BMJ Open 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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ABSTRACT

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

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.

at relevant conferences and potentially used to inform registration of ER morphine for chronic breathlessness.

Trial registration number NCT02720822; Pre-results.

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.⁵ It is not only a highly feared symptom in those approaching end of life⁴ but unlike many other symptoms, breathlessness typically worsens, despite treatment, as death approaches.^{5,6}

Defined as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'⁷ breathlessness can be described as chronic when it persists despite the maximal treatment of reversible causes.^{8–10} Chronic breathlessness is a distinct syndrome with implications for patients, caregivers, health services, funders and researchers.¹¹ The subjective experience of chronic breathlessness cannot be accurately predicted by diagnosis^{12,13} or by standard physiological respiratory measures such as spirometry, oxygen saturations and respiratory rate.^{14–16} However, despite the lack of investigative predictors, chronic breathlessness is severely debilitating both physically and psychologically.^{4,13} 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.¹⁷ Anxiety can both aggravate chronic breathlessness as well as arise from it.¹⁸ Depression and overall reduced quality of life are also prevalent.^{19,20} Worsening chronic breathlessness is associated with worsening and physical and mental components of quality of life at a population level.²¹

Chronic breathlessness has a prevalence of 9%–11% in the general community.^{22,23} As the incidence of chronic obstructive pulmonary disease (COPD), heart failure and other causes of breathlessness²⁴ continue to rise globally,²⁵ 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^{10,26,27} although there is increasingly robust evidence for various non-pharmacological and pharmacological interventions.^{10,28} Systematic reviews support the use of walking aids²⁹ and pulmonary rehabilitation,³⁰ and there is randomised trial evidence for multidisciplinary breathlessness support services³¹ and for nurse-led clinic support.³² Phase III clinical trial data¹⁶ and a meta-analysis³³ 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.³⁴ Other studies have produced conflicting results³⁵ and data in daily life settings are limited.^{36,37}

The beneficial clinical role for morphine in chronic breathlessness is becoming increasingly established.³⁸ In vivo laboratory-controlled trials demonstrate opioids modulate the work of breathing during exercise and resistive load breathing in both healthy volunteers³⁹ and those with COPD.^{40,41} 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.^{9,42} These data are further validated in two recent systematic reviews and meta-analyses specifically exploring opioids for the relief of breathlessness in COPD.^{43,44} Although systemic morphine improves breathlessness in COPD, there is no evidence to date that it improves exercise capacity measured by 6 min walk test or duration on treadmill.⁴³

Pharmacovigilance data show no evidence of tachypnoea or tolerance during up to 22 months of follow-up of people using ER morphine for chronic breathlessness with dose titrated to benefit.⁴⁵ 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^{46–48} although the benefits can be easily negated by any side effects from the ER morphine.⁴⁹ 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.^{48,50} Additionally, there is some evidence demonstrating increased sleep quality when using opioids for breathlessness.⁵¹

Despite recent recommendations in several international clinical guidelines,^{15,26,27} 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'⁵² and that opiates can relieve dyspnoea,⁵³ some physicians remain reluctant to prescribe morphine and other opioids for breathlessness.^{46,54} 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 effects⁵⁵ and from other population data of opioid prescribing, it is highly unlikely that very many of these prescriptions were for chronic breathlessness.⁵⁶ 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.^{43,45} Additionally, all relevant systematic reviews comment on the low incidence of morphine-related serious adverse effects.^{38,43}

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.⁵⁷ Adherence is improved with the use of once daily preparations,⁵⁸ an approach which is also preferred by patients.⁵⁹ Further, randomised

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.

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 reporting^{62 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

Box 2 List of recruiting centres**New South Wales**

Sacred Heart Health Service, Darlinghurst
Calvary Mater, Newcastle
Calvary Healthcare, Kogarah
Liverpool Hospital, Liverpool
Concord Repatriation Hospital, Concord
Greenwich Hospital, Greenwich

Queensland

Mater Health Service, Brisbane
The Prince Charles Hospital, Chermside
Nambour Hospital, Nambour
St Vincents Private Hospital, Brisbane

South Australia

Southern Adelaide Palliative Services, Daw Park
Repatriation General Hospital, Daw Park

Victoria

Barwon Health, Geelong
Royal Melbourne Hospital, Melbourne
St Vincent's Hospital, Melbourne
Austin Hospital, Heidelberg

Western Australia

Sir Charles Gairdner Hospital, Nedlands

(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;

- 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) criteria⁶⁷;
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

