PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol: A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic breathlessness. The Breathlessness Exertion And Morphine Sulphate (BEAMS) Study Protocol.
AUTHORS	Currow, David; Watts, Gareth; Johnson, Miriam; McDonald, Christine; Miners, John; Somogyi, Andrew; Denehy, Linda; McCaffrey, Nikki; Eckert, Danny; McCloud, Philip; Louw, Sandra; Lam, Lawrence; Greene, Aine; Fazekas, Belinda; Clark, Katherine; Fong, Kwun; Agar, Meera; Joshi, Rohit; Kilbreath, S; Ferreira, Diana; Ekström, Magnus

VERSION 1 - REVIEW

REVIEWER	Steffen Simon Center for Palliative Medicine University Hospital of Cologne Germany I know the first and third author from congresses and research meetings on breathlessness.
REVIEW RETURNED	02-Jan-2017

GENERAL COMMENTS	The manuscript "Study Protocol: A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic breathlessness. The Breathlessness Exertion And Morphine Sulphate (BEAMS) Study Protocol" describes a protocol of a RCT evaluating morphine for chronic breathlessness in patients with COPD including eight sub-studies. The RCT aims to improve the evidence for the use of morphine to palliate chronic breathlessness assessing its effect on breathlessness severity and physical activity. Different doses (low doses) will be evaluated in a randomized design to give insights and further knowledge to the unanswered and clinical highly relevant question “Which is the optimal dose of morphine for the relief of breathlessness?”. The study group is well-known and very experienced in conducting high quality full powered RCTs in patients with palliative care needs. The study protocol is of high quality and meets/fulfills the criteria of SPIRIT. A few comments: • What is the rationale for using 8 and 16mg morphine – instead of 5 or 10 or 15 or 20mg (which will later be easier to deliver as most medicines have standard doses)? • Why do the authors include two questionnaires for sleep (ESS+KSS, page 16)? The differences are not explained in the protocol. • Most questionnaires are used at stage 0 and 1 but not at stage 2

	and 3 – why? The impact of different doses won't be evaluated leaving out stages 2+3.

REVIEWER	Nicholas Vozoris University of Toronto, Canada
REVIEW RETURNED	20-Feb-2017

GENERAL COMMENTS	Reviewer comments for "Study Protocol: A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic breathlessness. The Breathlessness Exertion And Morphine Sulphate (BEAMS) Study Protocol" (bmjopen-2016--015628) Major points: 1. Some of the study objectives are original and will advance our current knowledge on this topic, whereas others are not as novel. Specifically, a number of the secondary objectives (e.g., opioid dose efficacy analysis; predictors of who will benefit and not benefit from opioids; potential non-respiratory benefits of opioids) fall into the former category, but the two primary objectives (i.e., the short-term efficacy of opioids for breathless and exercise tolerance) fall into the latter category. A good number of studies have already been undertaken evaluating opioids short-term for breathless and exercise tolerance in COPD, such that two meta-analyses have been published, one of which is by these authors (Ekstrom et al., Ann Amer Thor Society, 2015). I think consideration should be given to making some of the more original secondary objectives in this study protocol the primary objectives. 2. While I do not oppose the authors including an evaluation of exercise tolerance by a FitBit device, this an non-standardized measure. The authors should additionally measure exercise tolerance by some more standardized measure, like a 6-minute walk test, or better yet, cycle/treadmill exercise testing. If they do not make this change to their protocol, this would render it inferior to previous studies regarding evaluating exercise tolerance. Furthermore, I request that the authors show in more detail how they arrived at the clinically meaningful difference of 940 steps per day with the FitBit device, as I had difficulty deriving this number looking at the Troosters et al. Resp Med paper. 3. Participation is the sub-studies, many of which pose novel research questions, will be voluntary among study participants. Therefore, I am concerned that the sub-study results will be limited by self-selection and have limited external generalizability. 4. The authors have powered this analysis to detect a difference in breathlessness at the end of week one between placebo vs morphine ER 8 mg vs morphine ER 16 mg. In previous work, the authors have shown improvement in dyspnea with morphine ER 20 mg vs placebo after 4 days (Abernathy et al., BMJ, 2003). This leads back my point #1 that some aspects of this study are not that original. Why don't the authors power this analysis at least the broader dose analysis (up to 32 mg daily) or to secondary analyses? 5. One of the study inclusion criterion is "stable medication for management of COPD related breathlessness for one week, except

