparison at the two-sided 2.5% significance level. The comparison will be deemed to be statistically significant if the associated p-value is less than 0.025.

Effects of any dose–response relationship will be assessed through comparison of the data obtained in stage 2 and 3 of the study of participants who achieve a ≥1 point benefit at primary endpoint.

The FitBit Charge HR will provide data on step count and sleep-related information for each participant. Differences in absolute and percentage change (average of the changes at days 5, 6 and 7 of stage 1) for these data will be analysed. The second collection period during randomisation 3 will be a secondary outcome.

Additional analysis will describe changes in worst breathlessness up to 14 days after last dose increment and any additional benefit in responders (>1 point improvement) after subsequent blinded dose increment.

**Ethical considerations**

As detailed previously, patient safety will remain of paramount importance throughout the study period. Adverse events and serious adverse events will be reported using a secure online reporting system to enable study wide reporting and reviewed by an independent contracted Data Safety Monitoring Committee. Serious adverse events will also be reported to the relevant human research ethics committee.

All study measures have been validated and selected to provide high-quality data while ensuring minimal physical stress to participants. The only invasive procedure involved is blood testing which while potentially uncomfortable has been kept to an absolute minimum.

It is acknowledged that this is a potentially vulnerable study population and discussion of sensitive issues related to functional status and quality of life may cause emotional or psychological stress. As such, the research team will always be attuned to monitoring for signs of participant distress and ongoing training will be provided to the research teams in conjunction with GCP principles. Carefully selected and trained staff will undertake all participant interactions.

Consent to participate in BEAMS and the relevant substudies will be obtained by a research team member not involved in the participant’s usual clinical care so that the potential participant is not in a dependant relationship with the person discussing the study. This will also assist with the separation of research and clinical responsibilities. All participants retain the ability to decline to participate in the study and participants can withdraw at any time without detriment to the provision or quality of their clinical care.

The protocol has been reviewed and approved by the Hunter New England Human Research Ethics Committee (HREC) (Reference No. 15/12/16/3.06) and New South Wales HREC (Reference No. HREC/15/HNE/502). Each individual collaborating site has also each obtained relevant Research Governance Office approvals to recruit to this study.

**Confidentiality**

Participants will be allocated a unique ID number at entry and investigators will only have access to data by ID number only for both monitoring and analysis. The master list linking participant personal information and ID number will be maintained in a password-protected hard drive. Records relating to the study will be retained for 15 years after study completion and then destroyed in accordance with PaCCSC standard operating procedures consistent with current HREC requirements.

**Dissemination**

The results of this trial will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences. If the study shows a net benefit, contact will also be made with key professional groups and regulatory and funding bodies. Negative findings will also be reported.

**DISCUSSION**

This study protocol describes a large, multisite randomised study to further increase the evidence base for the use of ER morphine for chronic breathlessness in patients with COPD. There is a continued need for adequately powered, high-quality studies investigating this important area of symptom control. Equally, there is a need to ensure...
adequate clinical evidence of benefit and minimal harms so physicians are reassured of the evidence-based safety of ER morphine for the symptom of chronic breathlessness, including benefits beyond 1 week.

The BEAMS study will answer several practical questions. First, it will address if regular, low-dose ER morphine at four possible once-daily doses over 3 weeks is more effective than placebo at improving breathlessness. It will therefore address the question of whether any beneficial clinical effect of ER morphine can be increased further by increased morphine dose. Through use of multiple assessments, BEAMS will allow determination of the effects on daily activity and quality of life while ensuring any potential serious side effects of ER morphine are documented and quantified. Regression analysis may also allow determination of participant subgroups that may be more likely to benefit from ER morphine for chronic breathlessness in COPD.

It is hypothesised that if the threshold for activity limited by breathlessness can be increased then, over time, mobility may also increase, even if the worst breathlessness experienced stays the same or even increases as people are able to tolerate activity better. Previous studies have shown that in patients with COPD, regular physical activity leads to both reduced COPD-related hospital admissions and mortality. The activity component to this study will therefore assess if ER morphine to manage chronic breathlessness may also improve activity.

BEAMS began recruitment in September 2016 and complete recruitment is anticipated within 2 years.

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A pragmatic, phase III, multisite, double-blind, placebo-controlled, parallel-arm, dose increment randomised trial of regular, low-dose extended-release morphine for chronic breathlessness: Breathlessness, Exertion And Morphine Sulfate (BEAMS) study protocol

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