Table 1 The five stages of the BEAMS study

	Time period	Detail
Stage 0	2 days	Baseline assessments: <ul style="list-style-type: none"> ► Diary entries for 2 days to provide stable baseline data and to become accustomed to data collection tools ► Baseline demographic data, physical assessment, research team mediated questionnaires, assessments and testing ► Fitbit assessment of baseline function ► Provided with handheld fan and practical advice on managing breathlessness
Stage 1	1 week	First randomisation: <ul style="list-style-type: none"> ► Randomisation 1:1:1 to receive either placebo or 8mg ER morphine or 16mg ER morphine ► Participants receiving ER morphine will also receive docusate with senna. Placebo arm will receive identical placebo laxative ► Fitbit assessment of function
Stage 2	1 week	Second randomisation: <ul style="list-style-type: none"> ► While continuing in arm assigned at first randomisation, add second randomised treatment. ► 1:1 randomisation to the addition of either placebo or 8mg ER morphine ► Blinded docusate with senna will replace laxative placebo for those newly randomised to receive ER morphine.
Stage 3	1 week	Third randomisation: <ul style="list-style-type: none"> ► While continuing in arms assigned at first and second randomisation, add third randomised treatment. ► 1:1 randomisation to addition of either placebo or 8mg ER morphine ► Blinded docusate with senna will replace laxative placebo for those newly randomised to receive ER morphine. ► Fitbit assessment of function
Stage 4	Up to 6 months	Optional extension study: <ul style="list-style-type: none"> ► Participant may continue blinded treatment for up to 6 months on the final dose to which they were titrated. ► Assessments establishing long-term net effects of study medication

BEAMS, Breathlessness, Exertion And Morphine Sulfate; ER, extended release.

breathlessness. They will also be provided with a battery-operated, handheld fan⁷⁰ 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 8mg or 16mg 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 50mg with sennosides 8mg) 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^{1 71} 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 8mg ER morphine and placebo and 16mg ER morphine and placebo. A difference of one point on NRS will be considered a clinically meaningful difference; consistent with consensus statements⁷² and empirical studies.⁷³

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.⁷⁴ This directly reflects previous work that compared the performance of NRS measures of breathlessness with a modified Borg scale in 1048 participants.⁷⁵ 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.⁷⁶ 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.⁷⁷

Box 3 Exclusion criteria

- ▶ Opioid use for breathlessness in the previous 7 days
- ▶ Regular opioid use for any other reason (including codeine preparations) at or above 8mg oral morphine equivalent per day in the previous 7 days
- ▶ History of adverse reactions to any study medications or placebo constituents
- ▶ An Australian-modified Karnofsky Performance Score¹⁰⁸ of less than 50 at baseline assessment
- ▶ Respiratory or cardiac event in the previous 7 days excluding upper respiratory tract infections. Acute illness should be deemed as resolved prior to baseline assessment by participant's treating physician
- ▶ A resting respiratory rate of <8 breaths per minute
- ▶ Documented central hypoventilation syndrome
- ▶ Current or recent history of abuse of alcohol or substance misuse
- ▶ Uncontrolled nausea, vomiting or evidence of gastrointestinal tract obstruction
- ▶ Renal dysfunction with calculated creatinine clearance of less than 20 mL/min
- ▶ Evidence of severe hepatic impairment as defined as greater than four times normal transaminase levels or bilirubin level (excluding Gilbert's syndrome)
- ▶ Current pregnancy or breastfeeding

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 8mg ER morphine and placebo and 16mg 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 COPD⁶⁷ in previous studies comparing exercise training in participants with varying levels of COPD.^{78 79} Accelerometers measure habitual physical activity with a 3–5 day period of recording considered sufficient to have stable data.⁸⁰ By contrast, a 6min walk test measures functional exercise capacity,⁸¹ 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.^{43 82}

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.⁸³

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 Scale⁸⁴ 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 2 Overview of the questionnaires and scales used in the BEAMS study

