A double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness; how to optimise recruitment, retention and selected outcome measures

Lovell, Natasha

Awarding institution:
King's College London

A double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness; how to optimise recruitment, retention and selected outcome measures.

A thesis incorporating publications submitted to
King's College London for the degree of Doctor of Philosophy

Natasha Bethan Lovell

Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation
Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care

Supervisors:

Professor Irene Higginson

Dr Matthew Maddocks

Dr Sabrina Bajwah

2020

Abstract

Background: Chronic or refractory breathlessness is common and distressing with few effective treatment options. New treatments urgently need to be developed and trialled. Conducting clinical trials in advanced illness can be challenging, with difficulties recruiting and retaining participants. Outcome measures that capture changes important to people living with breathlessness are also necessary.

Aim: To explore the feasibility of, and ways to optimise recruitment, retention, and outcome measures in a double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness.

Methods: This thesis reports a mixed-methods study embedded within a randomised trial comprising semi-structured qualitative interviews and quantitative outcome measures. Data were collected as part of a double blind randomised feasibility trial of mirtazapine for chronic breathlessness (ISRCTN registration 33236160). Participants were studied over 35 days with contacts at baseline, and days 7, 14, 21, 28 and 35. Qualitative interviews were conducted at the end of the trial and included questions about; experience of recruitment to the trial, experience of being in the trial, whether participants had perceived any change during the trial period, and if so what had changed.

The quantitative data was analysed using descriptive statistics to provide measurements of feasibility and included: screening and recruitment data, number of adverse events, number of participants who discontinued the intervention, and the proportion of missing data in the trial-based questionnaires.

The qualitative interviews were analysed for themes relating to recruitment and retention using thematic analysis, and then considered in relation to the core elements of person-centred care (PCC). Qualitative interviews were also analysed for themes relating to change in experience of breathlessness during the trial and considered within the domains of 'total breathlessness'. The outcome measure data was analysed quantitatively to derive a change score according to available guidance. The qualitative and quantitative data relating to change

was then integrated and where change was seen in the qualitative data evidence of change was looked for in the quantitative data and vice versa.

Results: The trial was open to recruitment at three centres between 17th August 2016 and 30th November 2017. Each centre was open for 12 months, during which time 409 patients were screened, of whom 150 were eligible, and 64 randomised. The screening to recruitment ratio was 6.4:1. The intervention was well tolerated during with trial with few adverse effects reported. There was only one adverse event (grade 3) which was reported in the placebo arm. In total 12 serious adverse events were reported, 7 in the mirtazapine arm and 5 in the placebo arm. Twelve patients (six per arm) discontinued treatment prematurely. There was 100% completion of questionnaires at baseline and few missing data throughout the trial.

Paired data were available for 22 of 64 participants who participated in the trial. 11 had a diagnosis of COPD, 8 ILD, 2 CHF and 1 cancer. Median age was 71 (56-84) years. 16 were male. 20 had completed the trial, 2 withdrew due to adverse effects. Prioritisation of the relationship between the patient and professional; person-centred processes including home visits, assistance with questionnaires, and involvement of the carer; and enabling people to participate by having processes in line with individual capabilities appeared to support recruitment and retention in the trial. Themes were considered in relation to PCC and a model of the person-centred trial was developed. Participants described change in experience across all domains of 'total breathlessness' during the trial. Changes in the qualitative data were commonly captured in the NRS (worst and average) and CRQ. However, agreement was highest with the NRS worst, which despite being a single item measure appeared to capture changes across multiple domains.

Conclusions: In this feasibility trial recruitment targets were met, and attrition levels were low. Aspects of the person-centred approach were viewed positively by trial participants and appeared to support high rates of recruitment and retention. Future work should aim to evaluate the application of a person-centred approach to clinical trials in different settings. A single item outcome measure, the NRS worst, appeared to best capture important changes in the experience of breathlessness across multiple domains. It may therefore be a candidate primary outcome measure for this and other drug effectiveness trials. However, future work should ensure the validity of this specific format of question.

Statement of contribution

The contents of this thesis report research planned and undertaken by myself, under the supervision of Irene Higginson, Matthew Maddocks and Sabrina Bajwah. I was responsible for the design of this PhD thesis which was nested within a multicentre feasibility trial; 'Better Treatments for Refractory Breathlessness' (Better-B). I developed the thesis's aim and objectives, wrote the protocol for the qualitative study which was embedded within the feasibility trial and conducted the related research and its reporting. At the London trial site I was active in data collection; I attended clinics and multidisciplinary team meetings to identify potential participants, consented participants and collected quantitative data at six time points during the trial. I conducted all the qualitative interviews across all three sites. I analysed the data and led on the papers as below. I wrote the discussion and conclusions of this thesis.

My contribution to each of the papers included in this thesis are detailed below:

Background Paper 1: I formulated the ideas for this manuscript, identified relevant literature to include, and wrote the manuscript as first author.

Background Paper 2: I developed the systematic review protocol and search strategy, undertook the search, and screened and selected relevant papers. I extracted relevant data, conducted the thematic synthesis, and developed the model of total breathlessness. I wrote the manuscript as first author.

Results Paper 1:

I formulated the ideas for this manuscript and developed an analysis plan for integrating the qualitative and quantitative data. I undertook data collection at the London site and conducted all of the qualitative interviews. I analysed the data and wrote the manuscript as first author.

Results Paper 2: I formulated the ideas for this manuscript and developed the protocol for the qualitative study, including writing the topic guide. I conducted all of the qualitative interviews. I analysed the transcripts and developed the model of person-centred care in clinical trials. I wrote the manuscript as first author.

Results of feasibility trial published in Thorax (Appendix 8)

My contribution included development of the protocol, writing the topic guide, conducting the qualitative interviews, and analysing the data. I contributed to the drafting of the manuscript as a co-author. I led on the qualitative component of this manuscript.

Acknowledgements

I would like to acknowledge and thank all the study participants, without whom this research would not have been possible. I would also like to thank the clinicians who identified potential participants for this study, and the research nurses involved in data collection.

I would like to thank my supervisors for their guidance and advice throughout the course of my studies, and my supportive colleagues and friends at the Cicely Saunders Institute for their patience and encouragement. I would like to thank members of the Better-B Feasibility study team including our Patient and Public Involvement (PPI) representatives who dedicated so much time to this research.

I would like to acknowledge Marie Curie, Cicely Saunders International and The Atlantic Philanthropies for funding this research. I would like to acknowledge the additional support from Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London. The CLAHRC is a partnership between King's Health Partners, St. George's, University London and St George's Healthcare NHS Trust.

Finally, thanks to my family and friends for always believing.

Table of contents

List of Figures

List of Tables

List of Abbreviations

ATS	American Thoracic Society
Better-B	Better Treatments for Refractory Breathlessness
COPD	Chronic Obstructive Pulmonary Disease
CRQ	Chronic Respiratory Questionnaire
CTRU	Clinical Trials Research Unit
ILD	Interstitial Lung Disease
MDP	Multidimensional Dyspnea Profile
mMRC	Modified Medical Research Council
MORECare	Methods Of Researching End of life Care
MRC	Medical Research Council
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
PROM	Patient Reported Outcome Measure
RCT	Randomised Controlled Trial
TMG	Trial Management Group
TSC	Trial Steering Committee

Publications in peer-reviewed journals, incorporated in the thesis

Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. Control and context are central for people with advanced illness experiencing breathlessness: A systematic review and thematic-synthesis. Journal of pain and symptom management. 2018 Oct 4.

Lovell N, Wilcock A, Bajwah S, Etkind SN, Jolley CJ, Maddocks M, Higginson IJ. Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. Expert Review of Respiratory Medicine. 2018 Dec 31:1-8.

Lovell N, Bajwah S, Maddocks M, Wilcock A, Higginson IJ. Use of mirtazapine in patients with chronic breathlessness: a case series. Palliative medicine. 2018 Oct;32(9):1518-21.

Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. To What Extent Do the NRS and CRQ Capture Change in Patients' Experience of Breathlessness in Advanced Disease? Findings From a Mixed-Methods Double-Blind Randomized Feasibility Trial. Journal of pain and symptom management. 2019 Sep 1;58(3):369-81.

Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. What influenced people with chronic or refractory breathlessness and advanced disease to take part and remain in a drug trial? A qualitative study. Trials. Accepted for publication 01.02.20.

Chapter 1 -Introduction

Breathlessness, or dyspnoea in Latin, is defined by The American Thoracic Society as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity' (1). The experience is thought to derive from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses (1). Breathlessness can only be perceived by the person experiencing it and is a symptom not a physiological variable.

The focus of this thesis is breathlessness which persists despite optimal treatment of the underlying disease. This is often referred to as refractory, the original term, (2) or chronic, the latter being redefined recently as a specific syndrome following a Delphi exercise (3). The terms refractory and chronic breathlessness are used interchangeably in the literature. Chronic or refractory breathlessness is common, affecting approximately 10% of the general population (4). It is experienced by almost all people living with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), as well as most people with chronic heart failure and advanced cancer (5-7). The severity of breathlessness is at least moderate if not severe for one in four people approaching the end of life (8), and has been shown to increase as diseases progress (9, 10), although individual trajectories do vary (11).

Chronic or refractory breathlessness is distressing for those experiencing it, often resulting in anxiety, physical inactivity, and a poor quality-of-life (12-14). It also impacts significantly on those who are close including family and friends, with a considerable care burden (15, 16). In addition, chronic or refractory breathlessness is often accompanied by episodes of worsening breathlessness originally described by Reddy et al. and later defined as 'episodic breathlessness' following a Delphi exercise (17, 18). Episodic breathlessness is important and particularly challenging to treat due to its quick onset and short duration. It is a common reason for emergency department attendance, with 20% of 1212 ambulance presentations due to breathlessness in a recent study from a tertiary hospital (19).

First line treatment of breathlessness is usually optimal management of the disease, ensuring optimal inhaler technique, non-pharmacological therapies such as walking aids, hand-held fan, muscle strengthening, and with level I evidence, pulmonary rehabilitation (20, 21). In advanced disease breathlessness often continues, becoming more severe and protracted (9, 10). There are no licensed medicines for breathlessness anywhere in the world except for morphine in Australia. New effective treatments are urgently needed. To test new treatments randomised controlled trials (RCT's) are required. The challenges of conducting RCT's in advanced disease

include difficulties recruiting participants and high levels of attrition (22, 23). It is also important to choose the right outcome measure, which needs to be able to capture changes perceived as important to those living with breathlessness. The lack of specific information limits our ability to properly trial new treatment options. Therefore, the research in this thesis aimed to fill this evidence gap and provide recommendations on how to optimise recruitment, retention and the selected outcome measures in a randomised controlled drug trial for chronic or refractory breathlessness.

Chapter 2 -Background: Chronic or refractory breathlessness

2.1 Epidemiology

Breathlessness is a common symptom of advanced disease, in both cancer, and non-cancer conditions. The estimated population prevalence in Southern Australia is 8.9% (4), and 25% of those over the age of 70 years in the Unites States of America are affected (24). The prevalence in chronic heart and lung disease and cancer is much higher, with estimates of up to 98% in chronic obstructive pulmonary disease (COPD), 93% in interstitial lung disease, 88% in chronic heart failure, and 77% in cancer (5-7). This theses focuses on people experiencing severe breathlessness characterised by an mMRC breathlessness score of 3 of 4, which equates to 'I stop for breath after walking 100 yards or a few minutes on the level', or 'I am too breathless to leave the house or become breathless while dressing' (25). While the estimated population prevalence in Australia is only 1.3% (4), 46% of people living with COPD in the UK have been identified as having an mMRC score of 3 or 4 (n=22,770) (26), as well as two thirds of patients presenting to the emergency department with breathlessness (19).

Breathlessness can be distressing for those experiencing it, and often occurs alongside other symptoms, most commonly drowsiness, lack of energy and cough (27). Severe breathlessness often leads to a deterioration of functional status and increased dependency, which can reduce social roles and impact negatively on relationships (14). The psychosocial implications are substantial and those living with breathlessness commonly describe anxiety and panic, often associated with a fear of dying (12). Breathlessness is also distressing to those providing physical and psychosocial support, and can negatively impact on carer quality of life and psychological health (16). Informal carers describe a lack of support and feeling worried about the future, and a desire to learn strategies for the management of anxiety, panic and breathlessness (15, 28). Episodic breathlessness is challenging to manage in the home environment and often results in acute hospital admission (19, 29).

2.2 Terminology

The terminology used to describe breathlessness which persists despite optimal management of the underlying condition has continued to evolve and is often used inconsistently in the literature (Table 1). Breathlessness of this nature was originally described as intractable or refractory (2, 30), and later amended to include the word chronic (31, 32). The term 'chronic

breathlessness syndrome' has recently been proposed as a framework following Delphi consensus, with the aim of creating a common language across research and clinical disciplines (3). In addition, is has been recognised that chronic or refractory breathlessness can be accompanied by episodes of worsening breathlessness referred to as episodic breathlessness (33, 34). Episodic breathlessness is defined as 'breathlessness characterised by a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception' (18). Episodes are time-limited (seconds to hours), predictable or unpredictable, and can occur with or without underlying breathlessness (18). For the purpose of this thesis I use the term 'chronic or refractory breathlessness' to describe breathlessness that persists despite optimal treatment of the underlying disease and results in disability for the person, and 'episodic breathlessness' to describe a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the person's perception which is time limited.

Table 1. Terminology for breathlessness

Term	Citation	Definition
ATS definition of dyspnea or breathlessness	American Thoracic Society Statement (1)	A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity
Intractable breathlessness	Booth et al 2008 (30)	Breathlessness that persists despite treatment of the disease
Refractory breathlessness	Booth et al 2009, Horton et al 2010 (2, 35)	Breathlessness that persists despite optimal treatment of the underlying condition
Chronic breathlessness	Bowden et al 2011 (32)	Episodes of breathlessness lasting more than 3 months
Chronic refractory breathlessness	Currow et al 2013, Currow et al 2013, Johnson et al 2015 (31, 36, 37)	Chronic breathlessness which is refractory to treatments for the underlying condition
Episodic breathlessness	Simon et al 2013, Mercadante et al 2017, Mercadante et al 2018, Linde et al 2018 (33, 34, 38-41)	Severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception(39-41)

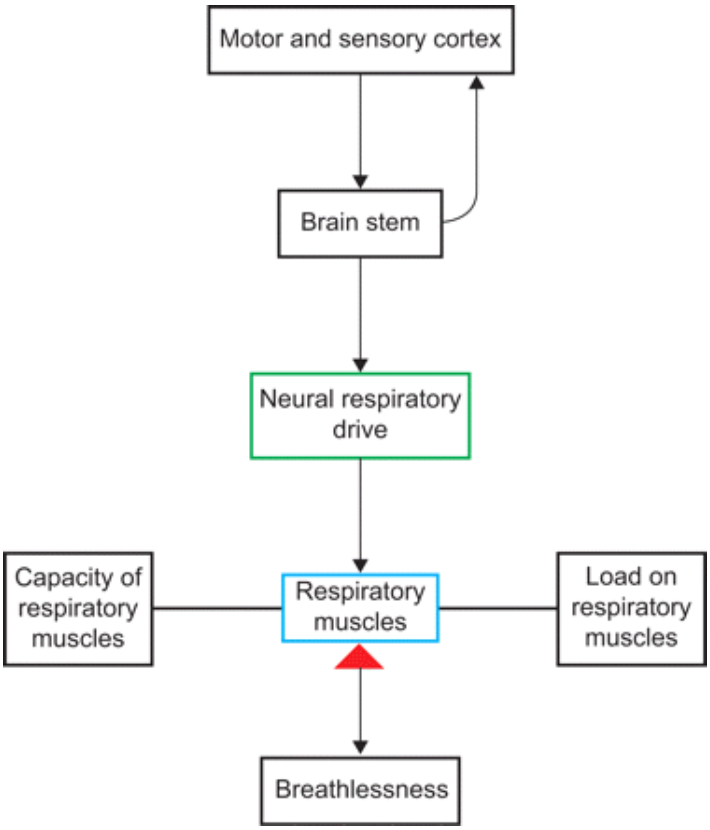
Chronic breathlessness syndrome	Johnson et al 2017 (3)	Breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient

2.3 Mechanisms of breathlessness

The mechanisms of breathlessness are complex. While not fully understood they likely encompass interactions between multiple physiological, psychological, social, and environmental factors (1). The genesis of breathlessness is thought to arise from an imbalance between load and capacity. In this model respiratory effort increases in response to an increase in load, or a decrease in capacity (42). This imbalance between load and capacity then causes an increase in neural respiratory drive. It is the mismatch between the corollary discharge and the afferent feedback from sensory receptors (termed neuromechanical uncoupling), which results in the perception of breathlessness (Figure 1) (43). An alternative theory of breathlessness perception is based on interoception. In this model the brain generates priors based on expectations from previous experiences. These priors are then reviewed when an afferent signal is incoming and a symptom is experienced based on the previous experience (44).

Neuroimaging studies are beginning to explore the complex interactions between neural networks in the brain which may underpin the perception of breathlessness (45). Studies of induced breathlessness in healthy volunteers confirm activation of the insula, amygdala, and anterior cingulate cortex, the areas of the brain known to be active during perceived threat and experience of fear (46-48).

Figure 1: Model of breathlessness, Jolley and Moxham 2009 (43)



2.4 Treatments for chronic or refractory breathlessness

The management of chronic or refractory breathlessness remains an important clinical challenge. The best current evidence is for non-pharmacological interventions and these should take priority initially alongside optimal management of the underlying disease (20, 21, 49). However, as diseases progress and the severity of breathlessness increases, participation in non-pharmacological interventions such as pulmonary rehabilitation can become more challenging, often limited by physical deconditioning and fatigue (50, 51). At this stage pharmacological treatments may be indicated, alongside the initiation of meaningful prognostic conversations and advance care planning (52).

The evidence base for pharmacological interventions remains limited, with no evidence of benefit of oxygen compared to room air for relieving breathlessness in the absence of hypoxia in a large randomised controlled trial (53). Additionally, a Cochrane Review published in 2016 identified eight controlled trials of benzodiazepines and found no evidence of benefit in the absence of breathlessness-related anxiety (54). There is some randomised controlled trial evidence from a Cochrane Review to support the use of parental and oral opioids, and a sustained release morphine capsule has recently been licensed for use in chronic or refractory

breathlessness in Australia (55, 56). However, optimal dosing, titration and potential issues arising from long-term use and safety remain to be determined (57-59). Further, not all patients are suitable for, want to take, or respond to opioids, and clinicians can be reluctant to prescribe them (60, 61). New drug treatments are therefore needed.

Drugs which modify processing and perception of afferent information in the brain such as antidepressants may have a role in the treatment of chronic or refractory breathlessness, by impacting on the areas of the brain relating to fear and anxiety. Case series has shown reduced breathlessness following the use of sertraline (a selective serotonin reuptake inhibitor) in people with chronic obstructive pulmonary disease (62, 63). However, in a large recently conducted trial sertraline was shown to have no benefit when compared to placebo (64). The trial was conducted in Australia and 223 people with breathlessness and a mMRC score of ≥2 were randomised to receive sertraline or placebo for four weeks. The primary outcome was improvement in intensity of current breathlessness >15% from baseline on a 100mm visual analogue scale. The proportion of people responding to sertraline was similar to placebo for current breathlessness on days 26–28 (OR 1.00, 95% CI 0.71–1.40) and for other measures of breathlessness.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant which may have beneficial effects on breathlessness by inhibiting fear circuits and fear conditioning, and also by causing bronchodilation (65). Mirtazapine is a potent antagonist of histamine H1, and may also be advantageous for other symptoms such as poor appetite, poor sleep and anorexia, which are all common in advanced disease and breathlessness (12, 66).

The following paper published in *Expert Review of Respiratory Medicine* considers the physiology of breathlessness, with an emphasis on central mechanisms including the role of fear circuits and associated neurotransmitters. It provides a potential rationale for how mirtazapine may improve chronic or refractory breathlessness and quality of life in patients with advanced disease (see accepted manuscript version below).

Mirtazapine for chronic breathlessness? A review of potentially beneficial mechanisms of action.

N Lovell1, A Wilcock2, S Bajwah1, SN, Etkind1, CJ Jolley3, M Maddocks1, IJ Higginson1

1. Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, Bessemer Road, London SE5 9PJ, United Kingdom

2. University of Nottingham, Palliative Medicine, Hayward House Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham, NG5 1PB, United Kingdom

3. Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London SE1 1UL, United Kingdom

*Corresponding Author Details:

Natasha Lovell. Email: Natasha.lovell@kcl.ac.uk. Tel: 02078485773.

Abstract

Introduction

Chronic breathlessness is a common and distressing symptom of advanced disease with few effective treatments. Serotonergic transmission plays a particular role in the central nervous system mechanisms important in respiratory sensation and control. Thus, there is interest in the potential role for antidepressants in this setting, with supporting animal and case series data. Of potentially suitable antidepressants, mirtazapine is an attractive option given its relatively good tolerability, low cost and wide availability, along with additional potential benefits.

Areas covered

The paper provides an overview of the physiology of breathlessness, with an emphasis on central mechanisms, particularly the role of fear circuits and the associated neurotransmitters, providing a potential rationale for how mirtazapine may improve chronic breathlessness and quality of life in patients with advanced disease. The evidence was identified by a literature search performed in PubMed and Medline through to August 2018.

Expert commentary

Currently, there is insufficient evidence to support the routine use of antidepressants for chronic breathlessness in advanced disease. Mirtazapine is a promising candidate to pursue, with definitive randomised controlled trials required to determine its efficacy and safety in this setting.

Key words

Breathlessness perception, chronic lung disease, control of breathing, dyspnea, palliative medicine, pharmacology

1. Introduction

Breathlessness is a common and distressing symptom of advanced disease, affecting most people living with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) 1-3. Breathlessness is 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity'4. Chronic breathlessness has recently been defined as 'breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient'5.

There are few effective pharmacological treatment options, and currently no drugs are licenced for chronic breathlessness6. A comparison of oxygen and room air found no symptomatic benefit in the absence of hypoxia7, and whilst benzodiazepines are sometimes used to treat breathlessness-related anxiety, there is no evidence that they relieve breathlessness per se in people with advanced cancer and COPD8. There is some evidence to support the use of parental and oral opioids. However, optimal dosing, titration and potential issues arising from long-term use and safety remain to be determined8-12. Further, not all patients are suitable for, or want to take opioids, and clinicians can be reluctant to prescribe them11 13-15. Thus, new effective treatments are required.

Breathlessness is a multidimensional symptom comprising of distinct sensory (intensity/ qualitative) and affective/cognitive components that can be manipulated and measured independently of each other16-19. Consequently, the focus for treatments has shifted towards drugs which may modify processing and perception of afferent information in the brain, such as antidepressants. Whilst data are limited, animal work20 and two case series of sertraline (a selective serotonin reuptake inhibitor antidepressant)21 22, found decreased breathlessness in patients with COPD23. More recently, a case series from our group reported the use of mirtazapine (a noradrenergic and specific serotonergic antidepressant) and found that patients described being less breathless and reported additional beneficial effects on symptoms of anxiety, panic, low appetite and poor sleep24.

Repurposing existing drugs has been effective in other areas of palliative care, for example antidepressants being used to treat pain, offering a potential opportunity to deliver improved symptom control in a timely manner25. Mirtazapine is an antidepressant which increases noradrenergic and serotonergic transmission in the CNS by antagonizing the α2-receptor, and by doing so, may modify the processing of afferent sensory information in the brain including the sensation of breathlessness. It is also an antagonist at serotonin (5-HT2A/2C/3) and

histamine (H1) receptors26 27. These actions contribute towards the antidepressant, anxiolytic, sedative, appetite stimulant and anti-emetic effects of mirtazapine, many of which could be of benefit to patients with advanced disease28.

The paper provides an overview of the physiology of breathlessness, with an emphasis on central mechanisms, particularly the role of fear circuits and the associated neurotransmitters, providing a potential rationale for how mirtazapine may improve chronic breathlessness and quality of life in patients with advanced disease. The evidence was identified by a literature search performed in PubMed and Medline through to August 2018.

2. Mechanisms of breathlessness

2.1 Physiology

The mechanisms of breathlessness are complex and incompletely understood, but are thought to encompass interactions between multiple physiological, psychological, social, and environmental factors4 29. There is evidence that qualitative appraisal of respiratory sensations is mechanistically distinct to breathlessness intensity16 30.

Current expert opinion considers breathlessness to be driven by cortical integration of 1) an ascending copy of descending motor activity to respiratory muscles the 'neural respiratory drive' (NRD); and 2) feedback from respiratory sensory afferents4. Patient-reported breathlessness intensity in chronic respiratory disease has been shown to be closely related to increased levels of NRD, reflecting the increased load on, and/or reduced capacity of, the respiratory muscles as a consequence of impaired respiratory mechanics31-34. These observations support the hypothesis that the perception of breathlessness intensity in humans is mechanistically linked to the awareness of increased NRD as sensed by increased 'central corollary discharge', which refers to the simultaneous projection of resultant neural signals from the motor cortex and/or respiratory centres of the brainstem to the respiratory muscles and sensory areas of the brain35 36. Distinct sensations of breathlessness, most importantly "work/effort", "air hunger" ("unsatisfied inspiration"/"urge to breathe") and "chest tightness", are however likely to originate from central integration of differing sources of afferent information4 29 34.

Neuroimaging studies are beginning to elucidate complex interactions between neural networks underpinning emotional and sensory perception of breathlessness, offering important insights into the role of higher cortical processing in respiratory sensation37-42. Initial studies of induced breathlessness in healthy volunteers have confirmed activation of the insula, amygdala and anterior cingulate cortex, areas of the brain known to be active during perceived threat37 39 42. More recently, studies have included people with chronic lung disease. For example, a feasibility study of magnetoencephalography scanning found increased β band activity indicating constant 'vigilance', or an anticipatory state with regard to peripheral respiratory stimuli43, and preliminary findings from a fMRI feasibility study suggest that the degree of disconnection between the left anterior insula and dorsal anterior cingulate cortex correlates with unpleasantness/discomfort of breathlessness (Meng D, Cottam W, Weller J, et al. European Society of Radiology Congress; 2018; Vienna, Austria).

2.2 Fear circuits and the perception of threat

The regions identified in the above studies closely relate to neurological circuits involved in threat perception and the experience of fear37 39 42. The ability to perceive threat is vital for survival. The response to threat is multi-faceted and regulated by numerous neuronal connections entering and leaving the amygdala (Figure 1). These pathways are responsible for the motor and endocrine features of the 'fight or flight response', combined with the conscious perception of fear44 45. The fight or flight response is mediated by neuronal transmission from the amygdala to the periaqueductal grey area. Ongoing transmission to the hypothalamus and areas of the brainstem results in a rapid release of cortisol, and an autonomic response is triggered by the locus coerulus which can include an increase in heart rate and blood pressure45. The emotional response to a threat involves neural transmission between the amygdala, the orbitofrontal cortex and the anterior cingulate cortex45 46. Given the potential role of fear circuits in the perception of breathlessness, drugs acting within these regions may be beneficial.