	as needed medications". Is one week of 'medication stability' sufficient to ensure no unstable patients are enrolled and possibly subjected to harm by receiving opioids? For example, a patient could have been prescribed a one week course of prednisone and antibiotic two weeks before being evaluated for possible study entry. This patient would have been off their recently prescribed prednisone and antibiotic medications the week before possible study entry, yet they may not have recovered to baseline. Would such a patient truly be stable and safe to participate in this study? Another example: if a frequent COPD exacerbator was prescribed roflumilast two weeks before being evaluated for possible study entry, this patient would meet the protocol's 'medication stability' criteria, but would such an individual truly be stable? I think some consideration to widening the period of 'medication stability' is needed. 6. One study exclusion criterion is "respiratory or cardiac event in the previous seven days excluding upper respiratory tract infections". Several previous studies that have evaluated for opioid efficacy in COPD have considered a wider time period of respiratory status stability, excluding individuals without acute respiratory exacerbation in the past month or so (Rocker et al., CMAJ Open, 2013; Johnson et al., NEJM, 1981; Johnson et al., BMJ, 1983; Light et al., Chest, 1996; Poole et al., AJRCCM, 1998). Some consideration should be given to widening the period of respiratory status stability from a safety perspective. Furthermore, how do the authors justify including individuals with recent upper respiratory tract infections? Opioids are known to suppress cough - can this not lead to mucous impaction and possibly cause harm in the setting of an upper respiratory tract infection? 7. In the introduction section, on page 8 second paragraph, the authors do not acknowledge drug safety studies demonstrating that use of opioids is associated with increased risk of adverse respiratory outcomes. First, the authors do not mention a recent study by Vozoris et al. in ERJ, where incident use of opioids (and specifically, those not combined with either aspirin or tylenol) were observed to be associated with increased outpatient respiratory exacerbations, emergency room visits and hospitalizations for COPD or pneumonia, COPD or pneumonia-related mortality and all-cause mortality. Furthermore, adverse respiratory outcomes were observed with incident opioid use in this study, where the daily morphine equivalent use was <= 30 mg/day, which is how the authors are defining "low dose morphine" in their protocol. Second, the authors should cite their own previous work published in the BMJ, showing that daily morphine equivalent use of >30 mg/day was associated with increased all-cause mortality risk. This is relevant because some individuals with COPD according the study protocol will be titrated to >30 mg/day dose. All of the aforementioned information and references should be included by the authors in the respective paragraph to give a more balanced and comprehensive message to the reader. Minor points: 1. In the introduction section, at the top of page 8, the authors write that systemic morphine "might" not improve exercise capacity in COPD. The authors should more definitively state the evidence to date does not support systemic morphine improving exercise capacity. Their own meta-analysis in Ann Amer Thor Society, and an earlier meta-analysis by Jennings et al. Thorax, concluded this.

	2. In the introduction section, on page 8 second paragraph, the authors write that "Despite recommendation in various international clinical guidelines, some physicians remain reluctant to prescribe...". While the authors cite several supportive clinical guidelines, they do not cite or reference the most important and influential COPD guideline, GOLD. While GOLD acknowledges the opioids can be effective for treating dyspnea in COPD, this guideline also expresses caution that opioids may help a select, few patients. There should be some acknowledgement of the GOLD position, as this may be influencing at least some physicians' perceptions and practices.