Breathlessness assessments	<p>Intensity of worst breathlessness over the previous 24 hours</p> <ul style="list-style-type: none"> ▶ NRS ▶ 0–10 (11-point) scale ▶ 0 = ‘no breathlessness’ to 10 = ‘worst possible breathlessness’ <p>Unpleasantness of worst breathlessness over the previous 24 hours</p> <ul style="list-style-type: none"> ▶ NRS ▶ 0–10 (11-point) scale ▶ 0 = ‘breathing is not unpleasant’ to 10 = ‘most unpleasant breathlessness possible’ <p>mMRC^{109 110}</p> <ul style="list-style-type: none"> ▶ Five-point (0–4) categorical breathlessness scale ▶ Descriptive measure of functional impairment due to breathlessness; lower scores indicate less breathlessness. <p>CRQ-DS^{111 112}</p> <ul style="list-style-type: none"> ▶ Total of 20 questions covering social and emotional symptoms and perceptions of breathlessness in relation to five activities over the preceding 2 weeks ▶ Higher scores indicate better respiratory function. <p>CRQ-M¹¹³</p> <ul style="list-style-type: none"> ▶ Assessment of perceived change in patient mastery over their breathlessness ▶ Higher scores indicate better mastery.
Baseline assessments	<p>CCMI¹¹⁴</p> <ul style="list-style-type: none"> ▶ Severity and number of comorbid conditions incorporated into a single score. ▶ Score will be unweighted and not include participants life-limiting illness. ▶ Independent predictor of long-term survival¹¹⁵ <p>SLUMS⁶⁸</p> <ul style="list-style-type: none"> ▶ 11-item questionnaire scored out of 30; testing memory, orientation, attention and executive functions ▶ Score adjusted for school education. <p>ESAS¹¹⁶</p> <ul style="list-style-type: none"> ▶ Rating of severity of coexisting symptoms on a numeric rating scale from 0 to 10 ▶ Sum of scores is termed symptom distress score. Higher scores equate higher levels of distress.
Performance and activity assessors	<p>Activity monitoring</p> <ul style="list-style-type: none"> ▶ Daily step count measured by Fitbit Charge HR wearable step count technology device ▶ Provides data and insight into overall physical activity including steps per day, sleep minutes and sleep activity, activity and sedentary levels and total energy expenditure¹¹⁷ ▶ Motion sensors provide an objective, reliable, valid and responsive measure^{118 119} <p>AKPS¹⁰⁸</p> <ul style="list-style-type: none"> ▶ Validated variant of Karnofsky Performance Status ▶ 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. <p>Barthel Index (clinician rated)^{120–122}</p> <ul style="list-style-type: none"> ▶ Assess impairment of ADLs through assessment of 10 variables ▶ Higher scores indicate associated with increased independence with ADLs.
Mood	<p>HADS¹²³</p> <ul style="list-style-type: none"> ▶ 14-item questionnaire consisting of two seven-item subscales looking at depression and anxiety, respectively ▶ Higher scores are associated with greater morbidity.

Continued

Table 2 Continued

Quality of life assessments	Quality of Life EQ-5D-5L ¹²⁴
	<ul style="list-style-type: none"> ▶ 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 ¹²⁵
	<ul style="list-style-type: none"> ▶ 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 ¹²⁶
	<ul style="list-style-type: none"> ▶ 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 original¹²⁷ ▶ Higher scores imply better global quality of life.
Sleep assessments	ESS ¹²⁸
	<ul style="list-style-type: none"> ▶ Validated tool for characterising daytime sleepiness ▶ Eight questions rated on a four-point scale
	LSEQ ¹²⁹
	<ul style="list-style-type: none"> ▶ 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 ^{130 131}
	<ul style="list-style-type: none"> ▶ 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 ¹³²
	<ul style="list-style-type: none"> ▶ Caregiver well-being assessment 12-item short form questionnaire¹³³ ▶ Commonly used questionnaire assessing level of subjective caregiver burden rated on a five-point Likert scale
Adverse effects	SOWS ⁸⁴
	<ul style="list-style-type: none"> ▶ 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.

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)⁸⁵ grade ≥ 3 for cognitive

Table 3 Overview of assessments by stage of study

Time point	Stage 0		Stage 1	Stage 2	Stage 3	Stage 4	End
	Eligibility	Baseline	End of week 1*	End of week 2	End of week 3	End of 3 months	Withdrawal or completion
History and demographics	✓						
	✓						
		✓					✓
	✓						
	✓						
	✓						
Investigations	✓						
	✓						
	✓						
		✓	✓	✓	✓		
		✓	✓	✓	✓		
		✓	✓	✓	✓		✓
		✓	✓		✓		
		✓	✓				
Participant mediated			✓	✓	✓	✓	✓
	Diary entries	✓	✓	✓	✓	✓	✓
	HADS	✓	✓				✓
	CAT	✓	✓			✓	✓
	CRQ-DS and CRQ-M	✓	✓			✓	✓
	EQ-5D-5L	✓	✓			✓	✓
	Epworth SS	✓	✓			✓	
	LSQ	✓	✓			✓	
	KSS	✓	✓				
	ESAS	✓	✓				✓
	Blinded preference		✓	✓	✓	✓	✓
	SOWS		✓				✓