Figure 1: Fear circuits and the amygdala

Whilst fear is often experienced and forgotten, the amygdala assimilates stimuli associated with previous fearful situations, and when exposed to this stimuli again, triggers a response (fear conditioning)45. This could explain how an episode of breathlessness and severe panic may lead to recurrent panic when the patient is exposed to a similar trigger. A number of other factors have been associated with an increased perception of threat including the environment, psychiatric illness, and personality traits47-50.

2.3 The function of neurotransmitters in breathlessness

A number of neurotransmitters have been identified as important, in particular, serotonin (5-HT). This plays a role in the central control of respiration, contributing to chemosensitivity and mediating ventilatory response to changes in CO2/pH, and by maintaining regulatory function as part of respiratory neuroplasticity51-55. 5-HT also regulates anxiety and panic through connections between the amygdala, and the prefrontal cortex, striatum and thalamus56. An inhibitory effect on the amygdala results in suppression of fear circuits and thus drugs which increase 5-HT can reduce levels of anxiety and panic 45 57. Further, the importance of serotonergic modulation is suggested by a reduction in panic following administration of L-5-hydroxytryptophan (the immediate precursor of 5-HT), sertraline or citalopram to patients with panic disorder breathing a mixture containing 35% CO258 59 60.

Norepinephrine (NE) is important in neuronal connections between the amygdala and the locus coeruleus, the centre involved in generating the physiological response to stress and panic, e.g. increased heart rate, blood pressure and respiratory rate45. Whilst the role of NE during an acute stress is hyperactivity, chronic stress (for example in mood disorders) causes hypo-reactivity of the NE system61, and in animal studies exposure to chronic stress has been correlated with a decrease in the release of NE in the brain, as well as atrophy of NE axonal projections62 63. Further, venoarterial levels of NE and 3-methoxy-4-hydroxyphenylglycol (the metabolite of NE) are significantly lower in people diagnosed with depression compared to controls64. Other neurotransmitters of interest include endorphins65, cannabinoids66 and neurokinin67.

3. Mirtazapine for chronic breathlessness

3.1 Mechanism of action

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) which is well tolerated, relatively cheap and available in generic form worldwide28 68 69. Mirtazapine antagonizes α2 auto- and hetero-receptors resulting in enhanced noradrenergic transmission and reduced inhibition of 5-HT release (Figure 2)26 27. NE release in the raphe nuclei also stimulates postsynaptic α1 receptors of neuronal cell bodies, causing 5-HT release from downstream axon terminals such as those in the cortex (Figure 2)45. This enhanced noradrenergic and serotonergic transmission is mostly responsible for the antidepressant and anxiolytic effects of mirtazapine.

Figure 2: Mechanism of action of mirtazapine: (1) Blockade of α-2 autoreceptors increases synaptic norepinephrine, stimulating α1 receptors and resulting in serotonin release. (2) Blockade of α2 heteroreceptors reduces inhibition of serotonin release (adapted from Stahl's essential psychopharmacology 2013.)

Mirtazapine also antagonizes 5-HT2 and 5-HT3 receptors and as a consequence, unlike with SSRIs, gastro-intestinal effects (e.g. nausea, diarrhoea) and sexual dysfunction are uncommon27. It is a potent antagonist of histamine H1 receptors26 explaining the most common side effects of somnolence, increased appetite and weight gain28. At higher doses, sedation is less commonly reported, possibly due to increased noradrenergic transmission counteracting the antihistamine effect. It is not known to be associated with a reduced respiratory drive which is an advantage in chronic lung disease management70.

Mirtazapine is authorised for the treatment of depression; additional beneficial effects on anxiety, psychological distress and sleep disturbance are seen compared with placebo71. Mirtazapine is significantly more effective at two weeks compared to selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) 72. A systematic review and meta-analysis of the efficacy and acceptability of 21 antidepressant drugs in adults with depression found that mirtazapine had a higher response rate and lower dropout rate than the other antidepressants when compared with placebo68. Although an anxiolytic effect has been demonstrated for mirtazapine73, it is inconsistent, and mirtazapine

is not currently authorised for the treatment of anxiety disorders. It is however, free from the initial worsening of anxiety or agitation that can occur with SSRIs.

3.2 Mirtazapine as a treatment for breathlessness and other symptoms in chronic lung disease

The serotonergic properties of mirtazapine mean that it may be of benefit in chronic breathlessness, through inhibition of fear circuits, thought to be important in the breathlessness perception. Mirtazapine may also act to reduce the process of fear conditioning. Even in healthy volunteers, mirtazapine has rapid effects. Two hours after a single dose of mirtazapine, there are changes in keeping with a decreased processing of threatening stimuli, an increased processing of positive or rewarding stimuli and reduced self-referential processing74-77. At the neural level, there are decreased right amygdala-hippocampal and fronto-striatal responses to fearful vs. happy facial expressions, increased responses of the parietal cortex to a reward task, and reduced responses in the dorsomedial prefrontal cortex, ventromedial prefrontal cortex and ventral anterior cingulate cortex, considered the self-referential network74 76 77. In response to more natural and complex emotional stimuli, mirtazapine leads to large-scale changes spanning limbic, sensorimotor and cortical midline structures78. Taken together, these changes suggest that mirtazapine impacts rapidly on neural circuits involved in vigilance and the perception of, and the emotional response to, unpleasant stimuli.

In addition to a potential specific effect on the perception of chronic breathlessness, mirtazapine may benefit additional symptoms. For example, patients with chronic lung disease commonly report sleep disturbance, poor appetite and weight loss.79 80 Further, depression, anxiety and panic are also common in this group, and frequently associated with increased healthcare utilisation81-87. Generally, mood disorders are underdiagnosed and thereby undertreated in the medically ill. In a large study of 1334 people with chronic lung disease, 80% screened positive for depression, anxiety or both, yet only 31% were receiving treatment for anxiety or depression88. Thus, by treating an underlying anxiety or depressive mood disorder, mirtazapine may have beneficial effects on the emotional and behavioural response to chronic breathlessness45.

Conclusions

Antidepressants have effects that are potentially beneficial for the management of chronic breathlessness, predominantly through their ability to modify processing and perception of afferent information in the brain. Mirtazapine is an attractive candidate to explore in this setting. It is well-tolerated, affordable and available, with a quick onset of action. Antagonism of 5-HT2 and 5-HT3 receptors means mirtazapine does not share some of the common side effects of other commonly used antidepressants, and antagonism of H1 receptors can result in improved appetite and sleep which may be beneficial in patients with advanced disease. Definitive randomised controlled trials are needed to determine the effectiveness of antidepressants, including mirtazapine, on the distressing and common symptom of breathlessness.

Expert Commentary

Chronic breathlessness remains a common and distressing symptom of advanced disease with few effective treatment options. Whilst there is evidence to support the use of parental and oral opioids, not all patients report benefit from this, and long term safety data is currently lacking. The goal needs to be to identify new effective treatments so that clinicians and patients have more options. In recent years thinking has moved towards drugs which may modify the processing and perception of afferent information in the brain, such as antidepressants. The repurposing of existing inexpensive medications that are off patent and widely available is an attractive option. However, data remains limited, with only case series' documenting the potential benefits of antidepressants in chronic breathlessness. Mirtazapine is a promising candidate, but there is currently insufficient evidence to support use to treat breathlessness in clinical practice. The concern is that clinicians may nevertheless opt to give antidepressants including mirtazapine for chronic breathlessness, particularly as they are inexpensive and off patent. It is important to ensure that patients are not being given medicines that are ineffective in treating breathlessness. Blinded randomised trials are therefore urgently needed to provide appropriate evidence on the effectiveness of mirtazapine in reducing breathlessness.

Five-year view

In the next 5 years we anticipate that blinded randomised trials will be conducted to determine the effectiveness of antidepressants including mirtazapine to treat chronic

breathlessness. Results of these trials will aid national and international clinical guidelines and policy recommendations by providing a much needed evidence base.

Key issues

- Chronic breathlessness remains a common and distressing symptom of advanced disease with few effective treatment options
- Whilst there is evidence to support the use of parental and oral opioids, not all patients report benefit, and long term safety data is currently lacking
- Therefore new effective treatments are urgently needed
- In recent years thinking has moved towards drugs which may modify the processing and perception of afferent information in the brain, such as antidepressants
- Mirtazapine is a promising candidate, but there is currently insufficient evidence to support routine use to treat breathlessness in clinical practice
- Definitive randomised controlled trials are needed to provide evidence to guide clinical practice

Conflict of Interest statement:

The authors declare that they have no conflict of interest.

Author Contributions:

Concept and development: NL, AW, SB, MM, IJH

Drafting: NL, AW, SE, CJJ, SB, MM, IJH

Review and approval of final draft: NL, AW, SE, CJJ, SB, MM, IJH

Funding:

This work is independent research funded by Marie Curie, Cicely Saunders International and The Atlantic Philanthropies in the Cicely Saunders Institute Fellowship Programme. NL is completing a training fellowship funded by Cicely Saunders International and Marie Curie (Grant Number A18859). MM is supported by an NIHR Career Development Fellowship (CDF-2017-10-009) and NIHR Health Services & Delivery Research grant (HSDR 16/02/18) and NIHR CLARHC South London. IJH is an NIHR Emeritus Senior Investigator and is supported by NIHR CLARHC South London. This research was supported by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, which is part of the National Institute for Health Research (NIHR), and is a partnership between King's Health Partners, St. George's, University London and St George's Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References

1. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. Journal of pain and symptom management 2006;31(1):58-69. doi: 10.1016/j.jpainsymman.2005.06.007 [published Online First: 2006/01/31]

2. Moens K, Higginson IJ, Harding R. 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. Journal of pain and symptom management 2014;48(4):660-77. doi: 10.1016/j.jpainsymman.2013.11.009 [published Online First: 2014/05/08]

3. Bajwah S, Higginson IJ, Ross JR, et al. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190(2):215-20. doi: 10.1007/s00408-011-9355-7 [published Online First: 2012/01/06]

4. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. American journal of respiratory and critical care medicine 2012;185(4):435-52. doi: 10.1164/rccm.201111-2042ST [published Online First: 2012/02/18]

5. Polkey MI, Lyall RA, Yang K, et al. Respiratory Muscle Strength as a Predictive Biomarker for Survival in Amyotrophic Lateral Sclerosis. American Journal of Respiratory and Critical Care Medicine 2017;195(1):86-95. doi: 10.1164/rccm.201604-0848OC

6. Mahler DA, Sethi S. To Improve COPD Care: A New Instrument Is Needed to Assess Dyspnea. Chest 2018;154(2):235-37. doi: 10.1016/j.chest.2018.02.020 [published Online First: 2018/08/07]

7. 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 (London, England) 2010;376(9743):784-93. doi: 10.1016/s0140-6736(10)61115-4 [published Online First: 2010/09/08]

8. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. The Cochrane database of systematic reviews 2016;10:Cd007354. doi: 10.1002/14651858.CD007354.pub3 [published Online First: 2016/11/02]

9. Barnes H, McDonald J, Smallwood N, et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. The Cochrane database of systematic reviews 2016;3:Cd011008. doi: 10.1002/14651858.CD011008.pub2 [published Online First: 2016/04/01]

10. Johnson MJ, Bland JM, Oxberry SG, et al. Clinically Important Differences in the Intensity of Chronic Refractory Breathlessness. Journal of pain and symptom management 2013;46(6):957-63. doi: 10.1016/j.jpainsymman.2013.01.011

11. Currow DC, McDonald C, Oaten S, et al. Once-daily opiods for chronic dyspnea: a dose increment and pharmacovigilance study. Journal of pain and symptom management 2011;42(3):388-99.

12. Gosport Independent Panel. Gosport War Memorial Hospital. The report of the Gosport Independent Panel, 2018.

13. Janssen DJ, Spruit MA, Uszko-Lencer NH, et al. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. J Palliat Med 2011;14(6):735-43. doi: 10.1089/jpm.2010.0479 [published Online First: 2011/04/23]

14. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols J, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. The European respiratory journal 2017;50(5) doi: 10.1183/13993003.01153-2017 [published Online First: 2017/11/24]

15. Graeme R, Jean B, James D. The New “Opioid Crisis”: Scientific Bias, Media Attention, and Potential Harms for Patients with Refractory Dyspnea. Journal of palliative medicine 2018;21(2):120-22. doi: 10.1089/jpm.2017.0619

16. von Leupoldt A, Seemann N, Gugleva T, et al. Attentional distraction reduces the affective but not the sensory dimension of perceived dyspnea. Respiratory medicine 2007;101(4):839-44. doi: 10.1016/j.rmed.2006.06.033 [published Online First: 2006/09/15]

17. von Leupoldt A, Taube K, Schubert-Heukeshoven S, et al. Distractive auditory stimuli reduce the unpleasantness of dyspnea during exercise in patients with COPD. Chest 2007;132(5):1506-12. doi: 10.1378/chest.07-1245 [published Online First: 2007/09/25]

18. von Leupoldt A, Dahme B. Differentiation between the sensory and affective dimension of dyspnea during resistive load breathing in normal subjects. Chest 2005;128(5):3345-9. doi: 10.1378/chest.128.5.3345 [published Online First: 2005/11/24]

19. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. The European respiratory journal 2015;45(6):1681-91. doi: 10.1183/09031936.00038914 [published Online First: 2015/03/21]

20. Rampin O, Pierrefiche O, Denavit-Saubie M. Effects of serotonin and substance P on bulbar respiratory neurons in vivo. Brain research 1993;622(1-2):185-93. [published Online First: 1993/09/17]

21. Papp LA, Weiss JR, Greenberg HE, et al. Sertraline for chronic obstructive pulmonary disease and comorbid anxiety and mood disorders. The American journal of psychiatry 1995;152(10):1531. [published Online First: 1995/10/01]

22. Smoller JW, Pollack MH, Systrom D, et al. Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics 1998;39(1):24-9. doi: 10.1016/s0033-3182(98)71377-5 [published Online First: 1998/04/16]

23. Watts GJ, Clark K, Agar M, et al. Study protocol: a phase III randomised, double-blind, parallel arm, stratified, block randomised, placebo-controlled trial investigating the clinical

effect and cost-effectiveness of sertraline for the palliative relief of breathlessness in people with chronic breathlessness. BMJ Open 2016;6(11) doi: 10.1136/bmjopen-2016-013177

24. Lovell N, Bajwah S, Maddocks M, et al. Use of mirtazapine in patients with chronic breathlessness: A case series. Palliat Med 2018:269216318787450. doi: 10.1177/0269216318787450 [published Online First: 2018/07/22]

25. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database of Systematic Reviews 2007(4) doi: 10.1002/14651858.CD005454.pub2

26. de Boer T, Maura G, Raiteri M, et al. Neurochemical and autonomic pharmacological profiles of the 6-aza-analogue of mianserin, org 3770 and its enantiomers. Neuropharmacology 1988;27(4):399-408. doi: https://doi.org/10.1016/0028-3908(88)90149-9

27. De Boer T, Ruigt G, Berendsen H. The α2-selective adrenoceptor antagonist org 3770 (mirtazapine, Remeron®) enhances noradrenergic and serotonergic transmission. Human Psychopharmacology: Clinical and Experimental 1995;10(S2)

28. Kent JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. Lancet (London, England) 2000;355(9207):911-8. doi: 10.1016/s0140-6736(99)11381-3 [published Online First: 2001/02/07]

29. Laviolette L, Laveneziana P. Dyspnoea: a multidimensional and multidisciplinary approach. Eur Respir J 2014;43(6):1750-62. doi: 10.1183/09031936.00092613 [published Online First: 2014/02/15]

30. von Leupoldt A, Mertz C, Kegat S, et al. The impact of emotions on the sensory and affective dimension of perceived dyspnea. Psychophysiology 2006;43(4):382-6. doi: 10.1111/j.1469-8986.2006.00415.x [published Online First: 2006/08/19]

31. Reilly CC, Ward K, Jolley CJ, et al. Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. Thorax 2011;66(3):240-6. doi: 10.1136/thx.2010.142646 [published Online First: 2011/02/03]

32. Jolley CJ, Luo YM, Steier J, et al. Neural respiratory drive and breathlessness in COPD. The European respiratory journal 2015;45(2):355-64. doi: 10.1183/09031936.00063014 [published Online First: 2014/10/18]

33. Jolley CJ, Moxham J. Dyspnea Intensity: A Patient-reported Measure of Respiratory Drive and Disease Severity. American journal of respiratory and critical care medicine 2016;193(3):236-8. doi: 10.1164/rccm.201510-1929ED [published Online First: 2016/02/02]

34. Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. American journal of respiratory and critical care medicine 2015;193(3):299-309. doi: 10.1164/rccm.201504-0841OC

35. Chen Z, Eldridge FL, Wagner PG. Respiratory-associated rhythmic firing of midbrain neurones in cats: relation to level of respiratory drive. The Journal of Physiology 1991;437:305-25. [published Online First: 1991/06/01]

36. Chen Z, Eldridge FL, Wagner PG. Respiratory-associated thalamic activity is related to level of respiratory drive. Respir Physiol 1992;90(1):99-113. [published Online First: 1992/10/01]

37. Banzett RB, Mulnier HE, Murphy K, et al. Breathlessness in humans activates insular cortex. Neuroreport 2000;11(10):2117-20. [published Online First: 2000/08/03]

38. von Leupoldt A, Sommer T, Kegat S, et al. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. American journal of respiratory and critical care medicine 2008;177(9):1026-32. doi: 10.1164/rccm.200712-1821OC [published Online First: 2008/02/12]

39. Peiffer C, Costes N, Hervé P, et al. Relief of Dyspnea Involves a Characteristic Brain Activation and a Specific Quality of Sensation. American journal of respiratory and critical care medicine 2008;177(4):440-49. doi: 10.1164/rccm.200612-1774OC

40. Faull OK, Hayen A, Pattinson KTS. Breathlessness and the body: Neuroimaging clues for the inferential leap. Cortex; a journal devoted to the study of the nervous system and behavior 2017;95:211-21. doi: 10.1016/j.cortex.2017.07.019 [published Online First: 2017/09/16]

41. Faull OK, Pattinson KT. The cortical connectivity of the periaqueductal gray and the conditioned response to the threat of breathlessness. eLife 2017;6 doi: 10.7554/eLife.21749 [published Online First: 2017/02/18]

42. Pattinson KT, Johnson MJ. Neuroimaging of central breathlessness mechanisms. Current opinion in supportive and palliative care 2014;8(3):225-33. doi: 10.1097/spc.0000000000000069 [published Online First: 2014/07/17]

43. Johnson MJ, Simpson MI, Currow DC, et al. Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot. BMJ Open 2015;5(6):e007535. doi: 10.1136/bmjopen-2014-007535 [published Online First: 2015/06/13]

44. Cannon WB. Bodily changes in pain, fear, hunger, and rage. New York, Appleton 1929

45. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications: Cambridge university press 2013.

46. Janak PH, Tye KM. From circuits to behaviour in the amygdala. Nature 2015;517(7534):284-92. doi: 10.1038/nature14188

47. Pineles SL, Vogt DS, Orr SP. Personality and fear responses during conditioning: Beyond extraversion. Personality and individual differences 2009;46(1):48-53. doi: 10.1016/j.paid.2008.09.003

48. Yang J, Yin Y, Svob C, et al. Amygdala Atrophy and Its Functional Disconnection with the Cortico-Striatal-Pallidal-Thalamic Circuit in Major Depressive Disorder in Females. PLoS ONE 2017;12(1) doi: 10.1371/journal.pone.0168239

49. Bremner JD, Randall P, Scott TM, et al. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. The American journal of psychiatry 1995;152(7):973-81. doi: 10.1176/ajp.152.7.973 [published Online First: 1995/07/01]

50. Buckley TC, Blanchard EB, Neill WT. Information processing and PTSD: a review of the empirical literature. Clinical psychology review 2000;20(8):1041-65. [published Online First: 2000/12/01]

51. Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. Annual review of neuroscience 2003;26(1):239-66.

52. Reid G, Rand M. Physiological actions of the partially purified serum vasoconstrictor (serotonin). Australian Journal of Experimental Biology & Medical Science 1951;29(6)

53. Douglas WW, Toh CC. The respiratory stimulant action of 5-hydroxytryptamine (serotonin) in the dog. The Journal of Physiology 1953;120(3):311-8.

54. Michelson AL, Hollander W, Lowell FC. The effect of 5-hydroxytryptamine (serotonin) on the respiration on nonasthmatic and asthmatic subjects. I. The Journal of laboratory and clinical medicine 1958;51(1):57-62. [published Online First: 1958/01/01]

55. Parks VJ, Sandison AG, Skinner SL, et al. The stimulation of respiration by 5-hydroxytryptamine in man. The Journal of Physiology 1960;151:342-51. [published Online First: 1960/05/01]

56. Bocchio M, McHugh SB, Bannerman DM, et al. Serotonin, Amygdala and Fear: Assembling the Puzzle. Frontiers in Neural Circuits 2016;10:24. doi: 10.3389/fncir.2016.00024

57. Grady CL, Siebner HR, Hornboll B, et al. Acute pharmacologically induced shifts in serotonin availability abolish emotion-selective responses to negative face emotions in distinct brain networks. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 2013;23(5):368-78. doi: 10.1016/j.euroneuro.2012.06.003 [published Online First: 2012/06/29]

58. Schruers K, van Diest R, Overbeek T, et al. Acute L-5-hydroxytryptophan administration inhibits carbon dioxide-induced panic in panic disorder patients. Psychiatry research 2002;113(3):237-43. [published Online First: 2003/02/01]

59. Bertani A, Caldirola D, Bussi R, et al. The 35% CO2 hyperreactivity and clinical symptomatology in patients with panic disorder after 1 week of treatment with citalopram: an open study. Journal of clinical psychopharmacology 2001;21(3):262-7. [published Online First: 2001/06/02]

60. Perna G, Bertani A, Caldirola D, et al. Antipanic drug modulation of 35% CO2 hyperreactivity and short-term treatment outcome. Journal of clinical psychopharmacology 2002;22(3):300-8. [published Online First: 2002/05/15]

61. Goddard AW, Ball SG, Martinez J, et al. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depression and anxiety 2010;27(4):339-50. doi: 10.1002/da.20642 [published Online First: 2009/12/05]

62. Kitayama I, Yaga T, Kayahara T, et al. Long-term stress degenerates, but imipramine regenerates, noradrenergic axons in the rat cerebral cortex. Biological psychiatry 1997;42(8):687-96. [published Online First: 1997/11/05]

63. Liu Y, Ishida Y, Shinoda K, et al. Effects of repeated stress on regeneration of serotonergic and noradrenergic axons in the cerebral cortex of adult rats. Neuroscience letters 2003;339(3):227-30. [published Online First: 2003/03/14]

64. Lambert G, Johansson M, Agren H, et al. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. Archives of general psychiatry 2000;57(8):787-93. [published Online First: 2000/08/02]

65. Mahler DA, Murray JA, Waterman LA, et al. Endogenous opioids modify dyspnoea during treadmill exercise in patients with COPD. The European respiratory journal 2009;33(4):771-7. doi: 10.1183/09031936.00145208 [published Online First: 2009/02/14]

66. Pickering EE, Semple SJ, Nazir MS, et al. Cannabinoid effects on ventilation and breathlessness: a pilot study of efficacy and safety. Chronic respiratory disease 2011;8(2):109-18.

67. Mahler DA, Gifford AH, Gilani A, et al. Antagonism of substance P and perception of breathlessness in patients with chronic obstructive pulmonary disease. Respiratory physiology & neurobiology 2014;196:1-7. doi: 10.1016/j.resp.2014.02.008 [published Online First: 2014/03/04]

68. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet doi: 10.1016/S0140-6736(17)32802-7

69. Montgomery SA. Safety of mirtazapine: a review. International clinical psychopharmacology 1995;10 Suppl 4:37-45. [published Online First: 1995/12/01]

70. Mason M, Welsh EJ, Smith I. Drug therapy for obstructive sleep apnoea in adults. The Cochrane database of systematic reviews 2013(5):Cd003002. doi: 10.1002/14651858.CD003002.pub3 [published Online First: 2013/06/04]

71. Kasper S. Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. International clinical psychopharmacology 1995;10 Suppl 4:25-35. [published Online First: 1995/12/01]

72. Watanabe N, Omori IM, Nakagawa A, et al. Mirtazapine versus other antidepressive agents for depression. The Cochrane database of systematic reviews 2011(12):Cd006528. doi: 10.1002/14651858.CD006528.pub2 [published Online First: 2011/12/14]

73. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 2001;34(10):1303-7. [published Online First: 2001/10/11]

74. Vollm B, Richardson P, McKie S, et al. Serotonergic modulation of neuronal responses to behavioural inhibition and reinforcing stimuli: an fMRI study in healthy volunteers. The European journal of neuroscience 2006;23(2):552-60. doi: 10.1111/j.1460-9568.2005.04571.x [published Online First: 2006/01/20]

75. Arnone D, Horder J, Cowen PJ, et al. Early effects of mirtazapine on emotional processing. Psychopharmacology 2009;203(4):685-91. doi: 10.1007/s00213-008-1410-6 [published Online First: 2008/11/26]

76. Rawlings NB, Norbury R, Cowen PJ, et al. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. Psychopharmacology 2010;212(4):625-34. doi: 10.1007/s00213-010-1983-8 [published Online First: 2010/09/03]

77. Komulainen E, Heikkila R, Meskanen K, et al. A single dose of mirtazapine attenuates neural responses to self-referential processing. Journal of psychopharmacology (Oxford, England) 2016;30(1):23-32. doi: 10.1177/0269881115616384 [published Online First: 2015/11/19]

78. Komulainen E, Glerean E, Meskanen K, et al. Single dose of mirtazapine modulates whole-brain functional connectivity during emotional narrative processing. Psychiatry research 2017;263:61-69. doi: 10.1016/j.pscychresns.2017.03.009 [published Online First: 2017/04/04]

79. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. BMC Palliative Care 2011;10:15-15. doi: 10.1186/1472-684X-10-15

80. Edmonds P, Karlsen S, Khan S, et al. A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. Palliat Med 2001;15(4):287-95. doi: 10.1191/026921601678320278 [published Online First: 2002/06/11]

81. Eisner MD, Blanc PD, Yelin EH, et al. Influence of anxiety on health outcomes in COPD. Thorax 2010;65(3):229-34. doi: 10.1136/thx.2009.126201 [published Online First: 2010/03/26]

82. 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. The Lancet Respiratory Medicine 2014;2(12):979-87. doi: https://doi.org/10.1016/S2213-2600(14)70226-7

83. Bausewein C, Booth S, Gysels M, et al. Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. Journal of palliative medicine 2010;13(9):1109-18. doi: 10.1089/jpm.2010.0068 [published Online First: 2010/09/15]

84. Coultas DB, Edwards DW, Barnett B, et al. Predictors of Depressive Symptoms in Patients with COPD and Health Impact. COPD: Journal of Chronic Obstructive Pulmonary Disease 2007;4(1):23-28. doi: 10.1080/15412550601169190

85. de Voogd JN, Wempe JB, Koeter GH, et al. Depressive symptoms as predictors of mortality in patients with COPD. Chest 2009;135(3):619-25. doi: 10.1378/chest.08-0078 [published Online First: 2008/11/26]

86. Blazer DG, Hybels CF. Shortness of breath as a predictor of depressive symptoms in a community sample of older adults. International journal of geriatric psychiatry 2010;25(10):1080-4. doi: 10.1002/gps.2477

87. Atlantis E, Fahey P, Cochrane B, et al. Bidirectional associations between clinically relevant depression or anxiety and COPD: a systematic review and meta-analysis. Chest 2013;144(3):766-77. doi: 10.1378/chest.12-1911 [published Online First: 2013/02/23]

88. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest 2005;127(4):1205-11. doi: 10.1378/chest.127.4.1205 [published Online First: 2005/04/12]

Chapter 3 -Background: Challenges of conducting randomised controlled trials

3.1 Outcome measures in breathlessness

Outcome measures are used to assess change in a person's health status, quality of life, or symptoms over time (67). They are usually reported by patients and can monitor change in health status and evaluate the effects of an intervention (68, 69). Outcome measures are commonly used within clinical trials. The Methods Of Researching End of Life Care (MORECare) guidance of methods for palliative and end of life care research, developed through literature reviews and transparent expert consultation, outlined that outcome measures in this setting need to capture clinically important data, be responsive to change, psychometrically robust, yet not burdensome to complete (70). The choice of measure will vary depending on the setting, population, allocated time and resources, and the purpose. Patient reported outcome measures (PROMs) are those reported directly by the patient and are increasingly used to capture an individual's perspective of their health. PROMs are particularly important when measuring a symptom like breathlessness which is subjective and can only be perceived by the person experiencing it (1). Therefore, patient report is the most appropriate way to measure breathlessness and determine any change over time.