REVIEWER	Manuel Martínez-Sellés H. Gregorio Marañón, Madrid, Spain
REVIEW RETURNED	23-Feb-2017

GENERAL COMMENTS	The authors present the design of an interest independent clinical trial in patients with chronic breathlessness. I have the following comments: 1) As the authors state there is stronge evidence is for using regular, low-dose, extended release oral morphine. This option is also recommended in current clinical guidelines. Performing a clinical trial with a placebo arm is questionable from an ethic perspective. 2) The recruitment started in September 2016. From this reviewer point of view it makes no sense to submit the design of a clinical trial that is already undergoing. If I suggest some changes in the study protocol it would be too late to incorporate them.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
"Study Protocol: A pragmatic, phase III, multi-site, double-blind, placebo controlled, parallel arm, dose increment randomised trial of regular, low dose extended release morphine for chronic breathlessness. The Breathlessness Exertion And Morphine Sulphate (BEAMS) Study Protocol" describes a protocol of a RCT evaluating morphine for chronic breathlessness in patients with COPD including eight sub-studies. The RCT aims to improve the evidence for the use of morphine to palliate chronic breathlessness assessing its effect on breathlessness severity and physical activity. Different doses (low doses) will be evaluated in a randomized design to give insights and further knowledge to the unanswered and clinical highly relevant question “Which is the optimal dose of morphine for the relief of breathlessness?”. The study group is well-known and very experienced in conducting high quality full powered RCTs in patients with palliative care needs. The study protocol is of high quality and meets/fulfills the criteria of SPIRIT.

Response from investigators:
Thank you.

Reviewer’s comment
What is the rationale for using 8 and 16mg morphine – instead of 5 or 10 or 15 or 20mg (which will later be easier to deliver as most medicines have standard doses)?

Response from investigators
Currently the lowest once daily extended release morphine preparation is 10mg/24 hours, which is alsois also the lowest dose of extended release morphine that has been prospectively studied in

people with chronic breathlessness. In surveying respiratory physicians, there was a desire to try an even lower dose, so an 8mg formulation has been created as the lowest dose for this study and, if the study is positive, will be made available to prescribers. Higher doses were multiples of the 8 mg base dose to establish any dose / response relationship in the relief of breathlessness for the first time.

Reviewer's comment
Why do the authors include two questionnaires for sleep (ESS+KSS, page 16)? The differences are not explained in the protocol.

Response from investigators
One of the study investigators is a sleep expert – Dr Danny Eckert. The Epworth Sleepiness Scale (ESS) and the Karolinska Sleepiness Scale (KSS) have been chosen as they complement each other by measuring different components of daytime sleepiness. The Epworth Sleepiness Scale (ESS) is widely used in sleep medicine clinical practice to assess the propensity to fall asleep on a 4-point scale during eight common daily activities. The recall period is 2-4 weeks. Conversely, the Karolinska Sleepiness Scale (KSS) assesses how sleepy the individual is at that particular moment in time on an alphanumeric 9-point scale.

Reviewer's comment
Most questionnaires are used at stage 0 and 1 but not at stage 2 and 3 – why? The impact of different doses won't be evaluated leaving out stages 2+3.

Response from investigators
The investigators have sought to balance eliciting sufficient detail from participants with minimising the burden on them. Importantly, the primary end-point of the study is at the end of the first week (placebo versus 8mg extended release morphine versus 16mg extended release morphine) so more information is sought during that period. With the exception of the Karolinska Sleep Scale, all other participant-completed measurement tools are also asked either at the end of stage 4 or on withdrawal from the study so longer term outcomes are collected.

Reviewer 2

Reviewer's comment
Some of the study objectives are original and will advance our current knowledge on this topic, whereas others are not as novel. Specifically, a number of the secondary objectives (e.g., opioid dose efficacy analysis; predictors of who will benefit and not benefit from opioids; potential non-respiratory benefits of opioids) fall into the former category, but the two primary objectives (i.e., the short-term efficacy of opioids for breathless and exercise tolerance) fall into the latter category. A good number of studies have already been undertaken evaluating opioids short-term for breathless and exercise tolerance in COPD, such that two meta-analyses have been published, one of which is by these authors (Ekstrom et al., Ann Amer Thor Society, 2015). I think consideration should be given to making some of the more original secondary objectives in this study protocol the primary objectives.