Continued

Table 3 Continued

Time point	Stage 0		Stage 1	Stage 2	Stage 3	Stage 4	End
	Eligibility	Baseline	End of week 1*	End of week 2	End of week 3	End of 3 months	Withdrawal or completion
Research team mediated	AKPS	✓	✓	✓	✓	✓	✓
	mMRC	✓	✓	✓	✓		
	GIC		✓	✓	✓	✓	✓
	Barthel Index	✓					✓
	Blinded preference		✓	✓	✓		
	Side effects	✓	✓	✓	✓	✓	✓
	CCI	✓					
	SLUMS	✓					
	Compliance		✓	✓	✓	✓	
	Inpatient stay days		✓	✓	✓	✓	✓
Economic	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 1 s 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).

impairment, confusion or somnolence. 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.⁸⁶ 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.⁸⁷ 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.⁸⁶ Previous work by the investigators has shown that different doses of morphine may be required by different people to manage chronic breathlessness.⁶ 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 inlaboratory 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.^{46 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 4 Brief description of the substudies included in the BEAMS study protocol

Substudy title	Participants	Substudy details
Morphine/morphine metabolite sub-study	55	<ul style="list-style-type: none"> ► 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	<ul style="list-style-type: none"> ► 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	<ul style="list-style-type: none"> ► 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	<ul style="list-style-type: none"> ► 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 30min 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	<ul style="list-style-type: none"> ► 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 questionnaire¹³³ ► 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	<ul style="list-style-type: none"> ► 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	<ul style="list-style-type: none"> ► 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	<ul style="list-style-type: none"> ► Aim: to further evaluate changes in total testosterone levels given concerns in previous studies that suggest morphine may reduce testosterone levels^{134 135} ► 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)	<ul style="list-style-type: none"> ► 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.⁹⁶ 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.⁹⁷ Incremental net monetary benefit⁹⁸ and cost-effectiveness acceptability curves⁹⁹ 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.¹⁰⁰ Importantly, flatter cortisol slopes have been shown to predict a decrease in function, worse physical performance and mortality in patients with chronic conditions.^{101–103} 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 trials¹⁰⁰:

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 8 mg ER morphine and placebo compared with 16 mg 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,¹⁰⁴ 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:

- ▶ Placebo MP342 compared with 8 mg ER morphine daily;
- ▶ Placebo MP342 compared with 16 mg 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 χ^2 . 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.⁶⁹ 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.¹⁰⁵ Previous studies have shown that in patients with COPD, regular physical activity leads to both reduced COPD-related hospital admissions and mortality.^{106 107} 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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the original study protocol for publication. MJJ: contributed to the concept and study design, manuscript drafts and approved the final version. CFM: contributed to study design, review of protocol and manuscript drafting and review. JOM: conception, design and review of final paper. AAS: contributed specifically to the pharmacogenomics aspect of the paper. LD: contributed to the grant that funds this research, particularly to the measurement protocol of physical activity; reviewed and contributed to the final submission of the paper. NM: substantial contribution to the design of the study, particularly the economic evaluation; critical revision of the manuscript for important intellectual content; approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DJE: provided feedback on the manuscript, designed the sleep components and assisted with the driving simulator aspects of the protocol. PM: performed a statistical review of the protocol and proposed sample size. SL: performed a statistical review of the protocol and proposed sample size. LL: provided statistical review for the manuscript as well as reviewed and commented on the drafts of the manuscript. AG: involved in protocol design and development and played a role in critique and developing the definitive journal article. BF: contributed to the development and critical review of the study protocol, critical and editorial review of the structure and content of the manuscript and provision of underlying data and explanations. KCC: contributed to the drafting of the manuscript. KF: read, reviewed and agreed with the final protocol. MA: involved in the study conception, design and methods and critical review of the manuscript. RJ: contributed to the design of the research project and review of the manuscript. SK: contributed to the design of the research project and review of the manuscript. DF: contributed to the critical review of the study protocol and the structure and content of the manuscript; contribution to the substudy design. ME: participated in designing the study protocol, revised the manuscript and approved the final version to be published.