A 2007 systematic review identified 35 validated tools used to measure breathlessness in advanced disease (71). Since then, many new measures have been developed. However, there remains no gold standard approach of which measure to use and when (72). Outcome measures of breathlessness can be described in different ways, some are specific to a disease or condition, others characterised by the number of questions or domains included. Terminology in the literature is inconsistent. The American Thoracic Society (ATS) proposes three domains of breathlessness measurement: sensory-perceptual experience, affective distress, and symptom impact or burden (1). Sensory-perceptual refers to what the breathing feels like and often includes a rating of intensity. Affective distress is the unpleasantness experienced, and symptom impact or burden is how breathing affects behaviours, beliefs or values, and commonly includes functional performance or disability. The ATS statement proposes that different instruments can be used to measure these domains (1). For example, a single item rating might be used to measure intensity within the sensory-perceptual domain, and a multidimensional scale might be used to measure the symptom impact or burden domain. Crucially the ATS emphasises the importance of knowing what domain(s) an

instrument is measuring, so that clinicians and researchers can select measures which are appropriate to their specific needs (1).

Single item, single domain or unidimensional tools have been described as providing a measure of the severity or intensity of breathlessness (71). The Numerical Rating Scale (NRS) is an example of an outcome measure described as unidimensional, used widely in randomised trials of breathlessness interventions (54, 55). A rating statement or question is accompanied by a scale (usually 0-10), and anchored by a descriptive statement at each end (73). Other comparable examples include the Visual Analogue Scale (74) and the Modified Borg Scale (75). Multiple item, multi domain or multidimensional measures in comparison aim to measure breathlessness across domains or dimensions identified as important for those experiencing breathlessness. The Multidimensional Dyspnoea Profile (MDP) is an example of a multidimensional measure and consists of 11 items which assess overall breathing discomfort, with the inclusion of sensory qualities and emotional responses (76). The Chronic Respiratory Questionnaire (CRQ) is another multidimensional measure sometimes referred to as a disease specific outcome measure (71). The CRQ is a 20-item health-related quality-of-life questionnaire validated in people with chronic respiratory disease. It measures four domains considered to be important in chronic respiratory disease; dyspnea, fatigue, emotional function, and mastery (77).

Choice of outcome measure used to assess breathlessness should be considered carefully and will vary depending on the purpose. For example, unidimensional measures are often used in clinical practice to determine the effectiveness of an intervention (71). Multidimensional measures can capture changes across more than one domain and therefore enable a more detailed assessment (78). It has been suggested that unidimensional measures are able to assess the magnitude of the 'box of breathlessness', but to understand the components contributing to this box, a multidimensional measure is needed (79). The National Cancer Research Institute Palliative Care Breathlessness Subgroup consensus statement (2009) recommended that breathlessness severity should be assessed in research using a single-item measure, but that researchers should also consider including a measure of fatigue, mastery, emotional state, and sleep (72). In research the intervention being evaluated is also an important consideration, to ensure that any change is captured. Some interventions might reduce the intensity of breathlessness, and others the associated distress.

3.2 Main concerns for people experiencing breathlessness

Chronic or refractory breathlessness remains under reported, under measured and under treated. To improve the management of such breathlessness, outcome measures which capture the concerns that matter to those experiencing it are required, but they must also be able to detect the effect of an intervention. Previous qualitative studies have explored the experience of living with breathlessness, often with the purpose of identifying unmet need (80-82), exploring experience of care and access to services (83-85), and understanding impact on carers (16, 86). However, there has been no attempt to systematically synthesise the concerns for people experiencing breathlessness with the aim of informing outcome measurement in clinical practice and research. This section presents background paper 2 of this thesis, which is a systematic review of the main concerns for people with advanced disease experiencing breathlessness.

Results from this synthesis emphasise how broad and extensive the main concerns for people living with breathlessness are, extending far beyond a single episode of breathlessness, encompassing multiple domains and impacting significantly on those around them (87). The model of "total breathlessness" was developed incorporating six domains: physical, emotional, spiritual, social, control, and context. The synthesis also provides new evidence to support the choice of outcome measures in chronic or refractory breathlessness. To capture the concerns which are important outcome measures need to capture change across multiple domains. Importantly measures should assess impact across social and spiritual domains, shown in this synthesis to be considerable, yet not often considered within current breathlessness outcome measures (87).

Review Article

Control and Context Are Central for People With Advanced Illness Experiencing Breathlessness: A Systematic Review and Thematic Synthesis

Natasha Lovell, MBChB, Simon N. Etkind, MB, BChir, Sabrina Bajwah, PhD, Matthew Maddocks, PhD, and Irene J. Higginson, PhD

Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, London, United Kingdom

Abstract

Context. Breathlessness is common and distressing in advanced illness. It is a challenge to assess, with few effective treatment options. To evaluate new treatments, appropriate outcome measures that reflect the concerns of people experiencing breathlessness are needed.

Objectives. The objective of this study was to systematically review and synthesize the main concerns of people with advanced illness experiencing breathlessness to guide comprehensive clinical assessment and inform future outcome measurement in clinical practice and research.

Methods. This is a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology. MEDLINE (1946–2017), PsycINFO (1806–2017), and EMBASE (1974–2017), as well as key journals, gray literature, reference lists, and citation searches, identified qualitative studies exploring the concerns of people living with breathlessness. Included studies were quality-assessed using the Critical Appraisal Skills Program checklist and analyzed using thematic synthesis.

Results. We included 38 studies with 672 participants. Concerns were identified across six domains of "total" breathlessness: physical, emotional, spiritual, social, control, and context (chronic and episodic breathlessness). Four of these have been previously identified in the concept of "total dyspnea." Control and context have been newly identified as important, particularly in their influence on coping and help-seeking behavior. The importance of social participation, impact on relationships, and loss of perceived role within social and spiritual domains also emerged as being significant to individuals.

Conclusion. People with advanced illness living with breathlessness have concerns in multiple domains, supporting a concept of "total breathlessness." This adapted model can help to guide comprehensive clinical assessment and inform future outcome measurement in clinical practice and research. J Pain Symptom Manage 2019;57:140–155. © *2018 The Authors. Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Key Words

Breathlessness, dyspnea, experience, concern, advanced disease, palliative care

Background

Although there are a number of definitions, breathlessness is usually referred to as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" as defined by the American Thoracic Society.[1] Breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient is often referred to as chronic breathlessness as agreed by recent Delphi consensus.[2]

Address correspondence to: Natasha Lovell, MBChB, Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, Bessemer Road, London SE5 9PJ, United Kingdom. E-mail: natasha.lovell@kcl.ac.uk

Accepted for publication: September 26, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.09.021

Chronic breathlessness may be accompanied by episodic breathlessness, defined as a severe worsening of breathlessness intensity or unpleasantness beyond usual fluctuations in the patient's perception.[3]

Chronic breathlessness is common and distressing, affecting almost all people living with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), and most people with chronic heart failure and advanced cancer.[4–6] Current treatment options for chronic breathlessness are limited, and its management remains an important clinical challenge. While clinicians often recognize the significant impact for patients, time constraints, and inadequate resources and training, they feel ill-equipped in assessment and management.[7] Furthermore, to establish the clinical effectiveness of new treatments, appropriate outcome measures that capture the concerns and problems that matter to patients are vital. Although over 30 different outcome measures have been validated for breathlessness, consensus is lacking on which measure to use and when.[8,9]

An improved understanding of the main concerns for people experiencing breathlessness can provide clinicians with a framework for assessment and guide the choice of appropriate outcome measures in clinical practice and research. It may also identify potential targets for new treatments. The American Thoracic Society provides a helpful framework to guide outcome measure selection and proposes three domains of breathlessness: "sensory-perceptual experience"; incorporating what breathing feels like to the patient; "affective distress" that may include the unpleasantness experienced during breathing; and "symptom impact or burden" that might include functional ability or health-related quality of life.[1] Individual qualitative studies have explored what it is like for people to live with breathlessness, including the experience of care and impact of illness, and a recent systematic review considers the role of coping, help-seeking behavior, and clinician responsiveness.[10] In this review, Hutchinson describes the concept of breathing space and highlights the importance of clinician response in determining future coping and help-seeking behavior.[10]

However, there has been no attempt to systematically synthesize the concerns for people experiencing breathlessness with the aim of informing outcome measurement in clinical practice and research. Our systematic review aims to determine the main concerns for people with advanced illness experiencing breathlessness, to guide comprehensive clinical assessment, optimize clinical interactions, and inform future outcome measurement in clinical practice and research.

Methods

Study Design

We conducted a systematic literature review and thematic synthesis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11]

Information Sources and Search Strategy

We searched titles, abstracts, and keywords of articles indexed within three databases: PsycINFO (1806 to March Week 4 2017), MEDLINE (1946 to March Week 5 2017), and EMBASE (1974 to 2017 Week 14). Search terms were developed and piloted to ensure inclusivity and included a combination of the following terms: dypsn* OR short* of breath OR breathless* AND experience* OR concern* OR expect* OR prefer* AND palliate* OR chronic lung disease OR advanced disease. The full electronic search strategy is shown in Appendix 1. Key journals, gray literature, reference lists, and forward citation searches identified additional relevant articles.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: Primary qualitative or mixed-method studies, from any setting (hospital, community, or outpatient), which explored the concerns of adults experiencing breathlessness and living with advanced illness (including but not limited to COPD, ILD, chronic heart failure, and cancer), were eligible for inclusion.

Exclusion criteria were as follows: Studies presenting only quantitative data, published in a language other than English, and where patient concerns were described in relation to their illness experience, and not explicitly breathlessness, were excluded.

Procedures for Study Selection and Data Extraction

Articles were initially screened by title and abstract. All full-text articles were assessed against the eligibility criteria by one researcher (N. L.), with 25% reviewed by another researcher. Any disagreements about inclusion of articles were resolved by discussion within the author team. Data were extracted using a *pro forma* on study setting, participants, and qualitative approach. All included articles were assessed against the Critical Appraisal Skills Program (CASP) qualitative research checklist. The CASP checklist is a recognized tool developed and piloted by a group of experts and includes 10 brief questions relating to methodological rigor, credibility, and relevance. The CASP checklist is suited to systematic reviews of qualitative research and was considered an appropriate choice for this review.[12,13]

All subsections of text relating to breathlessness in the "results" or "findings" sections of included articles

were extracted and imported verbatim into NVivo 11 qualitative data software (Version 11, 2015; QSR International Pty Ltd.). Extracted text included both direct quotations but also the authors' interpretation of findings.

Analysis

Data were collated and analyzed using thematic synthesis.[14] This involved three stages: 1) coding of text "line-by-line" to enable the translation of concepts from one study to another; 2) development of "descriptive themes"; and 3) the generation of "analytical themes." This process enabled the data to be considered in relation to the specific research question of this review and allowed for interpretation beyond what was been presented in the primary articles. During the course of the review, we also collated information on models of breathlessness and used this to structure the results.

Results

The search identified 5082 individual articles, of which 69 full-text articles were assessed against inclusion criteria and 38 separate articles were included

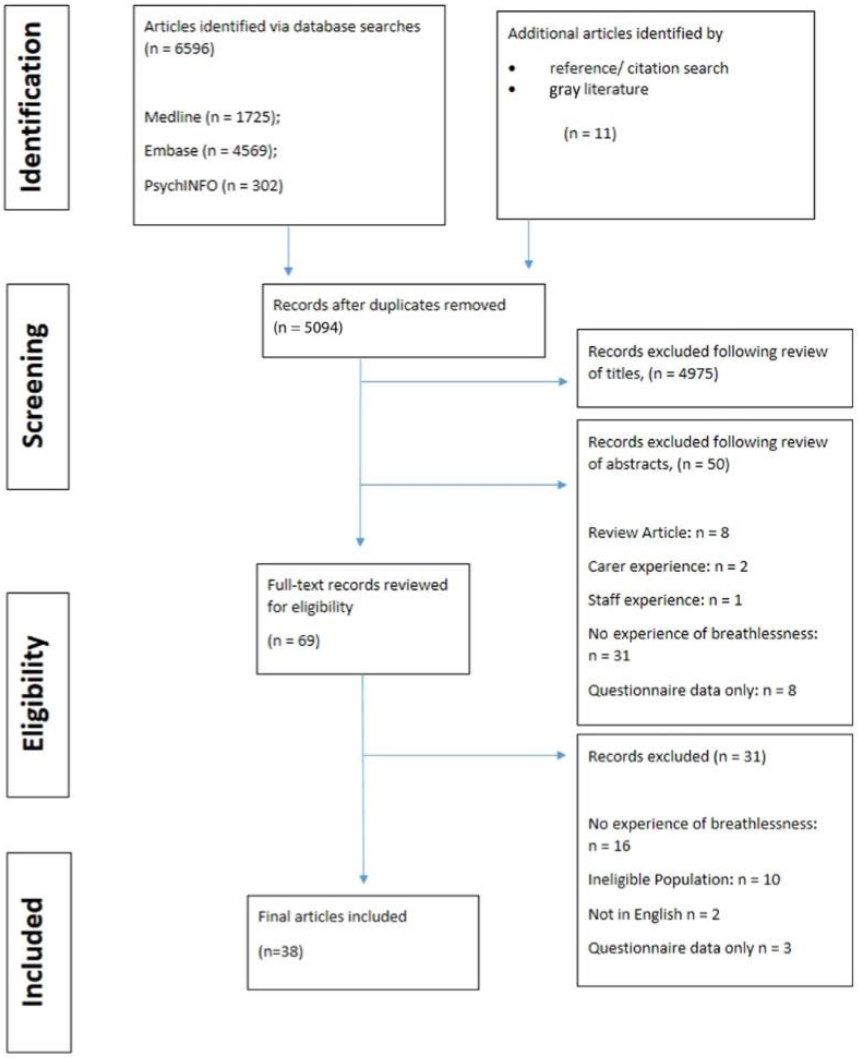


Fig. 1. PRISMA chart. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(Fig. 1). A total of 672 participants were included across all studies. The majority of studies were conducted in the U.K. ($n = 24/38$) and in the outpatient or community setting ($n = 30/38$). Twenty-four studies included participants with a diagnosis of COPD; four with cancer; two with chronic heart failure; two with interstitial lung disease; and six studies focused on the symptom not the disease, including participants across different disease groups.

Articles were published between 1993 and 2017. The method of data collection was varied although a semistructured interview format was most common ($n = 28/38$), with the remaining studies following a narrative or unstructured approach. Approaches to data analysis included thematic analysis, hermeneutic analysis, grounded theory, framework analysis, and phenomenological analysis. See Table 1 for full characteristics of included studies. Thirty-two of the included articles met at least nine of the 10 CASP checklist criteria when assessed, and none scored less than seven (see Appendix 2).

Synthesis and Model

While conducting the synthesis, we considered how concerns mapped onto existing models of breathlessness, and chose "total dyspnea" as our conceptual framework.[31,53] This model forms the basis for the presentation of synthesis results (Fig. 2). It is based on the concept of "total pain" described by Dame Cicely Saunders, comprising four domains: 1) physical, including subsequent effects on function; 2) psychological concerns; 3) social impact; and 4) spiritual distress.

In our model of "total breathlessness," psychological has been changed to emotional to reflect the synthesis findings, and "control" and "context" have been added for completeness. While concerns can be described within a single domain, most are not exclusive to one, and there is a considerable overlap between domains as demonstrated in our model of "total breathlessness."

Participants described how living with breathlessness pervaded every part of their life. The main concerns for people living with breathlessness were comprehensive and wide ranging, and the negative effects of breathlessness on quality of life were evident throughout the data. The experience of breathlessness was entirely unique to the individual and impacted not only them but also those around them. Breathlessness was also described as "invisible," disguised at rest,[29] or hidden due to embarrassment and stigma, as well as a perceived lack of interest and response from clinicians. Participants responded by retreating and not seeking help, and as a result, this distressing symptom remained unacknowledged and undertreated.

Physical Symptom of Breathlessness and Its Effects on Function

Breathlessness was described as affecting all activities of daily living. Breathlessness crept up on individuals and while initially noticed during more strenuous tasks, it soon prevented activities around the home such as cooking and cleaning. As their illness progressed, participants experienced further functional decline and became unable to climb the stairs or walk to the shops, resulting in social isolation. This trajectory of deteriorating physical function affected not only the person but also those around them. Participants became dependent on friends and family to assist with intimate tasks such as washing and dressing.

> … The worst thing I think is the stairs, going up and down the stairs. Ordinary household chores I find difficult. Very restrictive, because of your breathing. And now of late … even simple things like having a shower and getting dressed.
>
> Patient with COPD, Caress et al. 2010.

Participants recognized that they were becoming increasingly breathless, felt frustrated that this caused them to slow down, and meant they were unable to do the things they had previously done. Breathlessness had taken away their independence and left them feeling concerned about the future. Participants felt they were becoming an increasing burden to friends and family.

> … It (breathlessness) is over time slowing down everything.
>
> Female with COPD, Gysels et al. 2011.

Emotional

Participants described a cycle between breathlessness and anxiety, relating not only to acute episodes of breathlessness, but also within the wider context of a person's life affected by chronic breathlessness. The emotional impact of breathlessness extended beyond the individual to those people in a caring role, who were often left feeling helpless and powerless when breathlessness occurred.

> It [shortness of breath] would just take my breath away and just like somebody would grab me and start choking. I couldn't breathe and then when it happened my daughter would take me to emergency.
>
> Patient with Heart Failure, Lowey 2012.

The combination of feeling breathless and not having control over breathing created a frightening scenario. In some cases, it became so severe that the person experiencing it felt it may not resolve

> When you get shortness of breath, you're scared… scared you're gonna take your last breath.
>
> Male with COPD, Leidy et al. 1999.

Table 1
Characteristics of Included Studies

Author	Setting	Participants	Qualitative Approach	Aim of Study	Main Concerns Identified Within Study
Apps et al.[15]	Community setting in U.K.	Fifteen individuals with COPD, six male (aged between 65 and 82 yrs), nine female (aged between 55 and 82 yrs)	Semistructured interviews analyzed through thematic analysis	To understand the self-care experiences of patients with COPD who are primarily managed in primary care, and to examine the challenges of engaging in such behaviors.	Disruption of daily tasks, patients unsure about progression and the future
Bajwah et al.[16]	Outpatient and community setting in U.K.	Eight individuals with a diagnosis of NSIP, IPF, and IIP (five males aged between 65 and 81 yrs, three females aged between 56 and 75 yrs), four informal caregivers (three females aged between 41 and 63 yrs, one male aged 63 yrs), and six health professionals	Semistructured interviews analyzed through thematic analysis	To explore the specialist palliative care needs of people living with end-stage progressive idiopathic fibrotic interstitial lung disease.	Uncontrolled symptom, limitation on social activities, increased reliance on others
Barnett[17]	Outpatient setting in U.K.	Ten individuals with COPD (no other demographic information given)	Unstructured interviews analyzed through hermeneutic analysis	To explore the experience of living with chronic obstructive pulmonary disease by investigating the subjective phenomenon as described by the patient.	Impact on daily activities, feeling frightened, reduced ability to socialize and enjoy a normal life
Booth et al.[18]	Outpatient setting in U.K.	Ten individuals with COPD (six male, four female, aged between 51 and 80 yrs), 10 individuals with cancer (six males, four females aged between 51 and 77 yrs)	Semistructured interviews analyzed through thematic analysis	To investigate the experience of living with breathlessness in those suffering from advanced cancer or COPD and their carers, both to allow comparison of these potentially differing perspectives and to provide insights for future development of both clinical services and research.	Lack of warning signs, overwhelmed by fear, uncertainty and anxiety, increasingly limited mobility, unable to do activities of daily living or socialize, role reversal and loss
Caress et al.[19]	Outpatient setting in U.K.	Fourteen individuals with COPD, eight males, six females, mean age 68 yrs, range 60–80	Semistructured interviews analyzed through thematic analysis	To generate in-depth insights into patients' and family members' understanding of the causation, progression and prevention of chronic obstructive pulmonary disease, and the role of health promotion with this population.	Patients felt frightened and overwhelmed, mobility was affected because of fear of becoming dyspneic, resulting in feelings of helplessness, withdrawal from activities
Clancy et al.[20]	Community setting in U.K.	Nine individuals with COPD, six males, three females, age range 57–78 yrs	Focused-conversation style interviews analyzed through thematic analysis using hermeneutic phenomenological reflection	To explore the existential experiences of 10 patients with chronic obstructive pulmonary disease (COPD) who had been prescribed long-term oxygen therapy (LTOT) and their carers.	Reduced mobility, fear of losing breath, fear of the future, fear of not being in control

Cooney et al.[21]	Community setting in U.K.	Twenty-six individuals with COPD, 15 males (aged between 52 and 86 yrs), 11 females (aged between 49 and 79 yrs)	Semistructured interviews analyzed through grounded theory	Aims to understand the meaning of COPD for people and their response to this disease.	Challenge of day-to-day activities, struggling to live a normal life
Duck et al.[22]	Outpatient setting in U.K.	Seventeen individuals with IPF (seven males, 10 females), median age 67 yrs	Semistructured interviews analyzed through framework analysis	To understand the perceptions, needs, and experiences of patients with idiopathic pulmonary fibrosis.	Loss of independence, change of roles within relationships, increasing dependence
Dunger et al.[23]	Hospital, outpatient, and community setting in U.K.	Eight individuals with cancer (five males, three females, median age 67 yrs), 10 individuals with COPD (four male, six females, median age 66.5 yrs)	Semistructured interviews analyzed through framework analysis	To explore and contrast the experience and meaning of breathlessness in patients with chronic obstructive pulmonary disease (COPD) or lung cancer at the end of life.	Patients adapted and avoided triggers of breathlessness (e.g., physical activity), patients described a loss of independence, and fear of death
Edmonds et al.[24]	Hospital and outpatient setting in U.K.	Twenty-seven individuals with heart failure (20 males, seven females, aged between 38 and 94 yrs [mean 69])	Semistructured interviews analyzed through thematic analysis	To explore patient experience of breathlessness in heart failure.	Uncontrollable breathlessness resulted in a reduction in the number or intensity of activities
Ek et al.[25]	Outpatient setting in Sweden	Four individuals with COPD (one male aged 70 yrs, three females age range 66–75 yrs)	Seventeen interviews (four to five with each participant), 15 phone calls and field notes analyzed through hermeneutic analysis	To illuminate the meaning of living with advanced COPD and LTOT when living alone.	Concerns about self-image, not able to be spontaneous, thoughts about future, fear of dying
Fraser et al.[26]	Outpatient setting in U.S.	Ten individuals with COPD (five males, five females, age range 59–86 yrs (mean 71))	Semistructured interviews analyzed through hermeneutic phenomenology design	To explore the experiences of older adults with severe COPD to gain an understanding of how the disease had affected them and the ways in which they integrated the illness into their lives.	Loss of function, difficulty maintaining a sense of normality, concerns about the future
Gardiner et al.[27]	Community setting in U.K.	Twenty-one individuals with COPD (13 males, eight females, mean age 70.3 yrs)	Semistructured interviews (12 face-to-face, nine telephone), analyzed through thematic analysis	To determine prospectively the needs of patients in the advanced stages of COPD.	Concerns about the future, fear of dying from breathlessness
Gullick et al.[28]	Outpatient setting in Australia	Fifteen individuals with COPD (nine males, six females, age range 55–77 yrs), 14 close family members	Semistructured interviews (18 face-to-face, 40 telephone), analyzed through hermeneutic interpretation	To explore the experience of the person who lives within a body with emphysema—a form of COPD.	Limited ability to mobilize, self-care, or engage with social activities and hobbies, concerns about visibility of breathlessness to others
Gysels et al.[29]	Hospital and community setting in U.K.	Fourteen individuals with COPD in hospital setting (five males, nine females, median age 69 yrs), four individuals with COPD in community (two males, two females, median age 70 yrs)	Semistructured interviews analyzed through grounded theory	To explore the reasons for the disparity between the high needs and the low service use typically reported for breathless patients with COPD and their carers.	Restrictions due to breathlessness requiring adaptations, patients attempted to hide by avoiding contact with the outside world
Gysels et al.[30]	Outpatient setting in U.K.	Ten individuals with COPD (six females, four males, age range 42–78 yrs), six individuals with ILD (three females, three	Semistructured interviews analyzed through thematic analysis	To analyze what constitutes dignity for people suffering from refractory breathlessness with advanced disease, and its	Effect on function and independence limiting every activity, uncertainty regarding future, fear of dying

(*Continued*)