Response from investigators
The investigators agree that meta-analyses of a number of smaller studies show efficacy of regular, low dose, extended release morphine for the reduction of chronic breathlessness, however there is still no jurisdiction internationally that has registered any medication for the symptomatic relief of chronic breathlessness, in large part due to the absence of an adequately powered parallel group RCT. The investigators agree that there are several novel study features, especially in the secondary outcomes, but even in the primary outcome, no blinded study to date has studied two different doses of regular, low dose, extended release morphine to determine the net effect on chronic breathlessness. In itself, this will be an important contribution to the understanding of the interplay

between regular, low dose, extended release morphine and its impact on the subjective sensation of chronic breathlessness.

Reviewer's comment
While I do not oppose the authors including an evaluation of exercise tolerance by a FitBit device, this an non-standardized measure. The authors should additionally measure exercise tolerance by some more standardized measure, like a 6-minute walk test, or better yet, cycle/treadmill exercise testing. If they do not make this change to their protocol, this would render it inferior to previous studies regarding evaluating exercise tolerance. Furthermore, I request that the authors show in more detail how they arrived at the clinically meaningful difference of 940 steps per day with the FitBit device, as I had difficulty deriving this number looking at the Troosters et al. Resp Med paper.

Response from investigators
The investigators are not seeking to evaluate the impact of regular, low dose, extended release morphine on exercise tolerance. As noted by Reviewer 2 later in his review, a meta-analysis has shown no impact of opioids on exercise tolerance to date. The use of a FitbitR will measure a participant's actual functioning on a day-to-day basis, more closely reflecting this pragmatic trial's objectives to understand how regular, low dose, extended release morphine actually impacts on a person's daily life. Further, this is a safety measure, given that some clinicians have concerns that even the use of regular, low dose, extended release morphine may induce drowsiness and reduce physical activity. Primarily, the use of the FitbitR is to ensure that overall activity between groups is comparable and, specifically that activity is not compromised in the intervention arms. We have therefore chosen this activity measure carefully to balance new information being gathered with participant burden.

Reviewer's comment
Participation is the sub-studies, many of which pose novel research questions, will be voluntary among study participants. Therefore, I am concerned that the sub-study results will be limited by self-selection and have limited external generalizability.

Response from investigators
The study is based around a primary question which will be answered in the adequately powered trial. Some sub-studies, such as the effect on testosterone, will include all participants. To adequately inform clinical decision making, several of the sub-studies do not require the complete cohort and would be an undue burden on participants. Many sub-studies in phase III trials are exploratory but this does not detract from their importance. As noted in response to Reviewer 1, studies in this frail population need to carefully balance the information gathered with the burden imposed on participants.

Reviewer's comment
The authors have powered this analysis to detect a difference in breathlessness at the end of week one between placebo vs morphine ER 8 mg vs morphine ER 16 mg. In previous work, the authors have shown improvement in dyspnea with morphine ER 20 mg vs placebo after 4 days (Abernathy et al., BMJ, 2003). This leads back my point #1 that some aspects of this study are not that original. Why don't the authors power this analysis at least the broader dose analysis (up to 32 mg daily) or to secondary analyses?

Response from investigators
As noted, despite systematic reviews, no medication is registered for the symptomatic relief of chronic breathlessness. Thus, this study has been powered to the primary question of whether different doses of regular, low dose, extended release morphine have differential effects on chronic breathlessness. This is the novel aspect of the primary outcome and has not been studied before in chronic

breathlessness.

Reviewer's comment
One of the study inclusion criterion is "stable medication for management of COPD related breathlessness for one week, except as needed medications". Is one week of 'medication stability' sufficient to ensure no unstable patients are enrolled and possibly subjected to harm by receiving opioids? For example, a patient could have been prescribed a one week course of prednisone and antibiotic two weeks before being evaluated for possible study entry. This patient would have been off their recently prescribed prednisone and antibiotic medications the week before possible study entry, yet they may not have recovered to baseline. Would such a patient truly be stable and safe to participate in this study? Another example: if a frequent COPD exacerbator was prescribed roflumilast two weeks before being evaluated for possible study entry, this patient would meet the protocol's 'medication stability' criteria, but would such an individual truly be stable? I think some consideration to widening the period of 'medication stability' is needed.

Response from investigators
The investigators have used one week in a number of randomised controlled studies on the effect of regular, low dose, extended release morphine on chronic breathlessness. If there is 'instability' (and clinically any instability is likely to be minimal), this will be dealt with in randomisation and such people will be evenly distributed between the three arms of the primary study. As noted in the title, this is a pragmatic trial with eligibility criteria that need to reflect day-today practice.