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REFERENCES

- O'Donnell DE, Banzett RB, Carrieri-Kohlman V, *et al.* Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007;4:145–68.
- Burki NK, Lee LY. Mechanisms of dyspnea. *Chest* 2010;138:1196–201.
- Currow DC, Farquhar M, Ward AM, *et al.* Caregivers' perceived adequacy of support in end-stage lung disease: results of a population survey. *BMC Pulm Med* 2011;11:55.
- O'Driscoll M, Corner J, Bailey C. The experience of breathlessness in lung Cancer. *Eur J Cancer Care* 1999;8:37–43.
- Mercadante S, Casuccio A, Fulfaro F. The course of symptom frequency and intensity in advanced Cancer patients followed at home. *J Pain Symptom Manage* 2000;20:104–12.
- Currow DC, Smith J, Davidson PM, *et al.* Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the

- end of life? A consecutive cohort study. *J Pain Symptom Manage* 2010;39:680–90.
7. American Thoracic Society. Dyspnea: mechanisms, assessment, and management. A consensus statement. *Am J Respir Crit Care Med* 1999;159:321–40.
 8. Booth S, Bausewein C, Higginson I, et al. Pharmacological treatment of refractory breathlessness. *Expert Rev Respir Med* 2009;3:21–36.
 9. Abernethy AP, Currow DC, Frith P, et al. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *BMJ* 2003;327:523–9.
 10. Ekström MP, Abernethy AP, Currow DC. The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ* 2015;349:g7617.
 11. Johnson MJ OA, Yorke J, Hansen-Flaschen J, et al. An International Delphi process to delineate the clinical syndrome of chronic breathlessness. *Eur Resp J*. In Press. 2017.
 12. Dudgeon DJ, Kristjanson L, Sloan JA, et al. Dyspnea in cancer patients: prevalence and associated factors. *J Pain Symptom Manage* 2001;21:95–102.
 13. Tanaka K, Akechi T, Okuyama T, et al. Factors correlated with dyspnea in advanced lung cancer patients: organic causes and what else? *J Pain Symptom Manage* 2002;23:490–501.
 14. Grønseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J* 2014;43:1610–20.
 15. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012;185:435–52.
 16. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010;376:784–93.
 17. Tanaka K, Akechi T, Okuyama T, et al. Prevalence and screening of dyspnea interfering with daily life activities in ambulatory patients with advanced lung Cancer. *J Pain Symptom Manage* 2002;23:484–9.
 18. Bruera E, Schmitz B, Pither J, et al. The frequency and correlates of dyspnea in patients with advanced Cancer. *J Pain Symptom Manage* 2000;19:357–62.
 19. Tanaka K, Akechi T, Okuyama T, et al. Impact of dyspnea, pain, and fatigue on daily life activities in ambulatory patients with advanced lung Cancer. *J Pain Symptom Manage* 2002;23:417–23.
 20. Hill K, Geist R, Goldstein RS, et al. Anxiety and depression in end-stage COPD. *Eur Respir J* 2008;31:667–77.
 21. 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 (Epub ahead of print 2017 Mar 29).
 22. Currow DC, Plummer JL, Crockett A, et al. A community population survey of prevalence and severity of dyspnea in adults. *J Pain Symptom Manage* 2009;38:533–45.
 23. Bowden JA, To TH, Abernethy AP, et al. Predictors of chronic breathlessness: a large population study. *BMC Public Health* 2011;11:33.
 24. Moens K, Higginson IJ, Harding R; EURO IMPACT. Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. *J Pain Symptom Manage* 2014;48:660–77.
 25. Celli BR, MacNee W, Agusti A; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–46.
 26. Marciniuk DD, Goodridge D, Hernandez P, et al. Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a canadian thoracic Society clinical practice guideline. *Can Respir J* 2011;18:69–78.