Table 1
Continued

Author	Setting	Participants	Qualitative Approach	Aim of Study	Main Concerns Identified Within Study
		males, age range 72–84 yrs), four individuals with cancer (all males, age range 63–77 yrs)		implications for the concept of dignity.	
Gysels et al.[31]	Hospital, outpatient, and community setting in U.K.	Ten individuals with cancer (five males, five females, age range 52–84 yrs), 14 individuals with COPD (five males, nine females, age range 52–78 yrs), 10 individuals with heart failure (seven males, three females, age range 61–80 yrs), and 10 individuals with MND (nine males, one female, age range 24–77 yrs)	Semistructured interviews analyzed through thematic analysis	To explore and compare the lived experience of breathlessness for patients with four conditions—COPD, heart failure, cancer, and MND	Impaired mobility, increasing dependence, anxiety restricting patients to home, worries about the future
Habraken et al.[32]	Outpatient setting in The Netherlands	11 individuals with COPD, eight males, three females, age range 61–83 yrs	Semistructured interviews analyzed through thematic analysis	To gain insight into why patients with end-stage COPD tend not to express a wish for help.	Fear of not being in control, fear of suffocating and dying
Hallas et al.[33]	Outpatient setting in U.K.	Twelve individuals with chronic respiratory disease (five males, seven females, age range 21–58 yrs)	Semistructured interviews analyzed through interpretative phenomenological analysis	To identify the complex cognitive system of beliefs, appraisals, and perceptions that underpinned patients' experiences of breathlessness and their relationship to the development and maintenance of panic.	Consequences of breathlessness, ability to manage panic, emotional isolation, adjusting to lifestyle changes, avoidance of activities
Harris et al.[34]	Community setting in U.K.	Sixteen individuals with COPD (12 males, four females, mean age 66.8 yrs)	Semistructured interviews analyzed through grounded theory	To identify a strategy for improving the uptake of pulmonary rehabilitation.	Impact on activities of daily living, unable to do domestic tasks or leisure pursuits, requirement to adapt
Hasson et al.[35]	Community setting in Northern Ireland	Thirteen individuals with COPD (10 males, three females, median age 65 yrs)	Semistructured interviews analyzed through thematic analysis	To explore the potential for palliative care among people living with advanced chronic obstructive pulmonary disease (COPD)	Restriction of day-to-day activities, fear that breathlessness could lead to death, concerns about carers
Henoch et al.[36]	Outpatient setting in Sweden	20 individuals with cancer (11 males, nine females, median age 68.5 yrs, range 56–79)	Semistructured interviews analyzed through thematic analysis	To describe lung cancer patients' experience of dyspnea and their strategies for managing dyspnea.	Physical limitations, increased dependence, psychological impact
Jones et al.[37]	Community setting in U.K.	Sixteen individuals with COPD, eight males, eight females, age range 62–83 yrs	Semistructured interviews analyzed through thematic analysis	To determine the needs of patients dying in primary care from chronic obstructive pulmonary disease	Lack of mobility resulting in difficulties around the house and with social contact, fear of dying
Jonsdottir[38]	Outpatient setting in Iceland	Ten individuals with COPD, six males, four females, mean age 61 yrs	In-depth interviews analyzed according to Newman's hermeneutic dialectic method	To explore the life patterns of people with COPD	Loss of control, impact on mobility, isolation, impact on ability to work
Jørgensen et al.[39]	Hospital setting in U.K.	Twelve individuals with COPD (six males [age range 45–79 yrs], six females [age range 64–80 yrs])	Video-based narrative analyzed through grounded theory	To explore how people with moderate to most severe COPD predominantly cope with breathlessness during daily living.	Concerns and anxiety about triggering breathlessness, meaning that activities need to be carefully regulated, feeling of defeat

Lai et al.[40]	Inpatient palliative care unit in Hong Kong	Eleven individuals with lung cancer (eight males, three females, age range 54–75 yrs)	Semistructured interviews analyzed through thematic analysis	To describe the experience of dyspnea and helpful interventions in Chinese patients with advanced lung cancer admitted in the palliative care unit in one region in Hong Kong	Loss of control, impact on activities of daily living, not able to do as much physically, negative perception of self, loss of independence, isolation
Leidy et al.[41]	Outpatient setting in U.S.	Twelve individuals with COPD, six males, six females, mean age 66.8 yrs, range 50–76	In-depth interviews analyzed according to Colaizzi's phenomenological method and consensus dialogue approach	To describe the meaning of functional performance from the perspective of patients themselves	Loss of control, fear of dying
Lowey[42]	Community setting in U.S.	Twenty individuals with heart failure or COPD (nine males, 11 females, mean age 73 yrs, age range 52–93 yrs)	Semistructured interviews analyzed through thematic analysis	Describe the care preferences of individuals living with advanced cardiac and respiratory illnesses about their current and future health, understanding about options for care at the end of life, and expectations from health care providers	Lack of control, unpredictable, fear of breathlessness and the consequences, unable to do hobbies
Luthy et al.[43]	Hospital setting in Switzerland	Thirty-two individuals with COPD, 19 males, 13 females, mean age 64.2 yrs	Interview including drawing task and comments analyzed through thematic analysis	To explore the perception of dyspnea in patients with severe chronic obstructive pulmonary disease	Fear of dying, no control over breathlessness
Nicholls[44]	Outpatient setting in New Zealand	Ten individuals with chronic respiratory disease, five males, five females, age range 60–78 yrs	Narrative interviews analyzed through thematic analysis	To explore how a person's personality or "self" affected the way his or her chronic breathlessness was expressed, and conversely, how the experience of breathlessness affected one's notions of "self"	Unpredictability of breathlessness, fear of dying, loss of independence, loss of normality, unable to do social activities
O'Driscoll et al.[45]	Outpatient setting in U.K.	Fifty-two individuals with lung cancer, 30 males, 22 females, mean age 60 yrs, age range 33–76 yrs	Assessment notes recorded by nurses during conversations with patients analyzed through thematic analysis	Understand the experience of breathlessness and the restrictions it imposes on daily life.	Fear of dying, unable to do activities around the house, restrictions on personal life, disruptions to social activities, unable to fulfill role in society
Oliver[46]	Hospital and community setting in U.K.	Sixteen individuals with COPD, 12 males, four females, mean age 65 yrs, age range 59–75 yrs	Semistructured interviews analyzed through thematic analysis	To explore the perceptions and needs of chronic obstructive pulmonary disease (COPD) patients	Unpredictable, fear of not being able to breathe, fear of dying, loss of self-esteem
Roberts et al.[47]	Community setting in Canada	Ten individuals with cancer, four males, six females, age range 62–80 yrs	Semistructured interviews analyzed through thematic analysis	Understand how patients and nurses interpret nature and meaning of breathlessness	Fear of dying, restriction on daily activities
Robinson[48]	Community setting in U.K.	Ten individuals with COPD, six males, four females, mean age 65.4 yrs, age range 51–74 yrs	Narrative interviews analyzed through a mind map	To describe the experience of living with severe oxygen-dependent chronic obstructive pulmonary disease (COPD)	Impact on physical activities including personal care, fear of breathlessness
Victorson et al.[49]	Outpatient setting in U.S.	Fifteen individuals with COPD, 12 males, three females, mean age 81 yrs, age range 72–92 yrs	Semistructured interviews analyzed through grounded theory	Identify important patient-reported concepts of dyspnea and associated activities to develop a dyspnea-specific conceptual model for chronic obstructive pulmonary disease (COPD).	Impact on physical activities, unable to do activities around the house, fear of not being able to breathe

(*Continued*)

Table 1
Continued

Author	Setting	Participants	Qualitative Approach	Aim of Study	Main Concerns Identified Within Study
Walthall et al.[50]	Outpatient setting in U.K.	Twenty-five individuals with heart failure (15 males, 10 females, mean age 72.66 yrs, age range 53–86 yrs)	Semistructured interviews analyzed through thematic analysis	To explore how patients with chronic heart failure describe their experiences of breathlessness, how daily life is affected and how they adjust to and manage these symptoms.	Impact on ability to undertake activities of daily living, fear of dying, feeling isolated and lonely, unable to fulfill societal role or undertake social activities
Williams et al.[51]	Outpatient and community setting in U.K.	Six individuals with COPD, four males, two females, age range 64–83 yrs	Semistructured interviews analyzed through thematic analysis	To explore what is most important to people living with COPD.	Impact on physical ability and mobility, therefore making it difficult to leave the house
Wortz et al.[52]	Outpatient setting in U.S.	Forty-seven individuals with COPD, 25 males, 22 females, mean age 68.4 yrs	Semistructured interviews analyzed through thematic analysis	To address gaps in the literature on self-management support by examining patients' responses to questions about goals, needs, and expectations regarding self-management using qualitative methods in a broadly representative sample of patients with moderate to severe COPD	Fear of dying, impact on mobility

COPD = chronic obstructive pulmonary disease; NSIP = nonspecific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; MND = motor neurone disease.

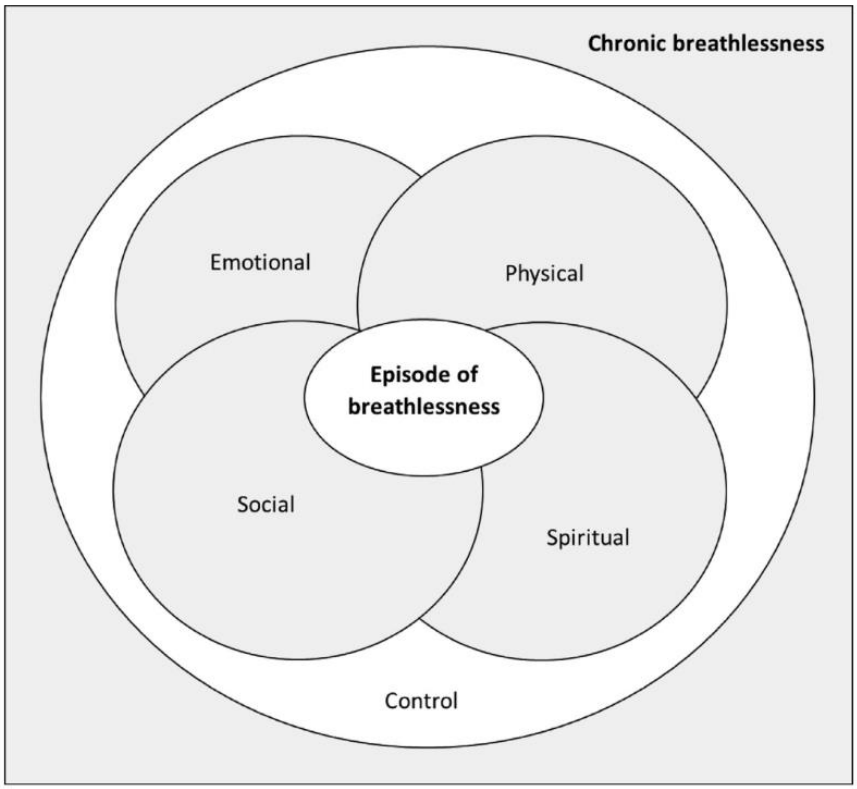


Fig. 2. Total breathlessness. Adapted from Abernethy and Wheeler (2008).

Participants described feeling vulnerable and perceived that an episode of breathlessness might become life threatening and result in death, often describing the sensation of drowning or suffocating.

> I had extreme shortness of breath and I felt I couldn't breathe at all. I felt rather as if I was drowning. I really thought that I was not, you know, going to survive without some form of treatment …
>
> Male with Heart Failure, Walthall et al. 2017.

Fear was also described in the wider context of an individual's life and included fear of triggering an episode of breathlessness, fear of deterioration, and fear of the future.

> It's just stops your life, stops you from living.
>
> Patient with COPD, Caress et al. 2010.

Fear of triggering breathlessness led to activity withdrawal, and participants were less likely to plan activities outside of the home resulting in social isolation.

> I'd like to go for walks but I can't. I just get too breathless. When I sit in a chair I'm fine. In the last six months I've only been out once.
>
> Patient with COPD, Barnett et al. 2005.

The consequences of activity avoidance have been described in the literature as the "downward spiral of disease" whereby breathlessness leads to inactivity and subsequent muscle deconditioning, therefore increasing ventilation and respiratory drive.[54] The vicious circle of dyspnea inactivity is a conceptual model recently developed and validated to explain the clinical course of COPD and emphasizes the importance of exercise capacity and exacerbations as drivers.[55]

Social

Breathlessness affected people's social lives, often excluding them from activities they previously enjoyed. The lost opportunity for routine social interactions was significant to the individual yet often unreported due to a lack of perceived relevance by health care professions. To provide high-quality care, health care professionals need to adopt a person-centered approach and invest the necessary time to

understand an individual's values and priorities, in so doing ensuring that patients feel their concerns are valid and important.

> If I went to a party people would say: "Oh come on, let's dance, its New Year's Eve," and I'd say, "No I don't want to dance," they'd say, "Oh come on, don't be so boring," coz I used to love dancing. I said: "No it's not worth that, we'll dance for five minutes and I'll be sitting down for the next hour, so I'd rather just sit down and watch you dancing." So it's gradually, little things were in my head but not enough to go to the doctor. You can't go to the doctor and say "I can't dance." It's a strange thing to say to the doctor.
>
> Patient with COPD, Gysels and Higginson, 2008.

Breathlessness also had impact significantly on relationships, both physically and emotionally. Physically, living with breathlessness resulted in reliance on family or friends to support and assist with activities of daily living, and as a consequence, participants worried about being a burden to those acting in a caring role.

> I have to rely on my family to cook for me. I don't have the ability to do so but I really don't wish to impose too much on them.
>
> Patient with Lung Cancer, Lai et al. 2007.

Furthermore, illness and increasing dependence often necessitated changes within relationships, for example, between a husband and wife where one becomes the patient and the other the carer. These changes were often significant and could include a loss of intimacy and difficulties maintaining a sexual relationship.

> It has an awful effect on my life. Making love, I can't make love very often because I can't breathe.

Changes in relationships also occurred within the wider family, sometimes associated with a loss of role or inability to maintain a previously assumed responsibility, for example, as a mother.

> I can't walk. [I can't] go running with the kids or play with them because I'm out of breath after 5 minutes. They're only young and they keep saying 'Will you play table tennis with me mammy?' 'I'm not able to, honey.' I'm drained all the time.
>
> Female with COPD, Cooney et al. 2013.

Spiritual

Spiritual distress relating to breathlessness included references to self-identify, sense of purpose, and connection to others. Participants described how living with breathlessness had altered their perception of self, resulting in a feeling of loss. Not being able to fulfill family roles and responsibilities that were once enjoyed left participants lacking in purpose, and they found it difficult to maintain a sense of identity.

> I try not to let it be seen… it's this role reversal which I find very hard… once a Mother Hen always a Mother Hen. Do you ever see the chicks look after the hen? No, you don't. And I haven't been able to do it.
>
> Female with Cancer, Booth et al. 2006.

Participants also described the impact of breathlessness on their perceived ability to live as a "normal person." Low self-worth resulted in a loss of confidence, and participants questioned their ability to cope with everyday tasks and challenges.

> It has changed my life considerably because I hate seeing someone come in … I just feel so useless and helpless … when you go to do something and you realise you can't do it and you mustn't do it … I feel mainly frustrated and disappointed. It's mainly the lack of the normal life I suppose and not being able to do, looking after myself properly and the housework and the cooking.
>
> Female with Heart Failure, Walthall et al. 2017.

Control

The impact of control was evident across domains, both in relation to acute episodes of breathlessness and within the wider context of a person's life affected by chronic breathlessness. Participants described a loss of control over breathing during an episode of breathlessness. The sensation of losing control left participants feeling vulnerable and overwhelmed, powerless to the sensation of breathlessness, and some participants questioned whether they would be able to regain control.

> It is nasty, it is an unpleasant feeling. It is something I did not have control over.
>
> Female with COPD, Ek et al. 2011.

The unpredictability of breathlessness also created a sense of loss of control in other aspects of participant's lives. Living with breathlessness not only prevented one from being spontaneous but also made it difficult to plan; participants did not know how they were going to feel next week, or tomorrow, or even in a few hours' time, reflecting the uncertainty of the symptom. Participants described feeling exposed and helpless, as though the breathlessness was controlling them. It interrupted the daily pattern of their lives and was exhausting.

> It just starts all of a sudden, and you just never know when it's coming on.
>
> Patient with COPD, Fraser et al. 2006.

It [shortness of breath] always just all of a sudden, it just comes on.

Female with COPD, Lowey et al. 2012.

Context of Concerns (Acute Episode and Chronic Breathlessness)

The context in which breathlessness occurs emerged as important, with concerns either relating directly to an episode of breathlessness or more broadly as a consequence of chronic breathlessness. Context influences how an individual experiences and responds to breathlessness and is important for health care professionals to consider when agreeing management strategies. In our model, this is presented as concerns within an "episode of breathlessness," compared to concerns due to "chronic breathlessness."

During an episode of breathlessness, participants described an immediate feeling of fear, with concerns relating to a loss of control.

When I am out of air everything gets out of order.

Patient with COPD, Jonsdottir 1998.

However, participants also described fear and control in the wider context of chronic breathlessness, including fear of triggering breathlessness, fear of the future, and the concept that breathlessness was taking control over their life as a whole.

It [dyspnea] controls me. It controls my life.

Patient with Lung Cancer, Lai et al. 2007.

Similarly, concerns relating to the physical impact of breathlessness are described within an episode and also in the wider context as a consequence of chronic breathlessness. Participants described how they may have to pause mid activity (e.g., walking) to enable an episode of breathlessness to resolve in the short term.

I have to sit down and take a proper break to make my body work again, and that is not easy.

Patient with Lung Cancer, Henoch et al. 2008.

The longer term physical impact included avoidance of activities resulting in physical deconditioning and social isolation.

I don't walk much now because I know that it would [make me breathless] I avoid anything that would.

Patient with COPD, Cooney et al. 2013.

Many of the concerns identified within the social and spiritual domains extended and impacted far beyond an episode of breathlessness. Concerns included changes to role both as an individual but also within society, strain on relationships, and a loss of perceived purpose in life as a whole. These wider concerns are significant and important to people experiencing breathlessness yet remain less commonly assessed in routine clinical practice.

It's just stops your life, stops you from living.

Patient with COPD, Caress et al. 2010.

Discussion

Although earlier work has highlighted the experience of living with breathlessness,[10,56] this is to our knowledge the first attempt to systematically identify and synthesize the main concerns for people with advanced illness experiencing breathlessness, to guide the choice of outcome measures in clinical practice and research. We consider these concerns within a model of "total breathlessness" that incorporates six domains: 1) the physical symptoms of breathlessness and subsequent effect on function; 2) emotional features; 3) the spiritual distress experienced; 4) the social impact of breathlessness; 5) concerns relating to aspects of control; and 6) the context of breathlessness (acute episode or chronic). The main concerns identified are complex and multifaceted and commonly impact across more than one domain, making breathlessness challenging to assess, measure, and research. Results from this synthesis highlight just how broad and extensive the main concerns for people living with breathlessness are, extending far beyond a single episode of breathlessness, encompassing multiple domains and impacting significantly on those around them.

Two additional domains—control and context—were required to fully encompass the findings of this qualitative synthesis and produce our model of "total breathlessness." Participants described the importance of control during an immediate episode of breathlessness. A lack of control left them feeling frightened and vulnerable and often resulted in crisis help-seeking. Control was also described in the wider context of a person's life affected by chronic breathlessness, the impact often resulting in disengaged coping for individuals. Participants described how the uncertainty and unpredictability of breathlessness meant they felt unable to make definitive plans, or be spontaneous. The concept of control was a recurring theme across domains within the "total breathlessness" model, and owing to its prominence within this synthesis, we decided it should be considered as a domain in its own right.

We also added context as a domain of "total breathlessness." Participants described concerns relating to the immediate episode of breathlessness and also in the wider context of chronic breathlessness. Existing literature shows that patients with advanced disease experience distinguishable types and patterns of episodic breathlessness relating to different contextual triggers.[57] Recent qualitative work has shown

that unpredictable episodes are experienced as unpleasant with a higher intensity when compared to predictable episodes.[58] The context of a concern is important and can shape an individual's response including how they cope and seek help as a consequence. The way a person copes and seeks help during an unpredictable episode of breathlessness is likely to be different to how they cope and seek help with the long-term physical impact of their illness. An understanding of the context within which a concern is positioned can help clinicians to tailor management strategies and enhance coping for patients.

This synthesis provides new in-depth understanding of the concerns for people experiencing breathlessness and again emphasizes the significant impact of breathlessness on the social and spiritual domains within a person's life. Synthesis of the included studies combined has highlighted the importance of social participation, demonstrating the significant impact of breathlessness on relationships and loss of perceived role within the family.[17,51] The challenge to meet existential distress and preserve personal integrity is identified as significant in this review,[36,41] yet these are aspects that are less frequently acknowledged and measured within clinical practice.

Recent work proposes that the concept of "breathing space" can be used by clinicians to assess the impacts of breathlessness and provide guidance to patients on coping, help-seeking behavior, and treatment.[10] This framework can be helpful in considering the underlying theory with implications mostly on a staff and systems level. The findings of our work are complementary but distinct, providing clinicians and researches with a practical framework that can identify concerns at an individual level and ensure that appropriate coping strategies and help-seeking behavior are adopted.

This review also provides new evidence to support the choice of outcome measures in clinical trials of interventions for breathlessness. Our model of total breathlessness demonstrates that people with advanced illness express concerns across multiple domains, supporting the use of multiple-domain outcome measures in clinical practice and research. An increasing number of multiple-domain measures have been developed and validated to assess breathlessness. Examples include the Multidimensional Dyspnea Profile, the Dyspnoea-12, and the Chronic Respiratory Disease Questionnaire.

The Multidimensional Dyspnea Profile was designed for use in laboratory and clinical research and assessed sensory and affective dimensions of breathlessness at a specific time or during a specific activity.[59] The Dyspnoea-12 is often used in clinical practice and measures breathlessness severity, incorporating physical and affective aspects. It does not depend on a reference level of activity or specific time period and refers to how breathing feels "these days".[60] The Chronic Respiratory Disease Questionnaire is a health-related quality of life questionnaire that measures breathlessness experienced in the past two weeks across several domains including emotional function and mastery.[61] The context in which breathlessness occurs emerged as important in this review, and these measures consider context by incorporating different questions about the timing of, or triggers of breathlessness. Context should be carefully considered to choose the most appropriate multiple-domain measures in clinical practice and research.

Although multiple-domain measures are increasingly used in clinical practice, they are less commonly used in interventional research, and in particular drug trials. Cochrane reviews have recently been conducted to determine the effectiveness of oxygen,[62] benzodiazepines,[63] and opioids[64] in the management of chronic breathlessness. For each of these reviews, the selected primary outcome was breathlessness as measured using one of several single-domain measures (Numerical Rating Scale, Visual Analogue Scale, and Modified Borg). These outcome measures have the advantage of being short and straightforward to complete and can be pooled across studies for purposes of comparisons. However, they are limited by their simplicity and do not assess all the domains of total breathlessness that have been identified in this review. Future trials in breathlessness should consider a combination of breathlessness assessment (using a single-domain measure), in conjunction with a multiple-domain measure to ensure comprehensive assessment of total breathlessness, including the concerns and problems that matter to patients.

Strengths and Limitations

The qualitative methodology is a strength of this systematic review because it has enabled an in-depth understanding of the main concerns for those experiencing breathlessness. Use of an established framework in the model development has ensured that the results are embedded within the current knowledge base.

However, the majority of studies included in this synthesis were of participants with a diagnosis of COPD, based in the outpatient/community setting, in the U.K. Although there are many similarities in terms of the symptom burden of breathlessness across disease groups in advanced illness, there are also differences in terms of patient experience. For example, the length of diagnosis and the speed of onset of symptoms are different for people with cancer or ILD, when compared to other chronic lung disease, and this is likely to have impact on the concerns expressed by these patients.[31,65,66] Further research is

needed to explore the concerns of people experiencing breathlessness in populations other than COPD and should build on the proposed model, to examine whether findings fit within these domains. This review also identifies the significant impact of breathlessness on those close to the people experiencing it. Further research should explore this impact and consider how it can be measured and addressed in routine clinical practice.

The original data were not available for analysis, and therefore, the synthesis relies on the quotes and results as interpreted and presented in the published papers.

Conclusions

People with advanced illness living with breathlessness have concerns in multiple domains, supporting a concept of "total breathlessness," which includes the original four domains of "total dyspnea," as well as two new domains (control and context) identified in this review. Control and context have been newly identified as important, particularly in their influence on coping and help-seeking behavior. The importance of social participation, impact on relationships, and loss of perceived role within social and spiritual domains also emerged as significant to the individual. Our model of "total breathlessness" provides a practical framework to guide comprehensive clinical assessment and optimize clinical interactions. Future trials in breathlessness should consider a combination of breathlessness assessment (using a single-domain measure), in conjunction with a multiple-domain measure to ensure comprehensive assessment of total breathlessness.

Disclosures and Acknowledgments

The authors declare that they have no conflict of interest.

N. Lovell is completing a training fellowship funded by Cicely Saunders International and Marie Curie (grant number A18859). M. Maddocks is supported by an NIHR Career Development Fellowship (CDF-2017-10-009) and NIHR Health Services & Delivery Research grant (HSDR 16/02/18) and NIHR CLARHC South London. I.J. Higginson is an NIHR Emeritus Senior Investigator and is supported by NIHR CLARHC South London. This research was supported by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, which is part of the National Institute for Health Research (NIHR), and is a partnership between King's Health Partners, St. George's, University London, and St George's Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

1. 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;185:435–452.

2. Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. The Eur Respir J 2017;49. https://doi.org/10.1183/13993003.02277-2016.

3. Simon ST, Weingartner V, Higginson IJ, et al. Definition, categorization, and terminology of episodic breathlessness: consensus by an international Delphi survey. J pain symptom Manag 2014;47:828–838.

4. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J pain symptom Manag 2006;31:58–69.

5. Moens K, Higginson IJ, Harding R. 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 Manag 2014;48:660–677.

6. Bajwah S, Higginson IJ, Ross JR, et al. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190:215–220.

7. 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 Medecin de famille canadien 2012;58:e401–e407.

8. Dorman S, Jolley C, Abernethy A, et al. Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. Palliat Med 2009;23:213–227.

9. Bausewein C, Farquhar M, Booth S, et al. Measurement of breathlessness in advanced disease: a systematic review. Respir Med 2007;101:399–410.

10. Hutchinson A, Barclay-Klingle N, Galvin K, et al. Living with breathlessness: a systematic literature review and qualitative synthesis. Eur Respir J 2018;51. https://doi.org/10.1183/13993003.01477-2017.

11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–269. w64.

12. Reid C, Seymour J, Jones C. A thematic synthesis of the experiences of adults living with hemodialysis. Clin J Am Soc Nephrol: CJASN 2016;11:1206–1218.

13. Garcia-Rueda N, Carvajal Valcarcel A, Saracibar-Razquin M, et al. The experience of living with advanced-stage cancer: a thematic synthesis of the literature. Eur J Cancer Care 2016;25:551–569.

14. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol 2008;8:45.

15. Apps LD, Harrison SL, Williams JE, et al. How do informal self-care strategies evolve among patients with chronic obstructive pulmonary disease managed in primary care? A qualitative study. Int J Chronic Obstructive Pulm Dis 2014;9:257–263.

16. Bajwah S, Higginson IJ, Ross JR, et al. The palliative care needs for fibrotic interstitial lung disease: a qualitative study

of patients, informal caregivers and health professionals. Palliat Med 2013;27:869–876.

17. Barnett M. Chronic obstructive pulmonary disease: a phenomenological study of patients' experiences. J Clin Nurs 2005;14:805–812.

18. Booth S, Silvester S, Todd C. Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. Palliat Support Care 2003;1:337–344.

19. Caress A, Luker K, Chalmers K. Promoting the health of people with chronic obstructive pulmonary disease: patients' and carers' views. J Clin Nurs 2010;19:564–573.

20. Clancy K, Hallet C, Caress A. The meaning of living with chronic obstructive pulmonary disease. J Nurs Healthc Chronic Illness 2009;1:78–86.

21. Cooney A, Mee L, Casey D, et al. Life with chronic obstructive pulmonary disease: striving for 'controlled co-existence'. J Clin Nurs 2013;22:986-995.

22. Duck A, Spencer LG, Bailey S, et al. Perceptions, experiences and needs of patients with idiopathic pulmonary fibrosis. J Adv Nurs 2015;71:1055–1065.

23. Dunger C, Higginson IJ, Gysels M, et al. Breathlessness and crises in the context of advanced illness: a comparison between COPD and lung cancer patients. Palliat Support Care 2015;13:229–237.