Reviewer's comment
One study exclusion criterion is "respiratory or cardiac event in the previous seven days excluding upper respiratory tract infections". Several previous studies that have evaluated for opioid efficacy in COPD have considered a wider time period of respiratory status stability, excluding individuals without acute respiratory exacerbation in the past month or so (Rocker et al., CMAJ Open, 2013; Johnson et al., NEJM, 1981; Johnson et al., BMJ, 1983; Light et al., Chest, 1996; Poole et al., AJRCCM, 1998). Some consideration should be given to widening the period of respiratory status stability from a safety perspective. Furthermore, how do the authors justify including individuals with recent upper respiratory tract infections? Opioids are known to suppress cough - can this not lead to mucous impaction and possibly cause harm in the setting of an upper respiratory tract infection?

Response from investigators
As noted in the response immediately above, this issue has been considered carefully by the investigators and is based on the fact that this is a pragmatic, randomised trial. Further, although there were wider windows in the studies cited by Reviewer 2, there is no evidence-based clinical rationale for this. Such differences may have affected several of the very small studies cited because just one person who was quantitatively different to the rest of the cohort could make a difference to the outcomes. By contrast, this is a large, adequately powered study where, if there were some 'instability', it would be equally distributed between treatment arms. There is no evidence to suggest that this criterion compromises participant safety.

Reviewer's comment
In the introduction section, on page 8 second paragraph, the authors do not acknowledge drug safety studies demonstrating that use of opioids is associated with increased risk of adverse respiratory outcomes. First, the authors do not mention a recent study by Vozoris et al. in ERJ, where incident use of opioids (and specifically, those not combined with either aspirin or tylenol) were observed to be associated with increased outpatient respiratory exacerbations, emergency room visits and hospitalizations for COPD or pneumonia, COPD or pneumonia-related mortality and all-cause mortality. Furthermore, adverse respiratory outcomes were observed with incident opioid use in this study, where the daily morphine equivalent use was <= 30 mg/day, which is how the authors are

defining "low dose morphine" in their protocol. Second, the authors should cite their own previous work published in the BMJ, showing that daily morphine equivalent use of >30 mg/day was associated with increased all-cause mortality risk. This is relevant because some individuals with COPD according the study protocol will be titrated to >30 mg/day dose. All of the aforementioned information and references should be included by the authors in the respective paragraph to give a more balanced and comprehensive message to the reader.

Response from investigators
The investigators agree that population-based pharmacovigilance studies are crucial to understanding the real world effects of prescribing. Such studies need to have several key factors if they are to help understand how to optimise the real-world use of the medication. Unfortunately, the paper cited has limited clinical data on why patients were sick enough for their clinicians to have made the serious decision to commence an opioid medication, and such granularity is required given the wide range of ways in which opioids are used by clinicians in a range of clinical specialties. (For example, see Agar MA et al Differing management of people with advanced cancer and delirium by four sub-specialties. Palliat Med 2008;22(5):633-640 where oncologists actually added another response box to include opioids for the clinical indication of delirium.)

Importantly, in the cited paper:
i) most opioids were likely given for musculoskeletal pain to people in the community, and
ii) ii) palliative care patients were excluded,
which seriously limits the relevance for the population in this current trial. Observational studies may find differences between those who were and were not prescribed opioids, but this should not be interpreted as a causal effect especially without adjusting for the clinical indication for which opioids were started, limiting the conclusions can be drawn. No attribution can be made, and, at best, an association can be established. Given the one other population-based study cited by Reviewer #2 had almost no people who were started on opioids for the symptomatic relief of chronic breathlessness, the applicability of the findings in Vozoris et al to this current study are limited. The Ekström et al paper to which Review 2 refers is cited in the manuscript.
By contrast, this current study is using doses that have been studied in this patient population where safety indices have been actively sought and closely followed, without evidence of treatment emergent adverse events such as respiratory depression, obtundation nor hospitalisation.
Importantly, in this current study, there is a clearly defined population with appropriate exclusion criteria, who will only be started on regular, low dose extended release morphine, and monitored very closely throughout the study, looking specifically for adverse events that could be attributed in any way to the use of regular, low dose extended release morphine.
Population pharmacovigilance and adequately powered phase III studies (together with well conducted meta-analyses) are needed to provide evidence to progress our understanding of any intervention. Each complements the other, and the current study will be an important contribution to understanding whether there is net benefit (balancing benefit and harms) of the use of regular, low dose, extended release morphine for the symptomatic treatment of chronic breathlessness.
A reference to Vozoris et al paper has been added, noting the important contribution that it makes to better understanding the current use of opioids in an unselected population in whom no clinical data are available as to why opioids were commenced.