 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;137:674–91.
 28. Uronis HE, Currow DC, Abernethy AP. Palliative management of refractory dyspnea in COPD. *Int J Chron Obstruct Pulmon Dis* 2006;1:289–304.
 29. Bausewein C, Booth S, Gysels M, et al. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev* 2008;2:CD005623.
 30. McCarthy B, Casey D, Devane D, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015;2:CD003793.
 31. Higginson IJ, Bausewein C, Reilly CC, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014;2:979–87.
 32. Bredin M, Corner J, Krishnasamy M, et al. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung Cancer. *BMJ* 1999;318:901–4.
 33. Uronis HE, Currow DC, McCrory DC, et al. Oxygen for relief of dyspnoea in mildly- or non-hypoxaemic patients with cancer: a systematic review and meta-analysis. *Br J Cancer* 2008;98:294–9.
 34. Moore RP, Berlowitz DJ, Denehy L, et al. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax* 2011;66:32–7.
 35. Uronis HE, Ekström MP, Currow DC, et al. Oxygen for relief of dyspnoea in people with chronic obstructive pulmonary disease who would not qualify for home oxygen: a systematic review and meta-analysis. *Thorax* 2015;70:492–4.
 36. Ringbaek T, Martinez G, Lange P. The long-term effect of ambulatory oxygen in normoxaemic COPD patients: a randomised study. *Chron Respir Dis* 2013;10:77–84.
 37. Currow DC, Agar M, Smith J, et al. Does palliative home oxygen improve dyspnoea? A consecutive cohort study. *Palliat Med* 2009;23:309–16.
 38. 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.
 39. Banzett RB, Adams L, O'Donnell CR, et al. Using laboratory models to test treatment: morphine reduces dyspnea and hypercapnic ventilatory response. *Am J Respir Crit Care Med* 2011;184:920–7.
 40. Mahler DA, Murray JA, Waterman LA, et al. Endogenous opioids modify dyspnoea during treadmill exercise in patients with COPD. *Eur Respir J* 2009;33:771–7.
 41. Gifford AH, Mahler DA, Waterman LA, et al. Neuromodulatory effect of endogenous opioids on the intensity and unpleasantness of breathlessness during resistive load breathing in COPD. *COPD* 2011;8:160–6.
 42. Jennings AL, Davies AN, Higgins JP, et al. A systematic review of the use of opioids in the management of dyspnoea. *Thorax* 2002;57:939–44.
 43. 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;12:1079–92.
 44. Ekström MP, Bajwah S, Bland JM, et al. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax* 2017 (Epub ahead of print 2017 April 4).
 45. 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;42:388–99.
 46. Rocker G, Young J, Donahue M, et al. Perspectives of patients, family caregivers and physicians about the use of opioids for refractory dyspnea in advanced chronic obstructive pulmonary disease. *CMAJ* 2012;184:E497–504.
 47. Rocker GM, Simpson AC, Horton R, Joanne Young B, et al. Opioid therapy for refractory dyspnea in patients with advanced chronic obstructive pulmonary disease: patients' experiences and outcomes. *CMAJ Open* 2013;1:E27–36.
 48. 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.
 49. Ferreira DH, Silva JP, Quinn S, et al. Blinded patient preference for morphine compared to placebo in the setting of chronic refractory breathlessness—an exploratory study. *J Pain Symptom Manage* 2016;51:247–54.
 50. 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;48:683–93.
 51. Martins RT, Currow DC, Abernethy AP, et al. Effects of low-dose morphine on perceived sleep quality in patients with refractory breathlessness: a hypothesis generating study. *Respirology* 2016;21:386–91.
 52. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017;195:557–82.