24. Edmonds PM, Rogers A, Addington-Hall JM, et al. Patient descriptions of breathlessness in heart failure. Int J Cardiol 2005;98:61–66.

25. Ek K, Sahlberg-Blom E, Andershed B, et al. Struggling to retain living space: patients' stories about living with advanced chronic obstructive pulmonary disease. J Adv Nurs 2011;67:1480–1490.

26. Fraser DD, Kee CC, Minick P. Living with chronic obstructive pulmonary disease: insiders' perspectives. J Adv Nurs 2006;55:550–558.

27. Gardiner C, Gott M, Small N, et al. Living with advanced chronic obstructive pulmonary disease: patients concerns regarding death and dying. Palliat Med 2009;23:691–697.

28. Gullick J, Stainton MC. Living with chronic obstructive pulmonary disease: developing conscious body management in a shrinking life-world. J Adv Nurs 2008;64:605–614.

29. Gysels M, Higginson IJ. Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. J pain symptom Manag 2008;36:451–460.

30. Gysels M, Reilly CC, Jolley CJ, et al. Dignity through integrated symptom management: lessons from the breathlessness support service. J pain symptom Manag 2016;52:515–524.

31. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. BMC Palliat Care 2011;10:15.

32. Habraken JM, Pols J, Bindels PJE, et al. The silence of patients with end-stage COPD: a qualitative study. Br J Gen Pract 2008;58:844–849.

33. Hallas CN, Howard C, Theadom A, et al. Negative beliefs about breathlessness increases panic for patients with chronic respiratory disease. Psychol Health Med 2012;17:467–477.

34. Harris D, Hayter M, Allender S. Improving the uptake of pulmonary rehabilitation in patients with COPD:: qualitative study of experiences and attitudes. Br J Gen Pract 2008;58:703–710.

35. Hasson F, Spence A, Waldron M, et al. I can not get a breath: experiences of living with advanced chronic obstructive pulmonary disease. Int J Palliat Nurs 2008;14:526–531.

36. Henoch I, Bergman B, Danielson E. Dyspnea experience and management strategies in patients with lung cancer. Psycho-oncology 2008;17:709–715.

37. Jones I, Kirby A, Ormiston P, et al. The needs of patients dying of chronic obstructive pulmonary disease in the community. Fam Pract 2004;21:310–313.

38. Jonsdottir H. Life patterns of people with chronic obstructive pulmonary disease: isolation and being closed in. Nurs Sci Q 1998;11:160–166.

39. Jørgensen LB, Dahl R, Pedersen PU, et al. Four types of coping with COPD-induced breathlessness in daily living: a grounded theory study. J Res Nurs 2012;18:520–541.

40. Lai YL, Chan CW, Lopez V. Perceptions of dyspnea and helpful interventions during the advanced stage of lung cancer: Chinese patients' perspectives. Cancer Nurs 2007;30:E1–E8.

41. Leidy NK, Haase JE. Functional status from the patient's perspective: the challenge of preserving personal integrity. Res Nurs Health 1999;22:67–77.

42. Lowey SE. Care preferences of individuals living with advanced cardiac and respiratory illness. Dissertation Abstr Int Section B: The Sci Eng 2012;72:5885.

43. Luthy C, Cedraschi C, Pasquina P, et al. Perception of chronic respiratory impairment in patients' drawings. J Rehabil Med 2013;45:694–700.

44. Nicholls DA. The experience of chronic breathlessness. Physiother Theor Pract 2003;19:123–136.

45. O'Driscoll M, Corner J, Bailey C. The experience of breathlessness in lung cancer. Eur J Cancer Care 1999;8:37–43.

46. Oliver SM. Living with failing lungs: the doctor–patient relationship. Fam Pract 2001;18:430–439.

47. Roberts DK, Thorne SE, Pearson C. The experience of dyspnea in late-stage cancer. Patients' and nurses' perspectives. Cancer Nurs 1993;16:310–320.

48. Robinson T. Living with severe hypoxic COPD: the patients' experience. Nurs times 2005;101:38–42.

49. Victorson DE, Anton S, Hamilton A, et al. A conceptual model of the experience of dyspnea and functional limitations in chronic obstructive pulmonary disease. Value Health: J Int Soc Pharmacoeconomics Outcomes Res 2009;12:1018–1025.

50. Walthall H, Jenkinson C, Boulton M. Living with breathlessness in chronic heart failure: a qualitative study. J Clin Nurs 2017;26:2036–2044.

51. Williams V, Bruton A, Ellis-Hill C, et al. What really matters to patients living with chronic obstructive pulmonary disease? An exploratory study. Chronic Respir Dis 2007;4:77–85.

52. Wortz K, Cade A, Menard JR, et al. A qualitative study of patients' goals and expectations for self-management of

COPD. Prim Care Respir J: J Gen Pract Airways Group 2012; 21:384–391.

53. Abernethy AP, Wheeler JL. Total dyspnoea. Curr Opin Support Palliat Care 2008;2:110–113.

54. Donaldson AV, Maddocks M, Martolini D, et al. Muscle function in COPD: a complex interplay. Int J chronic obstructive Pulm Dis 2012;7:523–535.

55. Ramon MA, Ter Riet G, Carsin A-E, et al. The dyspnoea-inactivity vicious circle in COPD: development and external validation of a conceptual model. Eur Respir J 2018;52.

56. Gysels M, Bausewein C, Higginson IJ. Experiences of breathlessness: a systematic review of the qualitative literature. Palliat Support Care 2007;5:281–302.

57. Simon ST, Higginson IJ, Benalia H, et al. Episodes of breathlessness: types and patterns—a qualitative study exploring experiences of patients with advanced diseases. Palliat Med 2013;27:524–532.

58. Linde P, Hanke G, Voltz R, et al. Unpredictable episodic breathlessness in patients with advanced chronic obstructive pulmonary disease and lung cancer: a qualitative study. Support Care Cancer 2018;26:1097–1104.

59. Banzett RB, O'Donnell CR, Guilfoyle TE, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. Eur Respir J 2015;45:1681–1691.

60. Yorke J, Moosavi SH, Shuldham C, et al. Quantification of dyspnoea using descriptors: development and initial testing of the Dyspnoea-12. Thorax 2010;65:21–26.

61. Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773–778.

62. Ekstrom M, Ahmadi Z, Bornefalk-Hermansson A, et al. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. Cochrane database Syst Rev 2016;11:CD006429.

63. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. The Cochrane database Syst Rev 2016;10:CD007354.

64. 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.

65. Bajwah S, Ross JR, Peacock JL, et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax 2013;68:867–879.

66. Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med 2017;5:968–980.

Appendix

Appendix 1
Search Strategy: Medline Search Strategy

Concept 1: Exposure	Concept 2: Outcome	Concept 3: Population
exp dyspnea/	exp patient preference/	exp Palliative Care/
dyspn*.tw.	exp health priorities/	exp Terminal Care/
short* of breath.tw.	experience*.tw.	exp Terminally Ill/
breathless*.tw.	expectat*.tw.	exp Hospices/
acute exacerbation*.tw.	prefer*.tw.	palliat*.tw.
	priorit*.tw.	terminal care.tw.
	concern*.tw.	end of life.tw.
	narrative.tw.	hospice*.tw.
		dying.tw
		chronic respiratory disease.tw.
		chronic lung disease.tw.
		chronic obstructive pulmonary disease.tw.
		end stage*.tw.
		life limit*.tw.
		advance*.tw.
		progressive*.tw.
		severe*.tw.
		chronic.tw.
		adj2
		illness.tw.
		condition*.tw
		disease.tw.
		diagnosis.tw.
		chronic obstructive pulmonary disease.tw.
		interstitial lung disease.tw.
		heart failure.tw.
		cancer.tw.

Appendix 2

Critical Appraisal Skills Program Checklist Appraisal

Author	Clear Statement of Aims	Appropriate Methodology	Appropriate Design	Appropriate Recruitment Strategy	Appropriate Data Collection	Relationship Between Researcher and Participants Considered	Ethical Issues Considered	Rigorous Data Analysis	Clear Statement of Findings	Value of Research
Apps et al.[15]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Bajwah et al.[16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Barnett, M.[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Booth et al.[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Caress et al.[19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Clancy et al.[20]	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Can't tell	Yes	Yes
Cooney et al.[21]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Duck et al.[22]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Dunger et al.[23]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Edmonds et al.[24]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Ek et al.[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fraser et al.[26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Gardiner et al.[27]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Gullick et al.[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gysels et al.[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gysels et al.[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gysels et al.[31]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Habraken et al.[32]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Hallas et al.[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Harris et al.[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hasson et al.[35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Henoch et al.[36]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Jones et al.[37]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Jonsdottir, H.[38]	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Can't tell	Yes	Yes
Jørgensen et al.[39]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Lai et al.[40]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Leidy et al.[41]	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Yes	Yes
Lowey, S.[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Luthy et al.[43]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Nicholls, D.[44]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
O'Driscoll et al.[45]	No	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
Oliver, S.[46]	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
Roberts et al.[47]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Robinson, T.[48]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Victorson et al.[49]	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Yes	Yes
Walthall et al.[50]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Williams et al.[51]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Wortz et al.[52]	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Yes	Yes

3.3 Challenges of conducting randomised controlled trials in advanced disease

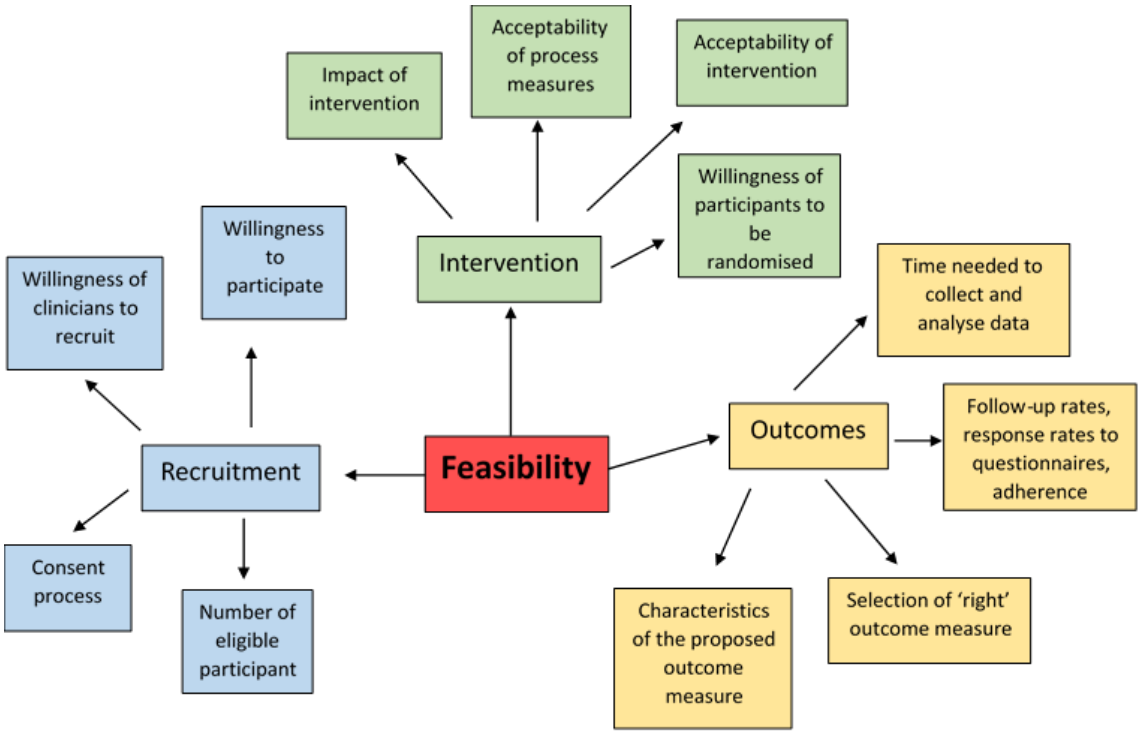
Conducting research with people living with advanced disease is invariably challenging (88). Practical and scientific considerations include: difficulties recruiting with eligibility and access important considerations, and unpredictable disease trajectories contributing to high levels of attrition (22, 89-95). Trial designs and procedures therefore need to be optimised to ensure good quality data, whilst minimising the burden of participation to patients, their families and healthcare professionals. Retention in clinical trials is perhaps even more important and has recently been identified as a top priority (96-98), with high levels of attrition a well-recognised problem (99). Reasons for attrition include a high symptom burden (21%), patient preference (15%), hospitalisation (10%), and death (6%) (23). A recent meta-ethnographic synthesis highlights the need for good quality primary studies which explore the barriers and enablers to trial retention from the participants perspective. The synthesis identifies five themes which may influence non retention in trials: 1) aspects of the trial did not fit with sense of self, 2) the trial design was not individualised, 3) trial processes were not in line with individual capabilities, 4) concerns about the trial medication, and 5) participation was not considered alongside the other challenges in life (100).

As more people approach the end of their lives with chronic and complex conditions, the need for robust research and evidence has never been greater (101, 102). It is therefore important to understand what affects retention so that we can minimise attrition and ensure high quality clinical trials of palliative care interventions in the future. Feasibility work is crucial and can help to identify methodological challenges prior to conducting effectiveness studies.

Before commencing a main study, it is therefore often recommended to test and improve the methods for a planned study through feasibility and/or pilot work (103, 104). The terminology relating to feasibility work is still evolving and the words ‘feasibility’ and ‘pilot’ are often used interchangeably. Both feasibility and pilot studies refer to activities carried out prior to conducting a large study, to test out uncertainties. Although a number of definitions exist, the most commonly referred to are those developed by the National Institute for Health Research (NIHR), in which feasibility studies are described as occurring earlier in the research process and often before a pilot study. NIHR defines feasibility studies as pieces of research done before a main study in order to answer the question ‘can this study be done?’ Within this definition they suggest that feasibility work can help to identify important parameters that are needed to design the main study (105). These parameters may relate to study recruitment, the intervention design and delivery, or measurement of study outcomes as outlined in Figure 2. In

comparison pilot studies are ‘a smaller version of the main study used to test whether the components of the main study can all work together’(105).

Figure 2: Components of Feasibility Work, developed from Thabane et al (2010)(106)



Qualitative research is increasingly undertaken alongside or embedded within RCTs and can be used to address a wide range of aspects including: the intervention being trialled, the design process and conduct of the trial, the outcomes and measures used in the trial, and the target condition for the trial (107). Qualitative research can improve the design and running of clinical trials, and in the prostate testing for cancer and treatment (ProtecT) study findings from an embedded qualitative study led to changes in the terminology, organisation and presentation of study information, subsequently improving trial recruitment (108). It has been suggested that qualitative research should be prioritised at the pre-trial phase so that results can be used to enhance trial procedures (107). Additionally, the purpose, objectives and results of the qualitative component need to be clearly reported or there can be a loss of learning for others (107).

3.4 Summary

Chronic or refractory breathlessness is common, distressing, and has a significant psychosocial impact and carer burden. The current evidence base for pharmacological interventions is limited and new treatments are urgently needed. Drugs which modify the processing and perception of afferent information in the brain may have a role in the treatment of chronic of refractory breathlessness by impacting on the areas of the brain relating to fear and anxiety. To test new treatments, we need to conduct randomised controlled trials, the challenges of which include difficulties recruiting and high levels of attrition. Choice of outcome measure is also important and while many measures are validated in the assessment of breathlessness, consensus is lacking on which to use and when. This thesis aims to fill this evidence gap and provide recommendations on how to optimise recruitment, retention and the selected outcome measures in a randomised controlled drug trial for chronic or refractory breathlessness.

Chapter 4 -Aim and Objectives

Aim

To explore the feasibility of, and ways to optimise recruitment, retention, and outcome measures in a double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness.

Objectives

1. To systematically review and synthesise the main concerns of people with advanced disease experiencing breathlessness, and consider these in relation to current outcome measures
2. To explore what outcomes are important to participants in a drug trial for chronic or refractory breathlessness and to what extent these are captured using standard measures
3. To explore experience and feasibility of trial processes and what influences participants to take part and remain in a in a drug trial for chronic or refractory breathlessness

Chapter 5 –Overview of methodology

5.1 Introduction

This chapter presents an overview of the thesis design, including the main theoretical and methodological considerations. Full methods are detailed in Chapter 6, and in Chapters 7 and 8. In order to meet the aim and objectives a prospective mixed methods design was used. Data collection followed a convergent design comprising of:

- Quantitative data collected during a randomised feasibility trial
- Qualitative interviews conducted at the end of the feasibility trial

The quantitative and qualitative data were collected and analysed separately, and then integrated and compared in an interpretation phase. Findings from the qualitative data were explored in the quantitative data and vice versa. In order to meet the thesis objectives there was a greater emphasis on the qualitative component with the quantitative data providing additional context.

5.2 Ontology and Epistemology

Ontology and epistemology are important considerations in research, and often guide the choice of study design (109). Choice of research paradigm can be considered in terms of the nature of reality (ontology), and how knowledge is gained about this reality (epistemology) (109). This thesis explores what influences people with chronic or refractory breathlessness to take part and remain in a randomised trial, and what are the important outcomes to measure. Breathlessness is a complex phenomenon, described by the American Thoracic Society as a subjective experience, which varies in intensity (1). It is however, also possible to objectively measure breathlessness, for example through the use of validated outcome measures (71). To understand what influences people to take part and remain in a trial requires exploration of individual experience and interpretation of reality. Therefore, both of these concepts have multiple realities.

This thesis uses pragmatism as a research paradigm, accepting that there can be multiple realities, and the process of acquiring knowledge is a continuum, and not two opposing poles of objectivity and subjectivity (109). In pragmatism the best method had been said to be that which is most effective in producing the desired consequences of the enquiry (110). In order to

meet the aim and objectives of this thesis mixed methods were chosen as the most appropriate methodology. This enabled a complex phenomenon, for example the experience of breathlessness to be considered across different realities. Using this example, the quantitative component of the study helps to determine the reality, and then the qualitative component considers how an individual then interprets this reality.

5.3 Mixed methods

Mixed-methods continue to develop as a methodology and approach to social inquiry, and is commonly seen in health services research (111-114). Initially described as the use of multiple methods, it is now commonly accepted that mixed methods integrate elements of qualitative and quantitative data to improve the breadth and depth of understanding, and for data corroboration (110). Quantitative and qualitative methods can both individually provide data on complex phenomenon for example the experience of breathlessness. However, the process of combining these data provides an enhanced and more comprehensive understanding when compared to the data from either source alone. Comparison of quantitative and qualitative data allows validation of the research findings, as well as identifying divergence.

Creswell describes three typologies within mixed methods: convergent, explanatory sequential, and exploratory sequential (109). In the convergent design both sets of data are collected and analysed concurrently. In the explanatory sequential design the quantitative data is collected first and then explained using the qualitative data. In the exploratory sequential design the qualitative data is collected and analysed prior to the quantitative data collection. The priority or dominance given to one methodology is also an important consideration (110). For this thesis a convergent design was chosen and quantitative and qualitative data were collected and analysed concurrently. The data were then integrated and compared during an interpretation phase. Dominance was given to the qualitative component, which was felt to be crucial in achieving the aim and objectives of the thesis.

Mixed-methods are commonly used in the context of randomised trials, and the addition of a qualitative approach can help to examine and address uncertainties prior to a full trial (115). Qualitative components are most commonly incorporated during or at the end of a trial, and often explore the intervention, trial processes, and outcome measures (107). This thesis aimed to explore study processes including what influenced people to take part and remain in the trial, what outcomes were considered to be important, and how participants' experience of

breathlessness changed during the trial. In order to best meet these objectives, the qualitative interviews were conducted at the end of the trial.

5.4 Study Population and Setting

The population of interest are people with a diagnosis of chronic respiratory disease, chronic cardiac disease, or cancer, living with chronic or refractory breathlessness. We were interested in those most severely affected by breathlessness and therefore the trial recruited people with an mMRC score of 3 or 4. This equates to 'I stop for breath after walking 100 yards or a few minutes on the level', or 'I am too breathless to leave the house or become breathless while dressing' (25). Conducting research with those most severely affected by breathlessness is a significant challenge. This group of patients are often extremely limited functionally and find it difficult to travel to attend appointments. Fatigue is common and therefore trial related procedures need to be carefully considered, and modified to reduce burden where possible (6, 27).

It is also important to consider where these patients might be recruited. The clinical trajectory for those living with advanced disease and breathlessness is uncertain, and admissions to hospital with acute breathlessness are common (19). However, the feasibility trial described in this thesis considers an intervention for chronic or refractory breathlessness and therefore participants need to be stable and at baseline from a clinical perspective at the point of entering the trial. Most people admitted acutely to hospital are unlikely to be at baseline. It was therefore agreed that to be considered eligible for the feasibility trial potential participants needed to have been stable for the seven days previous, with no changes to the management of the underlying condition. Part of the purpose of conducting a feasibility trial was to determine the feasibility of recruitment from different settings, and therefore we recruited hospital inpatients, outpatients, and those in the community. Clinicians in disease specific and palliative care teams identified potential participants. An expected prognosis of two months was agreed although it was acknowledged that prognosticating in advanced respiratory and cardiac disease is difficult and often imprecise.

5.5 Trial Design

The challenges of conducting randomised controlled trials (RCTs) are well recognised, with results often limited by sample size and levels of attrition (23, 116). Trials in advanced disease

are particularly challenging and in a recent review the target sample size was only achieved in 36.8% of trials assessing a therapeutic intervention (22). Recruitment is often difficult due to strict eligibility criteria, and the consequences of attrition can include high levels of missing data (23). Trial design is crucial and the amount of missing data has been shown to increase with an increasing study duration or number of questionnaires and/ or tests (116). Meta ethnographic review suggests that trial design not being individualised is an important consideration for trial retention (100).

Our trial design used a person-centred approach and attempted to minimise burden and ensure processes were in line with individual capabilities. Patient and public involvement helped to ensure that the information provided to participants was detailed yet easy to understand. The burden was minimised by offering home visits, flexibility of timings, and providing assistance in completing trial questionnaires.

5.6 Patient and Public Involvement

The contribution of Patient and Public Involvement (PPI) is increasingly recognised and can improve the relevance and quality of research conducted (117, 118). Involvement should start at the research design stage and can help to direct recruitment and retention strategies, and improve involvement (119). PPI contributed to all stages of this trial, from design to analysis with representatives on the Trial Management Group (TMG) and the Trial Steering Committee (TSC). Trial burden was highlighted as important, and changes were made to the patient information sheet to ensure a clear explanation of trial processes including the concept of randomisation.

5.7 Ethical Considerations

While there are often concerns about conducting research with people living with advanced disease research has shown that most people want the opportunity to contribute, and feel they benefit from doing so (120). Better-B (Feasibility) recruited NHS patients and therefore approval from a UK NHS research ethics committee was required. Ethical approval was received from the UK Health Research Authority (16/LO/0091) and the trial was prospectively registered (ISRCTN 32236160) (Appendix 1).

Chapter 6 -Specific methods

6.1 Introduction

This chapter discusses the specific methods used to collect data for this thesis which sat within a multicentre feasibility trial 'Better-B (Feasibility)'. I first outline the main aim of 'Better-B (Feasibility)' and the methods used. I then consider the aim of my thesis and describe my specific contributions. The design, setting, population, approach to data collection and analysis are then described in more detail, including which data were used to meet individual objectives. More detail about specific methods is provided in results chapters 7 and 8.

6.2 Better-B (Feasibility)

The research reported in this thesis was part of a multicentre feasibility trial 'BETter TreatmEnts for Refractory Breathlessness' (BETTER-B (Feasibility). It is therefore important to be clear about my specific contributions within this larger body of work. The aim of BETTER-B (Feasibility) was to determine the feasibility of performing a large scale double-blind, placebo-controlled randomised trial of mirtazapine for chronic or refractory breathlessness. Feasibility was determined through quantitative assessment of recruitment across different settings, ability to maintain the double blind, the amount of missing data, and compliance with treatment. The aim of my thesis was to explore ways to optimise recruitment, retention, and outcome measures in the trial, using a qualitative dominant mixed methods design. I developed the qualitative component of the trial and led on the integrated analysis of the qualitative and quantitative data.

Specific contributions are as follows:

- Development and writing of the interview topic guide
- Recruitment of participants and quantitative data collection at the London site
- All qualitative interview data collection (across all three sites)
- Analysis and interpretation of the data presented in this thesis

6.3 Design and Population

6.3.1 Design

The overall design was a multi-centre, randomised, placebo-controlled, double blind, mixed methods feasibility trial.

6.3.2 Setting

Participants were recruited from three UK sites; King's College Hospital, Nottingham City Hospital NHS Trust, and Castle Hill Hospital. Potential participants were identified through inpatient clinical teams, multi-disciplinary team meetings, hospital clinic lists, and hospital databases. At each site there was a small dedicated research team who were involved in both the recruitment and follow up data collection across all time points of the trial.

6.3.3 Population

Those eligible for the feasibility trial were:

- Male or female aged ≥ 18 years old
- Diagnosed with: Cancer, or Chronic obstructive pulmonary disease (COPD), or Interstitial lung disease (ILD), or Chronic heart failure (New York Heart Association (NYHA) class III or IV)
- Breathlessness severity: Modified MRC dyspnoea scale grade 3 or 4 (stops for breath after walking about 100 yards or after a few minutes on level ground, is too breathless to leave the house, or is breathless when dressing).
- On optimal treatment of the underlying condition in the opinion of the identifying clinician
- Management of the underlying condition unchanged for the previous 1 week
- Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
- Expected prognosis of ≥2 months
- If female and of child-bearing potential, must agree to use adequate contraception
- Able to complete questionnaires and trial assessments
- Able to provide written informed consent

The following exclusion criteria applied:

- Existing antidepressant use
- Known contraindication to mirtazapine
- Hypersensitivity to the active substance or to any of the components of the mirtazapine or placebo (e.g. lactose intolerance)
- Australia modified Karnofsky Performance Scale ≤40
- Pregnant or breast-feeding women
- Patients with acute cardiac events within 3 months of randomisation (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)
- Patients with known hepatic impairment
- Patients with known renal impairment
- Patients with uncontrolled blood pressure
- Patients with uncontrolled diabetes mellitus
- Patients with uncontrolled seizures, epilepsy or organic brain syndrome
- Patients with severe depression or suicidal thoughts
- Patients with a history of psychotic illness (schizophrenia, bipolar disorder, mania or hypomania, or other psychotic disturbances)

6.3.4 Sample Size

BETTER-B (Feasibility) aimed to assess the feasibility of conducting a definitive large-scale trial. As effectiveness is not being evaluated a formal sample size calculation is not required. However guidance does suggest that 30 participants are required in order to estimate the variability of a primary outcome, and therefore a target sample size of 60 was agreed (121).

6.3.5 Qualitative interviews

A subset of trial participants was interviewed. Prior to data collection a sampling frame was developed based on characteristics considered to be important including: primary diagnosis, age, gender, and whether or not they completed the trial. However, a pragmatic approach was agreed due to the limited pool of participants and all trial participants were offered the opportunity to take part in a qualitative interview. No sample size was set, and interviews would continue until no new themes were identified.