Reviewer’s comment
In the introduction section, at the top of page 8, the authors write that systemic morphine "might" not improve exercise capacity in COPD. The authors should more definitively state the evidence to date does not support systemic morphine improving exercise capacity. Their own meta-analysis in Ann Amer Thor Society, and an earlier meta-analysis by Jennings et al. Thorax, concluded this.

Response from investigators

The manuscript has been amended to reflect this.

Reviewer's comment
In the introduction section, on page 8 second paragraph, the authors write that "Despite recommendation in various international clinical guidelines, some physicians remain reluctant to prescribe...". While the authors cite several supportive clinical guidelines, they do not cite or reference the most important and influential COPD guideline, GOLD. While GOLD acknowledges the opioids can be effective for treating dyspnea in COPD, this guideline also expresses caution that opioids may help a select, few patients. There should be some acknowledgement of the GOLD position, as this may be influencing at least some physicians' perceptions and practices.

Response from investigators
Reviewer 2 makes an important point. The manuscript now cites GOLD 2017 recommendations (pg 62) which reflect the evidence base that continues to strengthen and contrasts with the advice in GOLD 2006. The paper also cites the Executive Summary that was published in the American Journal of Respiratory and Critical Care Medicine in March, 2017.

Reviewer 3

Reviewer's comment
The authors present the design of an interest independent clinical trial in patients with chronic breathlessness.

Response from investigators
Thank you.

Reviewer's comment
As the authors state there is strong evidence is for using regular, low-dose, extended release oral morphine. This option is also recommended in current clinical guidelines. Performing a clinical trial with a placebo arm is questionable from an ethic perspective.

Response from investigators
The investigators have worked closely with clinical experts, the Human Research Ethics Committee and regulatory agencies. Given that there is no medication registered anywhere in the world for the symptomatic treatment of chronic breathlessness, and that there is no single, adequately powered phase III study of regular, low dose extended release morphine for chronic breathlessness, it is ethically imperative to use a placebo arm in this study. Of note, this study is larger than the combined studies in the most recent systematic review on this topic and, if positive, will set a new standard of care. It is noteworthy to contrast the approaches of Reviewers 2 and 3 to the place for regular, low dose extended release morphine in the pharmacopoeia – this alone creates equipoise for an adequately powered, placebo controlled randomised trial.

Reviewer's comment
The recruitment started in September 2016. From this reviewer point of view it makes no sense to submit the design of a clinical trial that is already undergoing. If I suggest some changes in the study protocol it would be too late to incorporate them.

Response from investigators
The investigators welcome comments on the design of the study and of the context in which the study is presented.

The investigators appreciate this opportunity to revise the manuscript in the light of these comments
If there are any issues that I can clarify, please do not hesitate to contact me

VERSION 2 – REVIEW

REVIEWER	Nicholas Vozoris University of Toronto, Canada
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	Out of the seven "major comments" that I made, none were incorporated in the manuscript and instead a defensive rebuttal is offered in response to each point. My original concerns remain: the primary objectives of this study are not that original; using only a non-standardized measure to evaluate physical activity (when standardized measures also exist); and, potential safety concerns given some of the inclusion criteria. Reviewer #3 had made an important observation in his/her review that I had not picked up on, that is, that enrollment for this study began in September 2016. Because enrollment of subjects has already begun, perhaps the authors are not in a position to make any substantive revisions to their protocol. However, this study protocol then should not be submitted to a peer-reviewed health journal. Even the two "minor wording comments" that I suggested were not made in the way I had suggested. For example, while the authors mention the GOLD guidelines, they do not present the balanced wording that is present in GOLD, that is, while opioids can help relieve breathlessness in advanced COPD, this may be limited to few, selected individuals.