53. Global strategy for the diagnosis, management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease. 2017 <http://goldcopd.org>.
54. Young J, Donahue M, Farquhar M, *et al.* Using opioids to treat dyspnea in advanced COPD: attitudes and experiences of family physicians and respiratory therapists. *Can Fam Physician* 2012;58:e401–7.
55. Vozoris NT, Wang X, Fischer HD, *et al.* Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol* 2016;81:161–70.
56. Ahmadi Z, Berneld E, Currow DC, *et al.* Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. *Int J Chron Obstruct Pulmon Dis* 2016;11:2651–7.
57. Gourlay GK, Cherry DA, Onley MM, *et al.* Pharmacokinetics and pharmacodynamics of twenty-four-hourly kaptopril compared to twelve-hourly MS contin in the treatment of severe Cancer pain. *Pain* 1997;69:295–302.
58. Portenoy RK, Sciberras A, Eliot L, *et al.* Steady-state pharmacokinetic comparison of a new, extended-release, once-daily morphine formulation, Avinza, and a twice-daily controlled-release morphine formulation in patients with chronic moderate-to-severe pain. *J Pain Symptom Manage* 2002;23:292–300.
59. Broomhead A, Kerr R, Tester W, *et al.* Comparison of a once-a-day sustained-release morphine formulation with standard oral morphine treatment for Cancer pain. *J Pain Symptom Manage* 1997;14:63–73.
60. Klepstad P, Kaasa S, Jystad A, *et al.* Immediate- or sustained-release morphine for dose finding during start of morphine to Cancer patients: a randomized, double-blind trial. *Pain* 2003;101(1-2):193–8.
61. Kaplan R, Parris WC, Citron ML, *et al.* Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *Journal of Clinical Oncology* 1998;16:3230–7.
62. Chan AW, Tetzlaff JM, Altman DG, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
63. Chan AW, Tetzlaff JM, Gotzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
64. Schulz KF, Altman DG, Moher D. CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
65. Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;63:e1–37.
66. 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;16:881–6.
67. Vestbo J, Hurd SS, Agustí AG, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–65.
68. 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;14:900–10.
69. Group IEW. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice. Secondary ICH Harmonised Tripartite Guideline: guideline for Good Clinical practice. 1996 http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.
70. Galbraith S, Fagan P, Perkins P, *et al.* Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *J Pain Symptom Manage* 2010;39:831–8.
71. von Leupoldt A, Dahme B. Differentiation between the sensory and affective dimension of dyspnea during resistive load breathing in normal subjects. *Chest* 2005;128:3345–9.
72. Booth S. Improving research methodology in breathlessness: a meeting convened by the MRC clinical trials unit and the Cicely Saunders Foundation. *Palliat Med* 2006;20:219–20.
73. Johnson MJ, Bland JM, Oxberry SG, *et al.* Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage* 2013;46:957–63.
74. Currow DC, Ekström M, Fazekas B, *et al.* A Phase III, Multi-site, Randomised, Double Blind, Placebo Controlled Parallel Arm Study of Daily Extended Release (ER) Morphine for Chronic Breathlessness. . Madrid, Spain: 15th World Congress of the European Association for Palliative Care, 2017. Abstract number 98.
75. Johnson MJ, Close L, Gillon SC, *et al.* Use of the modified Borg scale and numerical rating scale to measure chronic breathlessness: a pooled data analysis. *Eur Respir J* 2016;47:1861–4.
76. Harris K, Li K, *et al.* Flynn CWorst, average or current pain in the Brief Pain Inventory: which should be used to calculate the response to palliative radiotherapy in patients with bone metastases? *Clin Oncol* 2007;19:523–7.
77. Atkinson TM, Mendoza TR, Sit L, *et al.* The brief pain inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med* 2010;11:337–46.
78. Troosters T, Gosselink R, Janssens W, *et al.* Exercise training and pulmonary rehabilitation: new insights and remaining challenges. *Eur Respir Rev* 2010;19:24–9.
79. Troosters T, Sciurba F, Battaglia S, *et al.* Physical inactivity in patients with COPD, a controlled multi-center pilot-study. *Respir Med* 2010;104:1005–11.
80. Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc* 2005;37:S531–S543.
81. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;14:270–4.
82. 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;12:1079–92.
83. Care CDoHaA. National Palliative Care Strategy: a National Framework for Palliative Care Service Development. . Publications Production Unit (Public Affairs, Parliamentary and Access Branch) Publications approval number 4065, 2000.
84. Handelsman L, Cochrane KJ, Aronson MJ, *et al.* Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987;13:293–308.
85. Institute NC. Common Terminology Criteria for adverse events (CTCAE) Version v4.0 NCI, NIH, DHHS. . NIH publication # 09-7473, 2009.
86. Somogyi AA, Barratt DT, Collier JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 2007;81:429–44.
87. Argoff CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain* 2010;26 Suppl 10(Suppl 10):S16–S20.
88. Currow DC, Quinn S, Ekstrom M, *et al.* Can variability in the effect of opioids on refractory breathlessness be explained by genetic factors? *BMJ Open* 2015;5:e006818.
89. Erman MK, Stewart D, Einhorn D, *et al.* Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med* 2007;3:387–92.
90. Ng SS, Chan TO, To KW, Ss N, Kw T, *et al.* Validation of a portable recording device (ApneaLink) for identifying patients with suspected obstructive sleep apnoea syndrome. *Intern Med J* 2009;39:757–62.
91. Kushida CA, Littner MR, Morgenthaler T, *et al.* Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep* 2005;28:499–523.
92. Van de Water AT, Holmes A, Hurley DA. Objective measurements of sleep for non-laboratory settings as alternatives to polysomnography—a systematic review. *J Sleep Res* 2011;20(1 Pt 2):183–200.
93. Desai AV, Wilshire B, Bartlett DJ, *et al.* The utility of the AusEd driving simulator in the clinical assessment of driver fatigue. *Behav Res Methods* 2007;39:673–81.
94. Vakulin A, Baulk SD, Catcheside PG, *et al.* Effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnea. *Ann Intern Med* 2009;151:447–55.
95. Oxberry SG, Jones L, Clark AL, *et al.* Attitudes to morphine in chronic heart failure patients. *Postgrad Med J* 2012;88:515–21.
96. Health Do. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) Version 4.5. Secondary Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) Version 4.5 2015 <http://www.pbac.pbs.gov.au/>.
97. Campbell MK, Torgerson DJ. Bootstrapping: estimating confidence intervals for cost-effectiveness ratios. *QJM* 1999;92:177–82.
98. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18(2 Suppl):S68–80.
99. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *Br J Psychiatry* 2005;187:106–8.
100. Ryan R, Clow A, Spathis A, *et al.* Salivary diurnal cortisol profiles in patients suffering from chronic breathlessness receiving supportive and palliative care services: a cross-sectional study. *Psychoneuroendocrinology* 2017;79:134–45.