6.4 Data collection

6.4.1 Identification, consent and randomisation

Potential participants were identified by staff at recruiting sites and Participant Identification Centre's (PIC's). Patients and carers were approached by their usual clinician and provided with some initial information about the trial. If they were in agreement they were then contacted by a researcher who was able to provide more detailed information including; the rationale for doing the study, the trial design, and what it would mean if they agreed to take part in terms of the intervention and study assessments. One site used an existing database of patients who had previously taken part in research and had consented to be contacted in the future. A member of the research team contacted these patients directly. All members of the research team had training and experience of working with people living with advanced disease. Patients were given a minimum of 24 hours to consider the trial and discuss with friends and family. Participants then provided written informed consent, and a more detailed eligibility assessment followed.

Following confirmation of written informed consent and eligibility, an authorised member of staff at the trial site randomised participants. The Clinical Trials Research Unit (CTRU) completed the randomisations using a computer-generated minimisation programme. Participants were allocated a trial number and unique kit number (specifying treatment allocation) and were randomised 1:1 to receive mirtazapine or placebo. Treatment groups were balanced by: disease (cancer versus non-cancer), Hospital Anxiety and Depression Scale score (≥15 vs <15), and whether they were currently receiving opioids).

Participants who agreed to be approached for a qualitative interview were contacted at the end of the trial by telephone. All participants provided written informed consent.

6.4.2 Data collection schedule

Participants received 28 days of trial treatment (either oral mirtazapine or placebo capsules). They were assessed face to face on day 0, day 14 and day 28, and via telephone on day 7, day 21, and day 35. Assessments were organised at a time which was convenient for the participant with some flexibility (+/-1 day). Participants were offered to be visited at home and assistance was provided with completing the trial-based questionnaires (Appendices 2-4). Continuity of the researcher was prioritised where possible.

Table 2: Data collection schedule

Time point	Eligibility assessment	Baseline	Day 7	Day 14	Day 21	Day 28	Day 35
Method	Face to face	Face to face	Phone call	Face to face	Phone call	Face to face	Phone call
Data collected							
Demographic and clinical data	X	X					
mMRC	X	X		X		X	
NRS		X	X	X	X	X	
CRQ		X		X		X	
GSES		X				X	
IPOS		X		X		X	
HADS		X		X		X	
EQ-5D-5L		X				X	
CSRI		X				X	
AKPS	X	X		X		X	
SPPB		X				X	
Toxicity assessment		X	X	X	X	X	X
Opioid med assessment		X	X	X	X	X	
Compliance assessment			X	X	X	X	X
Blinding assessment						X	

6.4.3 Qualitative interviews

Qualitative interviews were conducted at the end of the trial. Interviews were conducted in a place of the participants choosing. This was usually their own home, but some interviews were conducted in hospital. The topic guide was developed using existing literature and refined following feedback from PPI representatives and the Trial Management Group (Appendix 5). Interviews were digitally audio recorded and transcribed verbatim. A distress protocol was used to minimise the risk of potential harm.

6.5 Analysis

6.5.1 Data management

Quantitative Data

The CTRU was responsible for management of the quantitative data. The Clinical Report Forms (CRFs) and questionnaire booklets were posted to the CTRU for data entry, cleaning and checking. Attempts were made to minimise missing data, and individual sites were contacted with data queries.

Qualitative Data

Qualitative Data was recorded and transcribed verbatim. Transcriptions were checked for accuracy and audio recordings were deleted. All text was anonymised and uploaded to Nvivo.

6.5.2 Data Analysis

Objective 1: To systematically review and synthesise the main concerns of people with advanced disease experiencing breathlessness and consider these in relation to current outcome measures.

Objective 1 was achieved through a systematic search of the literature and did not use primary data collected in the feasibility trial. The thematic synthesis is presented in chapter 3.

Objective 2: To explore what outcomes are important to participants in a drug trial for chronic or refractory breathlessness and to what extent these are captured using standard measures.

Data used in analysis: Outcome measure data (NRS average, NRS worst and CRQ) and Qualitative data.

The quantitative and qualitative data were collected and analysed separately, then integrated and compared in an interpretation phase.

Quantitative data

The NRS was completed at baseline, days 7, 14, 21, and 28. Two NRS rating questions were asked "How has your breathlessness been over the last 24 hours on average?" (NRS average) and "What is the worst your breathlessness has been over the last 24 hours?" (NRS worst). The question was anchored with the statement "not breathless at all" positioned next to number 0, and "the worst possible breathlessness" next to number 10. The CRQ, a twenty-item health-related quality-of-life questionnaire, was completed at baseline, days 14 and 28. Questions are divided into four domains: dyspnea (the participant identifies five important activities and how short of breath each activity makes them feel), fatigue (four questions), emotional function (seven questions), and mastery (four questions). Each question is scored on a 7-point Likert scale, higher scores indicate less breathlessness or better quality of life. Mean scores for each domain enable comparisons between domains. Measures were compared to derive a change score from baseline to Day 28, a period comparable to that asked about in the qualitative interviews. Change was assessed according to the minimal clinically important difference guidance for each questionnaire (>1-point for the NRS, and >0.5 unit for each domain of the CRQ).

Qualitative data

The qualitative interviews were analysed using Braun and Clarke's framework for thematic analysis (122) using NVIVO version 10 (QSR International (UK) Ltd. Transcripts were read and re-read, and coded inductively for themes relating to change in experience of breathlessness during the trial. Themes were considered within the domains of "total breathlessness" (87). Perceived changes were categorised in terms of the extent of the change. This was based on the language used by participants to describe any change they had perceived. Three transcripts were double-coded by another researcher (SE) who produced their own coding frame. Areas of agreement and disagreement in particular relating to the degree of change were discussed until consensus was achieved.

Integration and interpretation

Examples were explored where the findings of the quantitative and qualitative data agreed and disagreed. If both data sets identified change or neither identified change, this was classified as agreement. If one data set identified change but the other did not, this was classified as disagreement. We also considered how change was captured across the domains of "total breathlessness," and whether there were patterns of change across domains. For further detail see published paper in chapter 7.

Objective 3: To explore participants experience and feasibility of trial processes and what influences participants to take part and remain in a in a drug trial for chronic or refractory breathlessness.

Data used in analysis: Quantitative and Qualitative data

Objective 3 was achieved through a combination of analysing the quantitative and qualitative data. Measurements of feasibility were: recruitment (screening and recruitment data, consent process, and willingness to participate), the intervention (acceptability and impact) and outcomes (acceptability and missing data).

Quantitative data

The quantitative data provided detail about the participants screened and recruited. This included the setting and main diagnosis. Acceptability of the intervention was evaluated by reviewing the number of adverse events and the number of participants who discontinued the intervention. Feasibility of the outcomes was evaluated by reviewing the proportion of missing data in the trial-based questionnaires.

Qualitative data

The qualitative interviews were analysed using Braun and Clarke's framework for thematic analysis (122) using NVIVO version 10 (QSR International (UK) Ltd.). Transcripts were read and re-read and then coded inductively for themes relating to feasibility including recruitment, the intervention and outcomes. Three transcripts were double coded by another researcher (SE) who produced their own coding frame. Areas of agreement and disagreement were then discussed until consensus was achieved.

During the interviews it became apparent that a number of participants had requested to be prescribed mirtazapine by their General Practitioner once the trial had finished. I therefore decided to do an interim analysis for these participants to explore aspects of feasibility including acceptability of the intervention and the outcomes. For further detail see published case series in chapter 8.

In order to meet the second part of objective 3 and explore what influences participants to take part and remain in a in a drug trial for chronic or refractory breathlessness transcripts were coded for themes relating to; reasons to participate in the trial, reasons not to participate in the trial, reasons to remain in the trial and reasons to discontinue the trial. Results were considered in relation to the core elements of person-centred care and our model of the person-centred trial. Further details are included in the published paper in chapter 8.

6.5.3 Monitoring

A monitoring plan was developed and agreed with the Trial Management Group (TMG) who met monthly and the Trial Steering Committee who met six-monthly (TSC).
The Trial Management Group (TMG) was made up of individuals responsible for the day-to-day management of the trial and included: the Chief Investigator (CI), statistician, trial manager, data manager, key members of staff from each recruiting site, and sponsor representatives. The role of the TMG was to monitor all aspects of the conduct and progress of the trial. Responsibilities of the TMG included:

- Trial set up and management
- Protocol development (Appendix 6)
- Case report form (CRF) development (Appendix 7)
- Applying for ethical approval
- Obtaining clinical trial authorization and approval from the Medicines and Healthcare products Regulatory Agency (MHRA)
- Monitoring of recruitment and consent processes
- Database development and data collection
- Reporting of serious adverse events

The TSC provided the overall supervision of the trial and was made up of members independent to the investigators, funders and sponsors. The TSC reviewed data on safety,

protocol adherence and recruitment. The CTRU prepared unblinded reports six months into recruitment and at the end of recruitment. It was agreed that a separate Data Monitoring and Ethics Committee was not required.

Chapter 7 –Results 1

7.1 Introduction

This chapter reports the findings for objective 2: 'To explore what outcomes are important to participants in a drug trial for chronic or refractory breathlessness and to what extent these are captured using standard measures.'

7.2 What outcomes are important?

The first part of objective 2 was to explore what outcomes are important to participants in a drug trial for chronic or refractory breathlessness. My systematic review (chapter 3) identified that people living with advanced disease and breathlessness report concerns across six domains: physical, emotional, social, spiritual, control, and context (87). The review synthesised primary qualitative or mixed-method studies from all settings, however, none of the 38 studies included were set within a drug trial. It was therefore important to explore what was important to participants in our trial, and to find out if these concerns were comparable.

Participants described important changes in their experience of breathlessness across multiple domains during the trial. This fits with the model of total breathlessness developed in chapter 2 of this thesis and is illustrated in Table 3.

Table 3: What is important to participants in a drug trial for chronic or refractory breathlessness?

Experience Within Trial	Domain of Total Breathlessness	Participant Quote
The physical impact of breathlessness was important for all participants, and many hoped to see improvements in activity levels from taking the trial medication.	Physical	*It would be nice that I would actually be able to walk down the hill, as well as erm, you know, I, I used to be able to, I had a problem coming up the hill, but erm, now I have a problem walking down the hill as well.* Participant ID 1010
The emotional impact of breathlessness was also common with participants	Emotional	*You can get out of breath and then you can panic, cause you're not getting*

describing a repeated cycle of breathlessness and anxiety. Some participants reflected on whether a medication which enabled them to feel calmer could break this cycle.		*your breath and you're not breathing through your nose and letting it out through your mouth, you're sort of gasping.* Participant ID 1018
The physical and emotional effects caused distress in other aspects of participant's lives, commonly impacting on social and spiritual domains.	Social and Spiritual	*It turns you into a prisoner really, not being able to do anything, without getting shortness of breath.* Participant ID 1013 I've been used to walking up mountains and, in the Lake District and erm, the Dales and I can't do any of that now. And er, it really does get me down that I can't do housework the same, gardening, everything. Participant ID 1015
Control and context were important across all domains. One participant described withdrawing from social activities for fear that an episode of breathlessness might occur. For another, the unpredictability of breathlessness left them feeling unable to make plans.	Context and Control	*Well, you, you're maybe struggling to breathe, and then you're getting yourself all hot and in a bother and then that sort of gets you churning in your stomach and then your chest seems to close up even more, and then you start sweating and all that type of thing, and I think, I was hoping that taking the, the medication would calm me down and it would be like 'right, relax, take a breath, everything's fine', and then I wouldn't be suffering those symptoms.* Participant ID 1021 I can't plan going out, cause, from day-to-day you can think, oh we'll go this tomorrow, then you wake up tomorrow and you just cant do anything. So plans, you just don't plan anything, you go day-to-day and see how you are. Participant ID 1013

7.3 Capture of important outcomes using standard measures

The second part of objective 2 was to explore the extent to which change in experience of breathlessness is captured using standard measures. A convergent mixed methods design was used comprising: 1) semi-structured qualitative interviews (considered to be the gold standard) and 2) outcome measure data collected pre- and post-intervention. Data were integrated, exploring examples where findings agreed and disagreed. The choice of outcome measure was important and needed to be able to capture the outcomes which are important to those participating in a drug trial for breathlessness.

To ensure that the trial was able to detect a change, it was also important to consider the mechanisms of action for the intervention. In chapter 2 I discussed how the mechanism of action of mirtazapine may include suppression of fear circuits, and changes to neural circuits involved in the perception and emotional response to unpleasant stimuli (123, 124). These changes could then impact on the experience of breathlessness and it was therefore important that the chosen outcome measures for the trial included an assessment of emotion.

In addition a consensus statement from 'The National Cancer Research Institute Palliative Care Breathlessness Subgroup' recommends that breathlessness severity should be assessed in research using a single-item measure, but that researchers should also consider including a measure of fatigue, mastery, emotional state, and sleep (72). Based on a combination of: the consensus statement, consideration of the mechanism of action of mirtazapine, and the concerns identified as important in the model of total breathlessness developed in chapter 2 I chose to use 2 single-item measures (The NRS average and worse) and 1 health related quality of life measure (the CRQ). The NRS is the most commonly selected primary outcome measure used in in breathlessness drug trials including oxygen, benzodiazepines, and opioids (54, 55, 125). The CRQ is a broader health-related quality-of-life questionnaire measuring 4 domains dyspnea, fatigue, emotional function, and mastery (77).

The findings are presented in the following paper, published in *The Journal of Pain and Symptom Management*. The study found that the changing experience of breathlessness during the trial was usually captured by the NRS worst, NRS average, and CRQ. A key finding was that the NRS worst appeared to capture changes across multiple domains including physical, emotional, spiritual, social and control suggesting that although it is a single item

measure, it is possible that is measures more than one construct. Future work should aim to determine the construct validity of the NRS worst.

Original Article

To What Extent Do the NRS and CRQ Capture Change in Patients' Experience of Breathlessness in Advanced Disease? Findings From a Mixed-Methods Double-Blind Randomized Feasibility Trial

Natasha Lovell, MBChB, Simon Noah Etkind, MB BChir, Sabrina Bajwah, PhD, Matthew Maddocks, PhD, and Irene Julie Higginson, PhD

Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, London, United Kingdom

Abstract

Context. Chronic or refractory breathlessness is common and distressing. To evaluate new treatments, outcome measures that capture change in patients' experience are needed.

Objectives. To explore the extent to which the numerical rating scale (NRS) worst and average, and the Chronic Respiratory Questionnaire capture change in patients' experience during a trial of mirtazapine for refractory breathlessness.

Methods. Convergent mixed-methods design embedded within a randomized trial comprising 1) semi-structured qualitative interviews (considered to be the gold standard) and 2) outcome measure data collected pre- and post-intervention. Data were integrated, exploring examples where findings agreed and disagreed. Adults with advanced cancer, chronic obstructive pulmonary disease, interstitial lung disease, or chronic heart failure, with a modified Medical Research Council dyspnea scale grade 3 or 4 were recruited from three U.K. sites.

Results. Data were collected for 22 participants. Eleven had a diagnosis of chronic obstructive pulmonary disease, eight interstitial lung disease, two chronic heart failure, and one cancer. Median age was 71 (56–84) years. Sixteen participants were men. Changes in the qualitative data were commonly captured in the NRS (worst and average) and the Chronic Respiratory Questionnaire. The NRS worst captured change most frequently. Improvement in the emotional domain was associated with physical changes, improved confidence, and control.

Conclusion. This study found that the NRS using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" captured change across multiple domains, and therefore may be an appropriate primary outcome measure in trials in this population. Future work should confirm the construct validity of this question. J Pain Symptom Manage 2019;58:369–381.

Key Words

Breathlessness, shortness of breath, advanced disease, outcome measure, randomized controlled trial

Introduction

Breathlessness is common and distressing in advanced disease,[1–3] resulting in anxiety, physical inactivity, and a poorer quality-of-life.[4–6] It is a common reason for emergency hospital admission, and remains a challenge to assess and treat.[7] There are few effective pharmacological treatment options, with some evidence for opioids, but concerns regarding side effects and small effect sizes.[8] New effective treatments are urgently required, and drugs which may modify processing and perception of afferent information in the brain such as antidepressants have been proposed.[9] Breathlessness is a subjective experience, derived

Address correspondence to: Natasha Lovell, MBChB, Cicely Saunders Institute, Bessemer Road, London, SE5 9PJ, United Kingdom. E-mail: Natasha.lovell@kcl.ac.uk

Accepted for publication: June 5, 2019.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2019.06.004

from interactions between multiple physiological, psychological, social, and environmental factors with evolving terminology (Fig. 1).[10] It is what the patient says it is and cannot be measured fully using physiological variables. Although there are a variety of patient-reported outcome measures validated for breathlessness,[11–13] there remains little consensus about which to use and when.[14] The treatment being evaluated can be an important consideration when selecting which outcome measure to use; some treatments may reduce the intensity of breathlessness, others may reduce the associated distress.

The National Cancer Research Institute Palliative Care Breathlessness Subgroup consensus statement (2009) recommended that breathlessness severity should be assessed in research using a single-item measure, but that researchers should also consider including a measure of fatigue, mastery, emotional state, and sleep.[15] However, people living with advanced disease and breathlessness report concerns across the following six domains of "total breathlessness": 1) physical including function, 2) emotional concerns, 3) social impact, 4) spiritual distress, 5) impact of control in relation to an episode of breathlessness and within the wider context, and 6) context (episodic and/or chronic).[6] Therefore, when testing new treatments it is important to capture change across these domains. The primary outcome measure in breathlessness trials of oxygen, benzodiazepines, and opioids is often a single-item measure, most commonly the numerical rating scale (NRS).[8,16,17]

The NRS is a 0–10 scale with a rating statement or question, anchored by a descriptive statement at each end.[18] The NRS was originally validated against another single-item measure (the visual analog dyspnea scale), and validation was based on correlation between the two measures in patients with chronic obstructive pulmonary disease (COPD) at rest and following exercise.[18–20] The NRS was validated with the following statement: "Indicate how much shortness of breath you are having right now."[18] However, the statement or question which accompanies the 0–10 scale has evolved over time, and intervention studies increasingly report an assessment of average (NRS average) and worst (NRS worst) breathlessness over the past 24 hours.[20–31] Even across studies there are subtle differences in the wording of the accompanying statement or question. Despite no validation of these adapted versions they are increasingly adopted as the primary outcome in breathlessness trials. Appendix I demonstrates the variability of rating statement/questions used across a number of studies. A comparison of studies assessing pain intensity has identified similar discrepancies, with unidimensional scales varying in length, period, number of response options, and verbal descriptors.[32] The review highlights the importance of psychometric testing, and suggests that consistency of wording, time frame, and format is important.[32]

Breathlessness: a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity(22)
Refractory breathlessness: breathlessness which persists despite maximal medical and other therapy being given for the underlying condition(23)
Chronic breathlessness: breathlessness which persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient(24)
Episodic breathlessness: episodes of worsening intensity or unpleasantness beyond usual fluctuations in the patient's perception(25)

Fig. 1. Common definitions.[52–55]

In addition, breathlessness trials sometimes include a multidimensional measure as a secondary outcome, one example of this is the Chronic Respiratory Questionnaire (CRQ). The CRQ is a broader health-related quality-of-life questionnaire, which measures the following four domains: dyspnea, fatigue, emotional function, and mastery.[33] The CRQ has been validated in a series of studies spanning item development, reproducibility, responsiveness, and validation against other questionnaires including a patient global rating score.[33]

To ensure better quality trials in the future, it is vital to understand whether frequently used measures capture change in patients' experience of breathlessness. This is particularly important for the NRS (average and worst) where wording has evolved and changed since the original validation. This study therefore aimed to explore whether and to what extent three commonly used measures (NRS worst, NRS average, and CRQ) capture change in patients' experience during a randomized trial of mirtazapine for refractory breathlessness.

Methods

Design

Convergent mixed-methods design embedded within a randomized trial comprising 1) semi-structured qualitative interviews and 2) quantitative outcome measure data collected pre- and post-intervention. Data were collected as part of a double-blind randomized feasibility trial of mirtazapine for refractory breathlessness (Fig. 2). Participants were randomized to receive 28 days of trial treatment, either oral mirtazapine or placebo. Ethical approval was received from the U.K. Health Research Authority (16/LO/0091). The trial was prospectively registered on ISRCTN 32236160 and the European Clinical Trials Database (EudraCT no: 2015-004064-11), where

main results are available. Recruitment to the trial occurred between August 2016 and December 2017. The qualitative and quantitative data were collected separately, then integrated and compared in an interpretation phase. The main researcher (NL) remained blinded during data collection and analysis. Examples were explored where the findings from both data sets agreed and where they disagreed.

Setting

Participants were recruited from three U.K. centers, in South London, Nottingham, and Hull. Potential participants were identified through inpatient clinical teams, multidisciplinary team meetings, hospital clinic lists, and hospital databases.

Study Participants and Sampling

Those eligible for the feasibility trial were adults with cancer, COPD, interstitial lung disease (ILD), or chronic heart failure, with a modified Medical Research Council grade 3 ("I stop for breath after walking about 100 yards or after a few minutes on the level") or 4 ("I am too breathless to leave the house" or "I am breathless when dressing"), with no current diagnosis of severe depression, and not currently prescribed an antidepressant medication. For full eligibility criteria see Appendix II.

All participants were informed of the possibility of a qualitative interview when they provided written informed consent for the trial. Purposive sampling was used to achieve maximum variation based on primary diagnosis, trial completion/non-completion, and age (<65 years or >65 years). The sample included participants from both arms of the trial. Participants were approached by telephone or in-person. All participants provided written informed consent before interview.

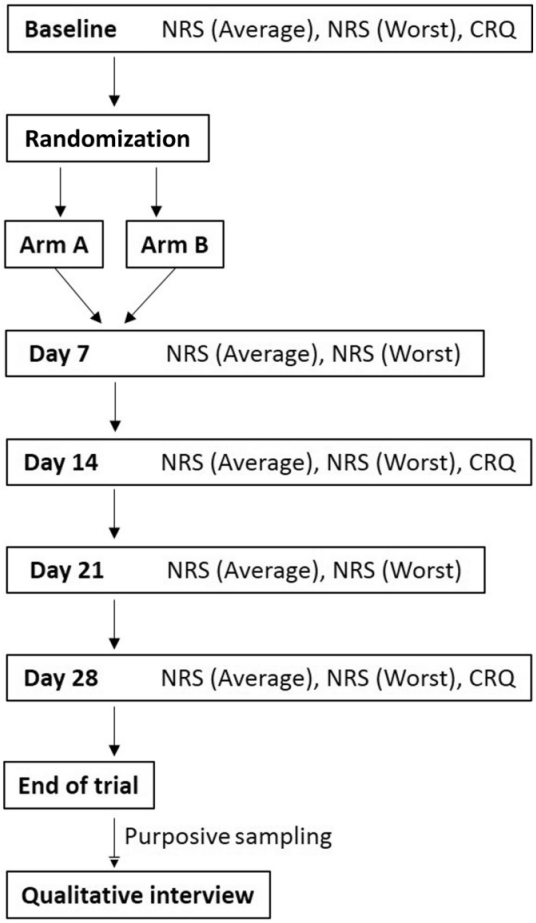


Fig. 2. Trial flow chart. NRS = numerical rating scale; CRQ = Chronic Respiratory Questionnaire.

Data Collection

Quantitative Outcome Measures. The NRS (average and worst) and CRQ were collected as part of the feasibility trial that took place over 35 days, with patient visit contacts at baseline, days 14 and 28, and phone contacts on days 7, 21, and 35 (Fig. 2). In the trial, participants were randomized to receive either mirtazapine or placebo for 28 days, with a final assessment on Day 35.

The NRS was completed at baseline, days 7, 14, 21, and 28. Two NRS rating questions were asked "How has your breathlessness been over the last 24 hours on average?" (NRS average) and "What is the worst your breathlessness has been over the last 24 hours?" (NRS worst). The question was anchored with the statement "not breathless at all" positioned next to number 0, and "the worst possible breathlessness" next to number 10.

The CRQ was completed at baseline, days 14 and 28. The CRQ is a 20-item questionnaire, asking about the last two weeks, with the following four domains: dyspnea (their five most important activities and how short of breath each activity made them feel), fatigue (four questions), emotional function (seven questions), and mastery (four questions). Each question is scored on a 7-point Likert scale, higher scores indicated less breathlessness or better quality of life. Mean scores for each domain enable comparisons between domains.[34]

Qualitative Interviews. Qualitative interviews were conducted at the end of the trial. Interviews were conducted in a place of the participants choosing, usually their own home, but some were conducted in hospital. A topic guide was developed based on the literature and refined after feedback from patient representatives and the Trial Management Group (Appendix III). The interview schedule included questions about whether participants had perceived a change during the trial period, and if so, what had changed. Open questions were used to ensure that participants were not restricted in their answers. Interviews were digitally audio recorded and transcribed verbatim. A distress protocol was developed to minimize the risk of potential harm. All interviews were conducted by one researcher (NL) who has a medical background and had completed training in in-depth interviewing. Interviews took place in 2017.

Analysis

The quantitative and qualitative data were collected and analyzed separately, then integrated and compared in an interpretation phase.

Quantitative Outcome Measures. Measures were compared to derive a change score from baseline to Day 28, a period comparable to that asked about in the qualitative interviews. Change was assessed according to the minimal clinically important difference guidance for each questionnaire.[35,36] The NRS was considered to have changed if there was a >1-point change,[35] and the CRQ threshold was >0.5 unit change for each domain.[36]

Qualitative Interviews. The qualitative interviews were analyzed through thematic analysis[37] using NVIVO, version 10 (QSR International (UK) Ltd., Warrington). The main researcher (NL) remained blinded during analysis to reduce the risk of interpretation bias, and improve confidence in the findings.[38,39] Transcripts were read and re-read, and coded inductively for themes relating to change in experience of breathlessness during the trial. Themes were considered within the domains of "total breathlessness" (Fig. 3).[6] Perceived changes were categorized in terms of the extent of the change. This was based on the language used by participants to describe any change they had perceived, for example, "I didn't really feel any different" was coded as no change, "the benefit that I thought I felt was quite small" was coded as small change, and "it has made a big difference" was coded as large change. To improve trustworthiness, the main researcher (NL) remained blinded during data collection and analysis. Three transcripts were double-coded by another researcher (SE) who produced their own coding frame. Areas of agreement and disagreement in particular relating to the degree of change were discussed until consensus was achieved. A reflexive diary was also used.

Integration. Changes in patients' experience of breathlessness were compared at an individual level; that is, where change was seen in the qualitative data, we looked for evidence of change in the quantitative data and vice versa. As patient report is considered the gold standard for assessing breathlessness, we considered the qualitative interview as gold standard in this study.[40] To understand whether and to what extent quantitative measures captured change in patients' experience of breathlessness, we explored examples where findings agreed and disagreed. If both data sets identified change or neither identified change, this was classified as agreement. If one data set identified change but the other did not, this was classified as disagreement. We also considered how change was captured across the domains of "total breathlessness," and whether there were patterns of change across domains.