VERSION 2 – AUTHOR RESPONSE

	Reviewer's comments	Response from authors
Reviewer 2:		
	Out of the seven "major comments" that I made, none were incorporated in the manuscript and instead a defensive rebuttal is offered in response to each point.	Three of the "major comments" from Reviewer 2's first set of comments are addressed in detail in the row immediately below. Other suggestions had already been incorporated in the manuscript when it was re-submitted the first time and those responses are outlined in the subsequent three rows
	My original concerns remain: the primary objectives of this study are not that original; using only a non-standardized measure to evaluate physical activity (when standardized measures also exist); and, potential	There are confirmatory and unique aspects to this protocol: both are important in building an evidence base. Reviewer 2 acknowledged in his first review '*Some of the study objectives are original and will advance our current knowledge on this topic*.' The investigators readily acknowledge that not all aspects of the study are novel, but as this is building an evidence base cautiously in an area that is contentious, each study needs

	safety concerns given some of the inclusion criteria.	to expand the scope of inquiry with care. Unique aspects of this protocol: Although, as Reviewer 2 observes, a 'good number of studies have already been undertaken evaluating opioids short-term for breathlessness', the following points stand out: i) None of the studies to date is of sufficient quality to satisfy regulatory agencies to change the indication for low dose, regular, extended release morphine ii) No study has offered blinded therapy for six months. This point specifically addresses concerns highlighted by Reviewer 2 about only having short term efficacy and toxicity clinical trial data to date. This will be the world's first study to have long term, blinded safety and effectiveness data. iii) This is the first blinded titration study in chronic breathlessness. This design will evaluate whether there is additional net benefit (taking into account any toxicities) with dose increase in people who have already derived symptomatic benefit from regular, low dose extended release morphine. iv) This is the first adequately powered multi-site phase III study to explore low dose extended release morphine only in people with chronic obstructive pulmonary disease (COPD). v) This is the first study to measure day-to-day function using a FitBit^{R} as an outcome measure in any study of extended release morphine for chronic breathlessness. The investigators disagree with Reviewer 2 regarding the standardisation of this last measure; there has been an evidence base for the use of accelerometers in clinical studies for more than a decade. [See Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. Medicine and science in sports and exercise. 2005 Nov 1;37(11):S531]. A six minute walk test (6MWT) estimates functional exercise capacity. [Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. European Respiratory Journal. 1999 Aug 1;14(2):270-4.]. By contrast, an accelerometer measures habitual physical activity with 3-5 days of data considered sufficient to estimate this reliably. [Trost et al] 6MWT and accelerometry are different measures which complement each other. It is biologically more plausible that habitual physical activity will improve, and this is why the investigators chose this measure. As pointed out by Reviewer 2, the meta-analyses conducted to date show no benefit on short term maximal exertion. The investigators agree that this study is unlikely to show any benefit in changing 6 minute walk distances in the 3 week time frame of the study, but that it is likely that accelerometry will at the least be stable (a measure of safety to ensure people do not do less because of, for example, drowsiness) and may even start to