101. Sephton SE, Lush E, Dedert EA, *et al.* Diurnal cortisol rhythm as a predictor of lung Cancer survival. brain, behavior, and immunity. *Brain Behav Immun* 2013;30:S163–70.
102. Gardner MP, Lightman S, Sayer AA, *et al.* Dysregulation of the hypothalamic pituitary adrenal (HPA) axis and physical performance at older ages: an individual participant meta-analysis. *Psychoneuroendocrinology* 2013;38:40–9.
103. Kumari M, Shipley M, Stafford M, *et al.* Association of diurnal patterns in salivary cortisol with all-cause and cardiovascular mortality: findings from the Whitehall II study. *J Clin Endocrinol Metab* 2011;96:1478–85.
104. Currow DC, Ekstrom M, Louw S, *et al.* A phase III, multi-site, randomised, double blind, placebo controlled, parallel arm study of daily, low dose extended release (ER) morphine for chronic breathlessness. , 2015. *ACTRN12609000806268*.
105. Currow DC, Abernethy AP, Johnson MJ. Activity as a measure of symptom control. *J Pain Symptom Manage* 2012;44:e1–e2.
106. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ* 2006;174:801–9.
107. Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006;61:772–8.
108. 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.
109. Stenton C. The MRC breathlessness scale. *Occup Med* 2008;58:226–7.
110. Bestall JC, Paul EA, Garrod R, *et al.* Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;54:581–6.
111. Puhan MA, Behnke M, Frey M, *et al.* Self-administration and interviewer-administration of the german chronic respiratory questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004;2:1–9.
112. Schünemann HJ, Guyatt GH, Griffith L, *et al.* A randomized controlled trial to evaluate the effect of informing patients about their pretreatment responses to two respiratory questionnaires. *Chest* 2002;122:1701–8.
113. Chauvin A, Rupley L, Meyers K, *et al.* Outcomes in Cardiopulmonary Physical Therapy: Chronic Respiratory Disease Questionnaire (CRQ). *Cardiopulm Phys Ther J* 2008;19:61–7.
114. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
115. de Groot V, Beckerman H, Lankhorst GJ, *et al.* How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol* 2003;56:221–9.
116. Bruera E, Kuehn N, Miller MJ, *et al.* The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7:6–9.
117. Van Remoortel H, Giavedoni S, Raste Y, *et al.* Validity of activity monitors in health and chronic disease: a systematic review. *Int J Behav Nutr Phys Act* 2012;9:84.
118. Pitta F, Troosters T, Probst VS, *et al.* Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J* 2006;27:1040–55.
119. Denehy L, Berney S, Whitburn L, *et al.* Quantifying physical activity levels of survivors of intensive care: a prospective observational study. *Phys Ther* 2012;92:1507–17.
120. Collin C, Wade DT, Davies S, *et al.* The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;10:61–3.
121. Novak S, Johnson J, Greenwood R. Barthel revisited: making guidelines work. *Clin Rehabil* 1996;10:128–34.
122. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud* 1988;10:64–7.
123. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
124. 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;20:1727–36.
125. Dodd JW, Hogg L, Nolan J, *et al.* The COPD assessment test (CAT): response to pulmonary rehabilitation. A multicentre, prospective study. *Thorax* 2011;66:425–9.
126. Oxberry SG, Bland JM, Clark AL, *et al.* Minimally clinically important difference in chronic breathlessness: every little helps. *Am Heart J* 2012;164:229–35.
127. Farrar JT, Young JP, LaMoreaux L, *et al.* Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.
128. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
129. Parrott AC, Hindmarch I. The Leeds Sleep evaluation questionnaire in psychopharmacological investigations - a review. *Psychopharmacology* 1980;71:173–9.
130. Kaida K, Takahashi M, Akerstedt T, *et al.* Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol* 2006;117:1574–81.
131. Akerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990;52(1-2):29–37.
132. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 1980;20:649–55.
133. Bédard M, Molloy DW, Squire L, *et al.* The Zarit Burden Interview: a new short version and screening version. *Gerontologist* 2001;41:652–7.
134. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. *Am J Med* 2014;127:1195–201.
135. Rubinstein AL, Carpenter DM, Minkoff JR. Hypogonadism in men with chronic pain linked to the use of long-acting rather than short-acting opioids. *Clin J Pain* 2013;29:840–5.