		improve. With regard to the inclusion criteria, the eligibility criteria in the study have been carefully formulated with the active involvement of senior respiratory physicians as investigators. To date, despite more than 400 people being randomised to placebo controlled studies of regular, low dose, extended release morphine, there have been no episodes of respiratory depression nor clinically significant worsening of carbon dioxide retention. The investigators acknowledge in the manuscript the important work of Vozoris *et al* in looking at large populations started on opioids and their subsequent within 30-day hospitalisations and deaths, but as noted, these are associations with no detail as to why opioids were started, nor how the patients were monitored. Similar Swedish data revealed that almost none of a similar cohort of patients had opioids started for chronic breathlessness. [Ahmadi Z, Bernelid E, Currow DC, Ekström M. Prescription of opioids for breathlessness in end-stage COPD: a national population-based study. Int J Chron Obstruct Pulmon Dis. 2016 Oct 21;11:2651-2657.] All of these issues are now included in the Discussion section of the manuscript.
Other major comments from the first review by Reviewer 2		
	Sub-study participation	By their nature, sub-studies are exploratory and are not powered to provide definitive answers but, instead, form the foundation for future research. Generalisability is therefore rarely a key feature of sub-studies. Further, sub-studies require additional time commitments from an already frail population. As such, participation in the main trial should not be predicated on a potential participant agreeing to participate in all sub-studies. It is therefore common practice to recruit sub-populations for such sub-studies.
	Widening the study period for stability after a cardio-respiratory event	In this randomised trial, the important considerations are safety and that the only factor that distinguishes the two groups will be the intervention. A one week period of stability after a cardio-respiratory event will be equally distributed between both study arms and is a reasonable time period. Different clinicians will have differing opinions as to the length of stability before someone should commence this trial – one week was considered reasonable by the senior respiratory clinicians contributing to this study design. Further the exclusion criteria already explicitly state that this requires the treating physician to deem that the acute illness has resolved. As such, the one week is a minimum and may be longer in the case of some specific participants.
	Drug safety from the population study by Vozoris	The study of Vozoris et al. was specifically referenced in the Discussion in the first revision in direct response to Reviewer 2's concern.
	In the introduction section, at the top of page 8, the authors write that systemic	This wording in the Introduction was changed as suggested in the previous Revision 1 of the manuscript. The investigators agree that the suggested wording is better than the original wording.

	morphine "might" not improve exercise capacity in COPD.	
	Reviewer #3 had made an important observation in his/her review that I had not picked up on, that is, that enrollment for this study began in September 2016. Because enrollment of subjects has already begun, perhaps the authors are not in a position to make any substantive revisions to their protocol. However, this study protocol then should not be submitted to a peer-reviewed health journal.	The investigators have been very clear about the fact that recruitment to the study has commenced. The governance requirements of conducting clinical trials are clear: ethical, institutional and, in the case of drug trials, regulatory approvals and clinical trial registration must be in place prior to recruitment. There is no requirement to wait on peer-reviewed publication of the trial protocol. On the contrary, externally funded trials, such as this, the science has *already* been *extensively* peer reviewed often by many more experts than is required for journal publication; this application was reviewed by the national competitive funding body for health and medical research and the grant is dependent upon their view that this is using the most robust science to underpin the design and conduct of this study. The suggestion that studies must wait on peer review publication before commencing does not reflect the reality of clinical trials and is a perplexing suggestion to any clinical trialist. Reasons for publishing the protocol include that more detail can be provided than is usually the case in the paper that presents the results. Publication of ongoing research study protocols is also actively encouraged by this journal to enable collaboration and share detailed methodology.
	Even the two "minor wording comments" that I suggested were not made in the way I had suggested. For example, while the authors mention the GOLD guidelines, they do not present the balanced wording that is present in GOLD, that is, while opioids can help relieve breathlessness in advanced COPD, this may be limited to few, selected individuals	As suggested by Reviewer 2, the investigators already quoted directly and in full from the 2017 GOLD document in Revision 1 of the manuscript, not the earlier 2006 version to which Reviewer 2 referred in his suggestion. The only mention of opiates (excluding references) is on page 62 of GOLD 2017. The statement is under the heading: '***Therapy relevant to all patients with COPD'*** *Even when receiving optimal medical therapy many patients with COPD continue to experience distressing breathlessness, impaired exercise capacity, fatigue, and suffer panic, anxiety & depression. Some of these symptoms can be improved by wider use of palliative therapies that in the past have often been restricted to end-of—life situations.* ***Palliative treatment of dyspnoea.*** *Opiates.*' The caveat that Reviewer 2 cites is from the GOLD 2006 document page 55 when referring to the use of morphine for dyspnea: *'(morphine's)… benefits may be limited to a few sensitive subjects'* As such, the manuscript has not been further amended in this respect from Revision 1 as the suggestion by Reviewer 2 to refer to the GOLD Guidelines *was* addressed in the first response by the investigators referring to the *current* edition of these guidelines.