Results

Qualitative and quantitative outcome measure data were collected for 22 participants (Appendix IV). Eleven had a diagnosis of COPD, eight ILD, two

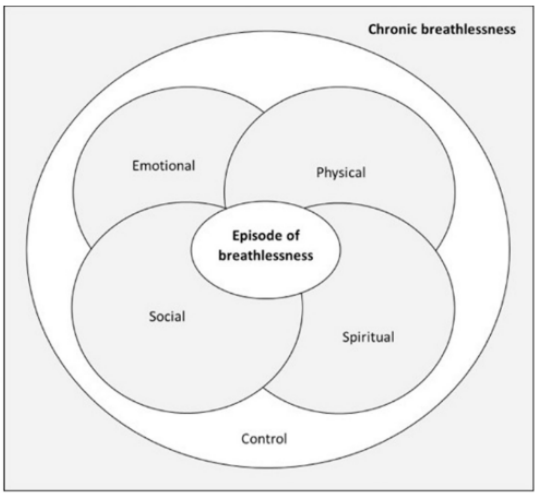


Fig. 3. Model of total breathlessness.[6]

chronic heart failure, and one lung cancer. Median age was 71 years (range 56–84 years). Sixteen were male. Twenty had completed the trial, whereas two withdrew because of reported adverse effects of the trial medication. The mean interview duration was 33 minutes (range 15–104 minutes). Eight of 264 items were missing in the quantitative data. A change score was calculated in the NRS average and worst for 21 of 22 participants and in the CRQ for 19 of 22 participants. The characteristics of participants based on the pre-determined sampling frame are shown in Table 1. The coding frame for the qualitative data is presented in Appendix V.

Patterns of Overall Agreement Between Qualitative and Quantitative Data

Changes in experience of breathlessness for each participant are shown in Table 2. Changes in the qualitative data are categorized in terms of the extent of the change (no change, small change, and large change). Change in the quantitative data is presented as a change score. An assessment of whether the change score is clinically important was calculated using guidance for each individual questionnaire, and also presented. In the qualitative data, 12 participants described changes in their experience of breathlessness during the trial. For the NRS worst and NRS average, there was a clinically important change in 13 and nine cases, respectively. For the CRQ, there was a clinically important change in 16 cases. There was agreement between the qualitative data and the NRS worst in 18 of 21 cases, the NRS average in 16 of 21 cases, and the CRQ in 15 of 21 cases. There was agreement for change or no change in the experience of breathlessness across all measures in 12 cases.

Agreement Between Patients' Experience and Outcome Measures

Participants described change in experience across all domains of "total breathlessness" during the trial (Appendix VI). For some participants, changes were wide-ranging and impacted across several domains. One male participant with COPD described physical changes including better breathing and sleeping, fewer emotional concerns, improved sense of well-being, and greater sense of control. His outcome measure data showed clinically important change in NRS worst, and emotion, mastery, and fatigue domains of the CRQ.

> *Everything was so much better. I would sleep better, so if I sleep better that means by breathing is better when I wake up in the morning, which it never was before. I used to struggle to get up with the breathing … they definitely really helped. Even, even all my friends and neighbours have said how different I am.*
>
> Participant ID 1003

Another participant reported that his breathing was eased by changes across emotional and spiritual domains. His outcome measure data showed a clinically important change in the CRQ emotion, and NRS worst and average.

> *What's the way to describe it, a wave of, wellbeing. Erm. Comfort, happy with my role, erm. It's almost like id got an extra security blanket for, for the period, you know, that's how it felt to me, it was one more thing protecting me. Easing my breathing. That's how it felt to me. It could be wrong, but that's how it felt, I felt it all the way through.*
>
> Participant ID 1009

For others, the change in experience of breathlessness was specific to one domain. It was common for participants to describe improvements within the emotional domain. One male participant with COPD

Table 1
Characteristics of Participants Based on Sampling Frame

	Male	Female
ILD		
<65 yrs old	1	
>65 yrs old	5	3 (1 did not complete trial)
COPD		
<65 yrs old	2	1
>65 yrs old	5	1
CHF		
<65 yrs old		
>65 yrs old	2 (1 did not complete trial)	
Cancer		
<65 yrs old		
>65 yrs old	1	1

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; CHF = chronic heart failure.

Table 2

Change in Qualitative and Quantitative Measures Over Trial Period

ID	Qualitative (Important Domains)	Qualitative (Perceived Change)[a]	Qualitative Direction of Change	NRS (Worst), Range 0–10				NRS (Average), Range 0–10				CRQ (Domains), Range 1–7			
				BL	D28	Change Score	Clinically Important[b]	BL	D28	Change Score	Clinically important[c]	BL	D28	Change Score	Clinically Important[d]
1001	Physical	No change	N/A	7	7	0	No	5	5	0	No	Emotion: 5.4 Mastery: 5.5 Fatigue: 5.0 Dyspnea: 2.4	Emotion: 4.7 Mastery: 3.5 Fatigue: 4.0 Dyspnea: 3.0	−0.7 −2.0 −1.0 +0.6	No No No Yes
1002	Physical Emotional Control	Small change	Easier breathing → increased confidence → increased activity	5	4	−1	Yes	5	4	−1	Yes	Emotion: 4.9 Mastery: 5.5 Fatigue: 4.3 Dyspnea: 3.0	Emotion: 4.1 Mastery: 5.5 Fatigue: 4.5 Dyspnea: 3.4	−0.8 0 +0.2 +0.4	No No No No
1003	Physical Emotional Social Control	Large change	Sleep better → breathing better → less frightened → can do more	8	5	−3	Yes	7	8	+1	No	Emotion: 2.3 Mastery: 2.5 Fatigue: 1.5 Dyspnea: 1.8	Emotion: 4.4 Mastery: 4.3 Fatigue: 4.0 Dyspnea: 2.2	+2.1 +1.8 +2.5 +0.4	Yes Yes Yes No
1004	Physical	Small change	Feeling a little less breathless during daily walk	4	3	−1	Yes	4	2	−2	Yes	Emotion: 5.9 Mastery: 6.0 Fatigue: 4.5 Dyspnea: 3.0	Emotion: 6.7 Mastery: 6.5 Fatigue: 5.8 Dyspnea: 3.2	+0.8 +0.5 +1.3 +0.2	Yes Yes Yes No
1005	Physical	No change	N/A	8	5	−3	Yes	4	3	−1	Yes	Emotion: 5.9 Mastery: 5.5 Fatigue: 2.8 Dyspnea: 4.2	Emotion: 5.3 Mastery: 5.5 Fatigue: 3.3 Dyspnea: 5.6	−0.6 0 +0.5 +1.4	No No Yes Yes
1006	Physical	Large change	Feeling less breathless →not using oxygen → able to walk further	10	7	−3	Yes	9	6	−3	Yes	Emotion: 3.9 Mastery: 3.5 Fatigue: 3.3 Dyspnea: 3.6	Emotion: 4.6 Mastery: 3.5 Fatigue: 3.3 Dyspnea: 2.4	+0.7 0 0 −1.2	Yes No No No
1007	Physical Emotional Social Spiritual	No change	N/A	8	9	+1	No	6	6	0	No	Emotion: 6.4 Mastery: 7.0 Fatigue: 4.0 Dyspnea: 2.2	Emotion: 5.1 Mastery: 6.0 Fatigue: 3.3 Dyspnea: 1.8	−1.3 −1.0 −0.7 −0.4	No No No No
1008	Physical Emotional Social Spiritual	No change	N/A	8	7	−1	Yes	5	6	+1	No	Emotion: 3.4 Mastery: 3.0 Fatigue: 2.8 Dyspnea: 1.4	Emotion: 3.3 Mastery: 2.8 Fatigue: 2.0 Dyspnea: 1.8	−0.1 −0.2 −0.8 +0.4	No No No No
1009	Physical Emotional Spiritual	Small change	Easier breathing → Sense of wellbeing → Can do more	8	5	−3	Yes	6	3	−3	Yes	Emotion: 5.4 Mastery: 5.3 Fatigue: 3.5 Dyspnea: 2.2	Emotion: 6.1 Mastery: 6.5 Fatigue: 5.3 Dyspnea: 4.0	+0.7 +1.2 +1.8 +1.8	Yes Yes Yes Yes
1010	Physical Control	Small change	Less breathless → able to forget breathlessness → feeling of wellbeing	4	2	−2	Yes	2	2	0	No	Emotion: 6.7 Mastery: 5.3 Fatigue: 5.8 Dyspnea: 4.4	Emotion: 6.3 Mastery: 6.0 Fatigue: 5.0 Dyspnea: [e]	−0.4 +0.7 −0.8 [e]	No Yes No [e]

1011	Physical Emotional	No change	N/A	8	8	0	No	4	4	0	No	Emotion: 5.1 Mastery: 3.3 Fatigue: 4.5 Dyspnea: 2.2	Emotion: 6.3 Mastery: 5.3 Fatigue: 5.3 Dyspnea: 4.0	+1.2 +2.0 +0.8 +1.8	Yes Yes Yes Yes
1012	Physical Emotional Control	Small change	Felt calmer/ more relaxed → increased confidence and control → increased activity	6	5	−1	Yes	3	3	0	No	Emotion: 5.0 Mastery: 5.3 Fatigue: 4.3 Dyspnea: 3.0	Emotion: 6.6 Mastery: 6.8 Fatigue: 5.8 Dyspnea: 5.0	+1.6 +1.5 +1.5 +2.0	Yes Yes Yes Yes
1013	Physical Emotional	No change	N/A	7	8	+1	No	4	5	+1	No	Emotion: 5.7 Mastery: 5.5 Fatigue: 5.3 Dyspnea: 2.4	Emotion: 5.7 Mastery: 5.3 Fatigue: 6.3 Dyspnea: 2.8	0 −0.2 +1.0 +0.4	No No Yes No
1014	Physical Emotional Social Control	Large change	Able to calm down quicker → breathe more easily → not panic → can do more	8	6	−2	Yes	6	4	−2	Yes	Emotion: 5.9 Mastery: 6.8 Fatigue: 5.3 Dyspnea: 1.6	Emotion: 6.6 Mastery: 6.5 Fatigue: 6.3 Dyspnea: 2.0	+0.7 −0.3 +1.0 +0.4	Yes No Yes No
1015	Physical Emotional Social Control	Large change	Felt calmer → breathing was easier → felt confident/ able to cope → physically do more	7	6	−1	Yes	4	4	0	No	Emotion: 3.7 Mastery: 4.3 Fatigue: 2.8 Dyspnea: 1.8	Emotion: 5.1 Mastery: 5.8 Fatigue: 3.8 Dyspnea: 2.4	+1.4 +1.5 +1.0 +0.6	Yes Yes Yes Yes
1016	Physical	No change	N/A	7	7	0	No	5	5	0	No	Emotion: 5.0 Mastery: 5.8 Fatigue: 3.3 Dyspnea: 3.6	Emotion: 4.6 Mastery: 4.8 Fatigue: 3.0 Dyspnea: [e]	−0.4 −1.0 −0.3 [e]	No No No [e]
1017	Physical Emotional Control	Small change	Breathing improved → felt more in control → able to do more	8	8	0	No	5	3	−2	Yes	Emotion: 5.3 Mastery: 5.0 Fatigue: 3.5 Dyspnea: 2.0	Emotion: 5.4 Mastery: 5.8 Fatigue: 3.3 Dyspnea: 2.6	+0.1 +0.8 −0.2 +0.6	No Yes No Yes
1018	Physical Emotional Social	No change	N/A	8	8	0	No	5	7	+2	No	Emotion: 4.3 Mastery: 3.8 Fatigue: 2.8 Dyspnea: 2.2	Emotion: 3.4 Mastery: 3.5 Fatigue: 2.5 Dyspnea: 2.4	−0.9 −0.3 −0.3 +0.2	No No No No
1019	Physical	No change	N/A	8	[e]	[e]	[e]	6	[e]	[e]	[e]	Emotion: 3.3 Mastery: 4.8 Fatigue: 2.5 Dyspnea: 1.2	Emotion: [e] Mastery: [e] Fatigue: [e] Dyspnea: [e]	[e] [e] [e] [e]	[e] [e] [e] [e]
1020	Physical Social Spiritual	No change	N/A	9	9	0	No	5	7	+2	No	Emotion: 5.4 Mastery: 5.5 Fatigue: 4.3 Dyspnea: 2.6	Emotion: 5.3 Mastery: 6.0 Fatigue: 4.0 Dyspnea: 2.6	−0.1 +0.5 −0.3 0	No Yes No No
1021	Physical Emotional Control	Small change	When breathing bad feeling less panicky	7	5	−2	Yes	4	3	−1	Yes	Emotion: 3.7 Mastery: 3.3 Fatigue: 4.3	Emotion: 4.6 Mastery: 5.5 Fatigue: 4.3	+0.9 +2.2 0	Yes Yes No

(*Continued*)

Table 2
Continued

ID	Qualitative (Important Domains)	Qualitative (Perceived Change)[a]	Qualitative Direction of Change	NRS (Worst), Range 0–10				NRS (Average), Range 0–10				CRQ (Domains), Range 1–7			
				BL	D28	Change Score	Clinically Important[b]	BL	D28	Change Score	Clinically important[c]	BL	D28	Change Score	Clinically Important[d]
			→ more in control → less anxious									Dyspnea: 2.2	Dyspnea: 3.0	+0.8	Yes
1022	Physical Emotional Control	Small change	Breathing better → feeling calmer → did not panic as much → more in control	10	7	−3	Yes	8	6	−2	Yes	Emotion: 2.9 Mastery: 2.8 Fatigue: 3.8 Dyspnea: 1.2	Emotion: 4.1 Mastery: 4.3 Fatigue: 4.0 Dyspnea: 2.2	+1.2 +1.5 +0.2 +1.0	Yes Yes No Yes

NRS = numerical rating scale; CRQ = Chronic Respiratory Questionnaire; BL = baseline; D28 = Day 28.
[a]Qualitative (perceived change) is the perceived change reported by participants during a qualitative interview.
[b]Clinically important improvement based on the minimal clinically important difference for the NRS (worst).
[c]Clinically important improvement based on the minimal clinically important difference for the NRS (average).
[d]Clinically important improvement based on the minimal clinically important difference for the CRQ.
[e]Missing data.

described how feeling calm resulted in easier breathing, and his outcome measure data showed a clinically important change in the CRQ emotion, and NRS worst and average.

> *It did something and it just helped me calm down a lot quicker than I normally would. I can calm down a lot quicker, so I can, I can breathe a lot easier. It helped me- something to me it just helped me relax so much and now I don- I don't panic anymore, you know.*
>
> Participant ID 1014

A female participant with clinically important changes in the NRS worst, CRQ emotion, and mastery domains described fewer episodes of panic and being able to cope better.

> *I seem as though I can cope better with it now as I say, you know, the panic, erm.*
>
> Participant ID 1015

Some participants described no change in their experience of breathlessness. This was also commonly captured in the quantitative outcome measures, and can be seen in the following examples. Both of these participants had no clinically important change in CRQ domains, or in NRS worst and average.

> *Perhaps find it that little bit easier to breathe. But unfortunately, it didn't happen for me.*
>
> Participant ID 1007

> *I just really didn't feel as though it made any difference*
>
> Participant ID 1020

Patterns of Change Across Domains

Where changes in experience were described, participants sometimes proposed a pattern of change, where a change in one domain was associated with a change in another. For some, improvements within the emotional domain were associated with improvements physically. The following two participants described feeling calmer and less frightened, and therefore being able to do more physically. Their outcome measure data showed clinically important changes in NRS worst, CRQ emotion, mastery, and fatigue.

> *Erm, I felt calmer. I felt as though I could do more, erm, er, I cou- yeah I could do more, because me breathing, obviously I'd settled that bit, yeah.*
>
> Participant ID 1015

> *It used to frighten me to get up because I thought, I'm not going to make it to the kitchen with the breathing, before I get (11.48), but now I can get up, go ahead and put the kettle on, make myself a cup of tea and I'm okay. Yeah, it's so, I-I-I am really glad that that I've done it.*
>
> Participant ID 1003

For some, a change in breathing led to improved confidence and a sense of feeling more in control. This increased confidence enabled participants to try to do more, a situation they might not have attempted in the past. This male participant with ILD described feeling more in control and therefore being able to do more. His outcome measure data showed a clinically important change in his CRQ mastery.

> *It didn't change my feelings, but, my breathing improved. Erm, stamina-wise and control-wise. And kind of, control-wise was that I, I didn't get out of breath as easy, I could do a bit more- not vast amounts, erm, but the breathing certainly was more comfortable.*
>
> Participant ID 1017

Another female participant with COPD described attempting to do things which she had previously avoided because she now felt she could do it, and was prepared to do it. Her outcome measure data showed a clinically important change in CRQ emotion and mastery, as well as in the NRS worst.

> *Well, I could do it, I could do it, and I was prepared to do it, but normally I just wouldn't dare to attempt doing it, cause I know how it would end up, yeah.*
>
> Participant ID 1015

Disagreement Between Patients' Experience and Outcome Measures

Sometimes, a perceived change in patients' experience of breathlessness was not captured by the quantitative outcome measures. One male participant with ILD described a slow gradual change in his breathing which he did not notice until finishing the trial and stopping the trial medication. Although there was no change in NRS worst scores, a clinically important change was captured in the NRS average and CRQ mastery or dyspnea.

> *Well I didn't recognise it at the time, but it did actually erm, improve my breathing. But, it was a noticeable improvement. When I came off the drug.*
>
> Participant ID 1017

Another participant perceived no change during the trial period, but his quantitative data suggested a clinically important change in NRS worst and CRQ. This participant described some difficulties completing scale-based outcome measures.

> *It was difficult to number, and whether, if I was getting any better or worse, it was difficult then to compare the last reading to this reading.*
>
> Participant ID 1005

Discussion

This study found that three commonly used measures (NRS average, NRS worst, and CRQ) captured the changes that participants reported in their qualitative experience. Agreement was highest with the NRS worst, which appeared to capture changes across multiple domains using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" We know that patients' describe concerns relating to breathlessness across multiple domains,[6] and therefore when testing new treatments, it is important to capture change across these domains.

In this mixed-methods study, the NRS average (using the question "How bad has your breathlessness felt on average over the past 24 hours?") appeared to capture physical changes consistently, and participants with a clinically important change commonly described easier breathing and improved physical activity. In comparison, the NRS worst (using the question "How bad has your breathlessness felt at its worst over the past 24 hours?") appeared to capture changes more extensively across multiple domains including physical, emotional, spiritual, social, and control. It is therefore possible that the NRS worst is measuring more than one construct.

These findings suggest that it is important to consider how the statement/question used to accompany the NRS impacts on what is being measured. The NRS was originally validated with the statement "Indicate how much shortness of breath you are having right now."[18] The accompanying statement/question has evolved over time with studies increasingly reporting an assessment of average (NRS average) and worst (NRS worst) breathlessness over the past 24 hours (Appendix I).[20–31,41,42] Even the wording used to describe "worst breathlessness" varies, with one study asking participants "What is the worst your breathlessness has been over the last 24 hours?" and another using the statement "Indicate how much shortness of breath you are having at worst at rest over the last 24 hours."[20,23] Appendix I demonstrates the variability in breathlessness studies of accompanying rating statement/question, none of which to our knowledge have been formally validated. This is an important area for future research, as the accompanying statement/question potentially changes what is being measured.

It is interesting that there is an example in our data where a participant has reported a higher score for the NRS average than the NRS worst (Participant ID 1003, Day 28). This is in keeping with the peak-end rule where evaluation of an episode is determined by the most distressing and final moments of the experience.[43] The peak-end rule has previously been demonstrated in induced breathlessness, with recalled

breathlessness higher relative to concurrent breathlessness.[44] More recently, a study investigated the relevance of the peak-end rule when assessing breathlessness using "NRS now," "NRS average," and "NRS worst." The study demonstrated fallibility of the "NRS average," which was affected by current breathlessness.[21] This strengthens the argument that the "NRS worst" may be more appropriate than the "NRS average" as an outcome measure in breathlessness trials.

In this mixed-methods study, change in patients' experience in the qualitative data was captured in at least one domain of the CRQ for 15 participants. When a change was perceived in the qualitative data, a clinically important change score was most commonly seen in the emotion or mastery domain suggesting that these domains may be particularly important as part of the experience of breathlessness. In comparison, change in patients' experience was less commonly captured in the dyspnea domain. This study recruited people with a modified Medical Research Council dyspnea scale grade 3 or 4, therefore those most severely affected by breathlessness. The dyspnea domain of the CRQ asks participants to identify important activities, and score how short of breath the activity has made them. It is possible that for this group of participants, despite an improvement in their overall experience of breathlessness, the activities identified in the dyspnea domain continue to result in severe shortness of breath, and therefore the scores do not reflect a clinically important change.

The qualitative data in this mixed-methods study also offer insights into how the domains of total breathlessness may be linked. Participants described how improvements within the emotional domain were associated with changes physically, and they were able to do more. A similar concept of "total pain" was described by Cicely Saunders in 1964 when a patient reported "the pain began in my back, but now it seems that all of me is wrong".[45] The model shows that pain is the sum of all domains. In our study, one participant described how a change in one domain was associated with changes in other domains. In his qualitative interview, he said "Everything was so much better" (Participant ID 1003).

Mirtazapine is licensed for the treatment of depression with potential additional beneficial effects on anxiety, both of which are common in those experiencing chronic breathlessness.[46,47] In this study, it is possible that by treating an underlying anxiety or depressive disorder, mirtazapine had a beneficial effect on the emotional response to breathlessness. However, although not powered to detect an effect, results from this feasibility trial did not find a difference when controlling for anxiety and depression using the hospital anxiety and depression scale (personal communication Higginson et al. 2019); however, this will be formally investigated in a full-scale trial.

Although the NRS (average and worst) and CRQ appeared to capture change in experience of breathlessness in this trial, it is important to consider whether a similar effect would be seen when evaluating a treatment which is not expected to impact on anxiety. The breathing, thinking, and functioning model described by Spathis et al. demonstrates how inefficient breathing, feelings of anxiety, and muscle deconditioning are all interlinked and can perpetuate the experience of breathlessness.[48] By using this model, you can see how an improvement in someone's functional ability (function) may lead to improved confidence and less anxiety (thinking), and so a treatment which does not target anxiety may have a beneficial effect on it. We therefore consider that the NRS (average and worst) and CRQ are valid measures to use in other treatment studies which do not specifically target anxiety.

Strengths and Weaknesses

This mixed-methods study uniquely combines qualitative with quantitative data collected within a blinded randomized feasibility trial. The main researcher (NL) remained blinded during data collection and analysis, which is unusual and strengthens confidence in the findings by reducing the risk of bias.[38,39] However, although the qualitative data were in-depth, a single interview may not have been sufficient to fully capture perceived change during and after the trial.

The NRS (24 hours) and CRQ (two weeks) assess different periods. Although patient recall is considered the gold standard for assessing breathlessness,[40] research suggests that patients have difficulty remembering symptom levels beyond several days,[49] and therefore a longer recall period can result in reduced accuracy.[50] In addition, even mild cognitive impairment has been shown to influence patient recall of symptom intensity.[51] Participants in this study were assessed for cognitive impairment during screening, but no formal evaluation of cognitive function was performed and therefore mild cognitive impairment may have been present. The period between the trial ending and a qualitative interview being conducted also varied, and this may have increased the risk of recall bias in the qualitative interviews.

A single researcher undertook all interviews increasing the risk of interpretation bias, and some participants had met the researcher during the trial

period. Risks of bias were minimized by double coding a random subset of transcripts, discussion of findings within the research team, and use of a reflexive diary. The quantitative data were collected by designated researchers and research nurses at each site, and there may have been variability in how outcome measures were administered between sites and individuals, although this was minimized by training, and use of a data collection manual.

What This Study Adds

This study provides new evidence to support choice of primary outcome measure in clinical trials of interventions for chronic or refractory breathlessness. Choice of measure is key, but for some measures such as the NRS, the accompanying statement/question is perhaps the most important consideration. Although multiple domain measures are often considered most appropriate to measure complex symptoms like breathlessness, lengthy questionnaires can cause an increased burden for participants and can lead to missing data in clinical trials and research. In comparison, the NRS is short, self-administered, and simple to complete.

The results of this study suggest that the NRS worst using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" is able to capture change in patients' experience of breathlessness across domains known to be important to patients.[6] It may therefore be an appropriate primary outcome measure in future breathlessness trials. However, it is important to acknowledge that validation work is first required to understand what constructs this question is measuring, and even whether individual constructs can be unpicked. These results also provide options to support the assessment and management of chronic or refractory breathlessness in clinical practice. For clinicians, where time constraints and wanting to minimize the burden to patients are key challenges, the NRS is an easily accessible outcome measure which could be integrated into routine clinical care. However, there may also be situations when a more detailed assessment is required to understand which particular domains of breathlessness are changing, and a multiple domain measure be most appropriate.

Conclusions

The changing experience of breathlessness during this trial was usually captured by the NRS worst, NRS average, and CRQ. Agreement was highest with the NRS worst, using the question "How bad has your breathlessness felt at its worst over the past 24 hours?" This study suggests that the NRS worst can capture important patient-reported changes in breathlessness, and therefore may be an appropriate measure in breathlessness trials. Future work should confirm the construct validity of the NRS worst using the rating question "How bad has your breathlessness felt at its worst over the past 24 hours?"

Disclosures and Acknowledgments

This work is independent research funded by Marie Curie, Cicely Saunders International, The Atlantic Philanthropies in the Cicely Saunders Institute Fellowship Programme, and Yorkshire Cancer Research. NL is completing a training fellowship funded by Cicely Saunders International and Marie Curie (Grant Number A18859). MM is supported by an NIHR Career Development Fellowship (CDF-2017-10-009) and NIHR CLARHC South London. IJH is an NIHR Emeritus Senior Investigator and is supported by NIHR CLARHC South London. This research was supported by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, which is part of the National Institute for Health Research (NIHR), and is a partnership between King's Health Partners; St. George's, University of London; and St. George's Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

The authors declare that they have no conflict of interest.

Ethical approval was received from the U.K. Health Research Authority (16/LO/0091). All participants provided written informed consent.

References

1. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage 2006;31:58–69.

2. Moens K, Higginson IJ, Harding R. Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. J Pain Symptom Manage 2014;48:660–677.

3. Bajwah S, Higginson IJ, Ross JR, et al. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung 2012;190:215–220.

4. Gysels M, Bausewein C, Higginson IJ. Experiences of breathlessness: a systematic review of the qualitative literature. Palliat Support Care 2007;5:281–302.

5. Malik FA, Gysels M, Higginson IJ. Living with breathlessness: a survey of caregivers of breathless patients with lung cancer or heart failure. Palliat Med 2013;27:647–656.

6. Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. Control and context are central for people with advanced illness experiencing breathlessness: a systematic review and thematic synthesis. J Pain Symptom Manage 2019;57:140–155.e2.

7. Hutchinson A, Pickering A, Williams P, Bland JM, Johnson MJ. Breathlessness and presentation to the emergency department: a survey and clinical record review. BMC Pulm Med 2017;17:53.

8. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev 2016;3:Cd011008.

9. Lovell N, Wilcock A, Bajwah S, et al. Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. Expert Rev Respir Med 2019;13:173–180.

10. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1999;159:321–340.

11. Bausewein C, Farquhar M, Booth S, Gysels M, Higginson IJ. Measurement of breathlessness in advanced disease: a systematic review. Respir Med 2007;101:399–410.

12. Mularski RA, Campbell ML, Asch SM, et al. A review of quality of care evaluation for the palliation of dyspnea. Am J Respir Crit Care Med 2010;181:534–538.

13. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. Palliat Med 2007;21:177–191.

14. Johnson MJ, Oxberry SG, Cleland JG, Clark AL. Measurement of breathlessness in clinical trials in patients with chronic heart failure: the need for a standardized approach: a systematic review. Eur J Heart Fail 2010;12:137–147.

15. Dorman S, Jolley C, Abernethy A, et al. Researching breathlessness in palliative care: consensus statement of the National cancer research Institute palliative care breathlessness Subgroup. Palliat Med 2009;23:213–227.

16. Ekstrom M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. Cochrane Database Syst Rev 2016;11:Cd006429.

17. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane database Syst Rev 2016;10:Cd007354.

18. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care 1998;7:200–204.

19. Placido R, Gigaud C, Gayat E, et al. Assessment of dyspnoea in the emergency department by numeric and visual scales: a pilot study. Anaesth Crit Care Pain Med 2015;34:95–99.

20. Wysham NG, Miriovsky BJ, Currow DC, et al. Practical dyspnea assessment: relationship between the 0-10 numerical rating scale and the four-level categorical verbal descriptor scale of dyspnea intensity. J Pain Symptom Manage 2015;50:480–487.

21. Wade J, Mendonca S, Booth S, Ewing G, Gardener AC, Farquhar M. Are within-person Numerical Rating Scale (NRS) ratings of breathlessness 'on average' valid in advanced disease for patients and for patients' informal carers? BMJ Open Respir Res 2017;4:e000235.

22. Tan JY, Yorke J, Harle A, et al. Assessment of breathlessness in lung cancer: psychometric properties of the dyspnea-12 questionnaire. J Pain Symptom Manage 2017;53:208–215.

23. 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;2:979–987.

24. Johnson MJ, Kanaan M, Richardson G, et al. A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease. BMC Med 2015;13:213.

25. Yorke J, Lloyd-Williams M, Smith J, et al. Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial. Support Care Cancer 2015;23:3373–3384.

26. Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough. J Palliat Med 2013;16:250–255.

27. Barton R, English A, Nabb S, Rigby AS, Johnson MJ. A randomised trial of high vs low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study. Lung Cancer 2010;70:313–319.

28. Molassiotis A, Charalambous A, Taylor P, Stamataki Z, Summers Y. The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial. Support Care Cancer 2015;23:1637–1645.

29. Oxberry SG, Bland JM, Clark AL, Cleland JG, Johnson MJ. Minimally clinically important difference in chronic breathlessness: every little helps. Am Heart J 2012;164:229–235.

30. Oxberry SG, Torgerson DJ, Bland JM, Clark AL, Cleland JG, Johnson MJ. Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. Eur J Heart Fail 2011;13:1006–1012.

31. 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;376:784–793.

32. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073–1093.

33. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987;42:773–778.

34. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). Thorax 2001;56:954–959.

35. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. J Pain Symptom Manage 2013;46:957–963.

36. Schunemann HJ, Puhan M, Goldstein R, Jaeschke R, Guyatt GH. Measurement properties and interpretability of the chronic respiratory disease questionnaire (CRQ). COPD 2005;2:81–89.

37. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77–101.

38. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? Can J Surg 2010;53:345–348.

39. Cooper C, O'Cathain A, Hind D, Adamson J, Lawton J, Baird W. Conducting qualitative research within Clinical Trials Units: avoiding potential pitfalls. Contemp Clin Trials 2014;38:338–343.

40. Ekstrom M, Currow DC, Johnson MJ. Outcome measurement of refractory breathlessness: endpoints and important differences. Curr Opin Support Palliat Care 2015;9: 238–243.

41. Sandberg J, Johnson MJ, Currow DC, Ekstrom M. Validation of the dyspnea exertion scale of breathlessness in people with life-limiting illness. J Pain Symptom Manage 2018; 56:430–435.e2.

42. Morris NR, Sabapathy S, Adams L, Kingsley RA, Schneider DA, Stulbarg MS. Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects. Respir Physiol Neurobiol 2007;157:360–365.

43. Fredrickson BL. Extracting meaning from past affective experiences: the importance of peaks, ends, and specific emotions. Cogn Emot 2000;14:577–606.

44. Walentynowicz M, Bogaerts K, Van Diest I, Raes F, Van den Bergh O. Was it so bad? The role of retrospective memory in symptom reporting. Health Psychol 2015;34: 1166–1174.

45. Saunders C. Care of patients suffering from terminal illness at St. Joseph's Hospice, Hackney, London. Nurs Mirror 1964;14:vii–x.

46. Bausewein C, Booth S, Gysels M, Kuhnbach R, Haberland B, Higginson IJ. Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. J Palliat Med 2010;13:1109–1118.

47. Kasper S. Clinical efficacy of mirtazapine: a review of meta-analyses of pooled data. Int Clin Psychopharmacol 1995;10(Suppl 4):25–35.

48. Spathis A, Booth S, Moffat C, et al. The breathing, thinking, functioning clinical model: a proposal to facilitate evidence-based breathlessness management in chronic respiratory disease. NPJ Prim Care Respir Med 2017;27:27.

49. Broderick JE, Schwartz JE, Vikingstad G, Pribbernow M, Grossman S, Stone AA. The accuracy of pain and fatigue items across different reporting periods. Pain 2008;139: 146–157.

50. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin 2009; 25:929–942.

51. Meek PM, Lareau SC, Anderson D. Memory for symptoms in COPD patients: how accurate are their reports? Eur Respir J 2001;18:474–481.

52. 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;185:435–452.

53. Booth S, Bausewein C, Higginson I, Moosavi SH. Pharmacological treatment of refractory breathlessness. Expert Rev Respir Med 2009;3:21–36.

54. Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J 2017;49.

55. Simon ST, Weingartner V, Higginson IJ, Voltz R, Bausewein C. Definition, categorization, and terminology of episodic breathlessness: consensus by an international Delphi survey. J Pain Symptom Manage 2014;47:828–838.

Appendix

Appendix I
Wording of NRS Across Studies

Manuscript Title	Author/Year/Journal	NRS Wording
No detail on wording in manuscript		
Fan Therapy Is Effective in Relieving Dyspnea in Patients With Terminally Ill Cancer: A Parallel-Arm, Randomized Controlled Trial.	Kako J, 2018, JPSM.	**No detail on wording in manuscript**
Low-Dose Morphine for Dyspnea in Terminally Ill Patients with Idiopathic Interstitial Pneumonias.	Matsuda Y, 2017, Journal of Palliative Medicine.	**No detail on wording in manuscript**
The Effect of Using an Electric Fan on Dyspnea in Chinese Patients With Terminal Cancer.	Wong SL, 2017, Am J Hosp Palliat Care.	**No detail on wording in manuscript**
Inspiratory High Frequency Airway Oscillation Attenuates Resistive Loaded Dyspnea and Modulates Respiratory Function in Young Healthy Individuals.	Morris T, 2014, PLoS One.	**No detail on wording in manuscript**
Dyspnea scales in the assessment of illiterate patients with chronic obstructive pulmonary disease.	Martinez JA, 2000, Am J Med Sci.	**No detail on wording in manuscript**
Breathlessness now		
Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness.	Sandberg J, 2018, JPSM.	How is your breathlessness right now?
Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects.	Morris NR, 2007, Respir Physiol Neurobiol.	How short of breath are you right now
Effect of Prophylactic Fentanyl Buccal Tablet on Episodic Exertional Dyspnea: A Pilot Double-Blind Randomized Controlled Trial.	Hui D, 2017, JPSM.	Dyspnea intensity now
Impact of Prophylactic Fentanyl Pectin Nasal Spray on Exercise-Induced Episodic Dyspnea in Cancer Patients: A Double-Blind, Randomized Controlled Trial.	Hui D, 2016, JPSM.	Dyspnea intensity "now"
Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot.	Johnson MJ, 2015 BMJ Open.	Breathlessness intensity "now," at maximal exertion, and then every minute during recovery.
Assessment of dyspnoea in the emergency department by numeric and visual scales: A pilot study.	Placido R, 2015, Anaesth Crit Care Pain Med.	Tell me on a scale of 0–10, what is the level of your shortness of breath. Zero is no shortness of breath and 10 is the worst possible shortness of breath you can possibly imagine.
Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: a preliminary double-blind, randomized, controlled trial.	Hui D, 2014, JPSM.	Intensity of dyspnea "now"
High Flow Oxygen and Bilevel Positive Airway Pressure for Persistent Dyspnea in Patients With Advanced Cancer: A Phase II Randomized Trial.	Hui D, 2013, JPSM.	Intensity of dyspnea "now"
Proposing a standardized method for evaluating patient report of the intensity of dyspnea during exercise testing in COPD.	Hareendran A, 2012, Int J Chron Obstruct Pulmon Dis.	Participants asked to indicate how much shortness of breath they are having right now
Average and worst breathlessness		
Are within-person Numerical Rating Scale (NRS) ratings of breathlessness 'on average' valid in advanced disease for patients and for patients' informal carers?	Wade J, 2017, BMJ Open Respir Res.	What is the worst your breathlessness has been over the last 24 hours? How has your breathlessness been over the last 24 hours on average?

(*Continued*)

Appendix I
Continued

Manuscript Title	Author/Year/Journal	NRS Wording
Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the Dyspnea-12 Questionnaire.	Tan JY, 2017, JPSM.	Average breathlessness Worst breathlessness Breathlessness-related unpleasantness Breathlessness-related distress patients' ability to cope with breathlessness
Practical Dyspnea Assessment: Relationship Between the 0–10 Numerical Rating Scale and the Four-Level Categorical Verbal Descriptor Scale of Dyspnea Intensity.	Wysham NG, 2015, JPSM.	How is your breathlessness right now? How has your breathlessness been over the last 24 hours, on average? What is the worst your breathlessness has been over the last 24 hours?
An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.	Higginson IJ, 2014, The Lancet Respiratory Medicine.	Indicate how much shortness of breath you are having on average over the last 24 hours? At worst at rest over the last 24 hours? On exertion over the last 24 hours?
A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease.	Johnson MJ, 2015, BMC Med.	Worst breathlessness over the previous 24 hours Average intensity of breathlessness over the past 24 hours Distress due to breathlessness Coping with breathlessness Satisfaction with care of breathlessness
Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial.	Yorke J, 2015, Supportive Care in Cancer.	Average breathlessness in the past 24 hours Worst breathlessness in the past 24 hours Distress associated with breathlessness Unpleasantness associated with breathlessness Relief from breathlessness Ability to cope with breathlessness
Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough.	Oxberry SG, 2013, Journal of Palliative Medicine.	Average and worst breathlessness over the past 24 hours Distress, satisfaction, and coping with breathlessness
A randomised trial of high vs. low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study.	Barton R, 2010, Lung Cancer.	Perceived severity of breathlessness (average and worst over the past 24 hours, and "now") Distress caused by breathlessness Ability to cope with breathlessness
The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial.	Molassiotis A, 2015, Support Care Cancer.	Perceived severity of breathlessness (average and "worst" over the past 24 hours, and "now") and distress caused by breathlessness Ability to cope with breathlessness
Minimally clinically important difference in chronic breathlessness: Every little helps.	Oxberry SG, 2012, Am Heart J.	Intensity of average breathlessness over the past 24 hours Worst breathlessness over the past 24 hours
Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial.	Oxberry SG, 2011, Eur J Heart Fail.	Severity of average breathlessness Worst breathlessness over the past 24 hours Breathlessness "now" Coping with breathlessness
Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.	Abernethy AP, Lancet, 2010.	Breathlessness right now Average dyspnea in the past 24 hours Worst breathlessness in the past 24 hours Relief of dyspnea over the previous 24 hours
Average breathlessness		
Association of Descriptors of Breathlessness With Diagnosis and Self-Reported Severity of Breathlessness in Patients With Advanced Chronic Obstructive Pulmonary Disease or Cancer.	Chowienczyk S, 2016, JPSM.	How has your breathlessness been over the last 24 hours on average? How distressed are you by your breathlessness?

(*Continued*)

Appendix I
Continued

Manuscript Title	Author/Year/Journal	NRS Wording
Worst breathlessness and breathlessness now		
Predictors of response to corticosteroids for dyspnea in advanced cancer patients: a preliminary multicenter prospective observational study.	Mori M, 2017, Support Care Cancer.	Dyspnea worst Dyspnea now
Distress due to breathlessness		
Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial.	Farquhar MC, 2014, BMC Med.	Patient distress due to breathlessness
The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial.	Farquhar MC, 2016, Trials.	Patient distress due to breathlessness
Other		
Acupuncture for Dyspnea in Lung Cancer: Results of a Feasibility Trial.	Bauml J, 2016, Integr Cancer Ther.	Dyspnea severity in the past 7 days
Morphine in the management of dyspnoea in ALS. A pilot study.	Clemens KE, 2008, Eur J Neurol.	Intensity of dyspnea
Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study.	Currow DC, 2010, JPSM.	Intensity of dyspnea

NRS = numerical rating scale.

Appendix II

Full eligibility criteria

Inclusion criteria:

1. Male or female aged ≥18 years
2. Diagnosed with cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or chronic heart failure (New York Heart Association (NYHA) Class III or IV)
3. Breathlessness severity: modified MRC dyspnea scale grade 3 or 4
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician
5. Management of the underlying condition has remained unchanged for the previous one week
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician
7. Expected prognosis of two months or more
8. If female and of childbearing potential agrees to use adequate contraception
9. Able to complete questionnaires and trial assessments
10. Able to provide written informed consent

Exclusion criteria:

1. Existing antidepressant use
2. Known contraindication to mirtazapine
3. Hypersensitivity to the active substance or to any of the components of the mirtazapine or placebo (e.g., lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤40
5. Pregnant or breast-feeding women
6. Patients with acute cardiac events within three months of randomization (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)
7. Patients with known hepatic impairment
8. Patients with known renal impairment
9. Patients with uncontrolled blood pressure

10. Patients with uncontrolled diabetes mellitus
11. Patients with uncontrolled seizures, epilepsy, or organic brain syndrome
12. Patients with severe depression or suicidal thoughts
13. Patients with a history of psychotic illness (schizophrenia, bipolar disorder, mania, hypomania, or other psychotic disturbances)

Appendix III

Topic Guide

You have recently taken part in a study called Better B. I would like to talk to you to understand your experience of taking part, what you expected, and what it was like.

If you want to stop the interview at any point let me know. You do not need to give a reason, and your clinical care will not be affected. Everything you say will be kept confidential.

Do you have any questions before we begin?

Introduction/Better-B

What did you understand about the study?

What was your experience of taking part?

Prompt: Can you tell me a bit about that?

Recruitment/joining the study

How were you asked to take part in the study?

What was that like?

Prompt: Who spoke to you? What were you told? Where were you at the time?

What were your expectations?

Why did you decide to take part?

Prompt: What specifically did you want to see improved? What change were you hoping for?

Trial Processes/Taking Part

What did you understand about the treatment you received?

Prompt: What did you think about taking an antidepressant medication? What do you understand about a placebo drug/randomization?

How did you find taking the medication?

Probe: Did you have any difficulties? How did you manage with your other medications? (Dosette Box/Blister Pack/Diary as reminder).

How did you being visited at home?

Would you have preferred to have been seen somewhere else?

How did you find it completing the questionnaires?

Probe: What did you think about the questions we asked? Do you think they were the right questions? Did they capture what is important to you?

Would anything have made it easier to take part?

Probe: What were the downsides to taking part?

Change

Tell me in what ways the drug changed how you felt?

Prompt: Did you notice any change in your breathing, sleep, appetite, drowsiness?

What did you hope would change?

For you what would be the most important change?

Were there any changes you had not expected?

Closing Section

Is there anything else that you think is important for me to know?
Is there anything that has worried you during the course of this conversation?
Is there anything else you would like to talk about?

Appendix IV
Participant Demographics

Participant ID	Age, yrs	Diagnosis	Gender	Trial Completer/ Noncompleter
1001	84	ILD	Male	Completer
1002	70	COPD	Male	Completer
1003	68	COPD	Male	Completer
1004	71	COPD	Male	Completer
1005	76	ILD	Male	Completer
1006	71	HF	Male	Completer
1007	66	ILD	Male	Completer
1008	64	ILD	Male	Completer
1009	78	COPD	Male	Completer
1010	70	ILD	Female	Completer
1011	70	COPD	Female	Completer
1012	67	ILD	Male	Completer
1013	73	COPD	Male	Completer
1014	64	COPD	Male	Completer
1015	74	COPD	Female	Completer
1016	82	HF	Male	Non completer
1017	72	ILD	Male	Completer
1018	83	Cancer	Female	Completer
1019	74	ILD	Female	Non completer
1020	62	COPD	Male	Completer
1021	56	COPD	Female	Completer
1022	81	COPD	Male	Completer

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; HF = heart failure.

Appendix V
Thematic Coding Framework

Overarching Theme	Theme	Subtheme	Node
Change in experience of breathlessness	Physical	Relief of symptom	Easier breathing
			Improved appetite
			Able to eat more
			Improved sleeping
		Able to do more	More active
			Able to do activities of daily living more easily
		Perceived adverse effects of trial medication	Feeling sick
			Feeling drowsy
	Emotional	Sense of wellbeing	Feeling more relaxed
			Feeling calm
			Feeling more upbeat and positive
		Response to episodes of panic	Able to calm down more quickly
			Not feeling frightened
	Spiritual	Able to do more	Feeling positive about being able to contribute
			Sense of purpose
			Sense of satisfaction
		Wellbeing	Feeling positive
			Able to enjoy life
	Social	Able to go out more	Able to socialize
			Able to meet other people
			Feeling less isolated
			Able to enjoy activities
		Impact on relationships	Positive impact on close relationships
			Less reliant on others
	Control	Sense of control	During episode of breathlessness
			Less likely to restrict or avoid activities
		Increase in confidence	Able to be more independent
			Less reliant on others

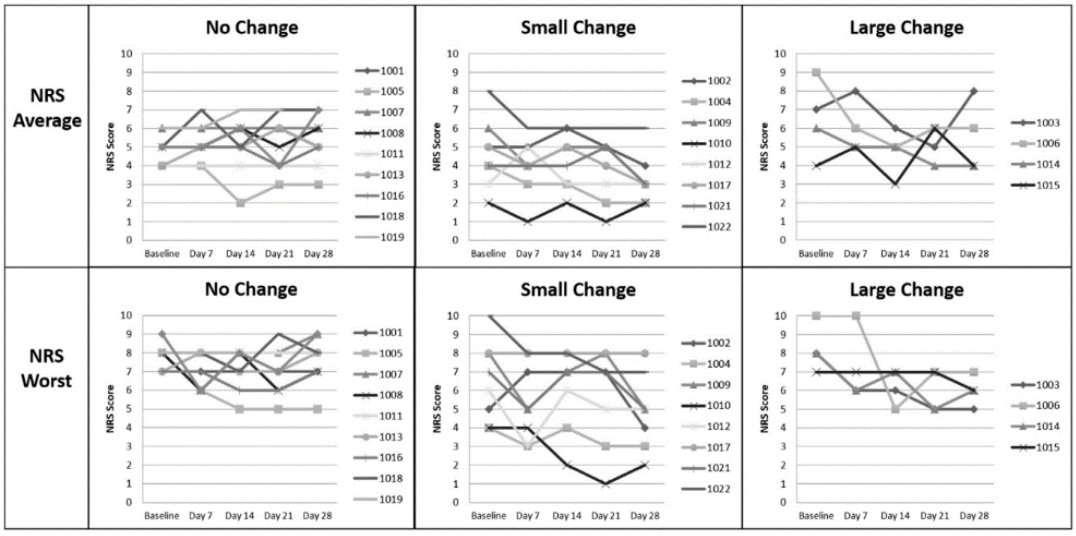
Appendix VI
Examples of Change in Experience Mapped Onto the Domains of "Total Breathlessness"

Experience Within Trial	Domain of Total Breathlessness	Participant Quote
The physical impact of breathlessness was prominent for all participants, and many hoped to see improvements in activity levels from taking the trial medication.	Physical	*It would be nice that I would actually be able to walk down the hill, as well as erm, you know, I, I used to be able to, I had a problem coming up the hill, but erm, now I have a problem walking down the hill as well.* Participant ID 1010
The emotional impact of breathlessness was also common with participants describing a repeated cycle of breathlessness and anxiety. Some participants reflected on whether a medication which enabled them to feel calmer could break this cycle.	Emotional	*You can get out of breath and then you can panic, cause you're not getting your breath and you're not breathing through your nose and letting it out through your mouth, you're sort of gasping.* Participant ID 1018
The physical and emotional effects caused distress in other aspects of participant's lives, commonly impacting on social and spiritual domains.	Social and Spiritual	*It turns you into a prisoner really, not being able to do anything, without getting shortness of breath.* Participant ID 1013
		I've been used to walking up mountains and, in the Lake District and erm, the Dales and I can't do any of that now. And er, it really does get me down that I can't do housework the same, gardening, everything. Participant ID 1015
Control and context were important across all domains. One participant described withdrawing from social activities for fear that an episode of breathlessness might occur. For another, the unpredictability of breathlessness left them feeling unable to make plans.	Context and Control	*Well, you, you're maybe struggling to breathe, and then you're getting yourself all hot and in a bother and then that sort of gets you churning in your stomach and then your chest seems to close up even more, and then you start sweating and all that type of thing, and I think, I was hoping that taking the, the medication would calm me down and it would be like 'right, relax, take a breath, everything's fine', and then I wouldn't be suffering those symptoms.* Participant ID 1021

(*Continued*)

Appendix VI
Continued

Experience Within Trial	Domain of Total Breathlessness	Participant Quote
		I can't plan going out, cause, from day-to-day you can think, oh we'll go this tomorrow, then you wake up tomorrow and you just cant do anything. So plans, you just don't plan anything, you go day-to-day and see how you are. Participant ID 1013



Appendix VII. NRS Change over time. NRS = numerical rating scale.

Chapter 8 –Results 2

8.1 Introduction

This chapter reports the findings for objective 3: 'To explore experience and feasibility of trial processes, and what influences participants to take part and remain in a drug trial for chronic or refractory breathlessness'. As discussed in chapter 3 feasibility studies are pieces of work done before a main study in order to answer the question 'can this study be done?' (105, 126). Feasibility work can help to identify methodological challenges and optimise trial design. In this chapter I first describe the main feasibility findings in terms of recruitment, the study outcomes, and the intervention, incorporating a published case series. I then present the findings of my qualitative study which explored what influenced participants to take part and remain in the trial. For further detail regarding the trial findings see paper published in Thorax (Appendix 8) (127).

8.2 Recruitment

BETTER-B (Feasibility) was open to recruitment at three centres between 17th August 2016 and 30th November 2017. Each centre was open for 12 months, during which time 409 patients were screened, of which 150 were eligible, and 64 randomised (Figure 3). The screening to recruitment ratio was 6.4 (Table 4). This is very favourable compared to other studies in Palliative Care which have reported a screening to recruitment ratio as high as 15 (128-130). Most participants were recruited at outpatient clinics 39% (n=25) or through database screening 36% (n=23). The main reasons for ineligibility were mMRC score <3 27% (n=71), and already taking an antidepressant 38% (n=98). 20% of those screened declined (n=83). These findings suggest that the BETTER-B trial is feasibility from a recruitment perspective, with clinicians who are willing to recruit, and eligible patients who are willing to participate. Further data from the qualitative study is presented in section 8.6.

Figure 3: Study Flow Chart

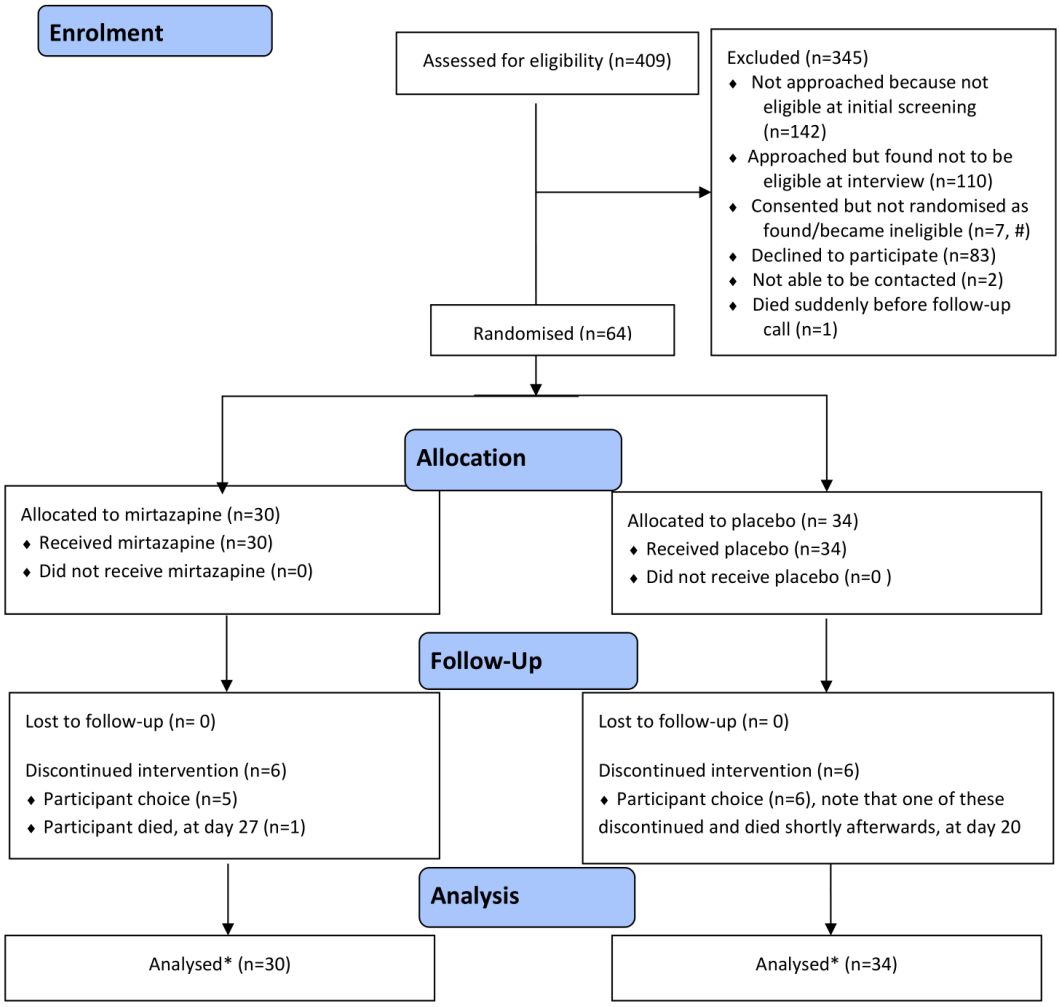


Table 4: Screening by setting and diagnosis

Setting	screened	randomised	screened to recruitment ratio	mirtazapine	placebo
outpatient	98	25	3.9	11	14
inpatient	35	4	8.8	3	1
community *	45	8	5.6	4	4
data base *	203	23	8.8	11	12
other	28	4	7.0	1	3
total	**409**	**64**	**6.4**	**30**	**34**
main disease					
cancer	19	1	19.0	0	1
lung disease	366	56	6.5	27	29
CHF	15	3	5.0	1	2
cancer + lung disease	8	3	2.7	2	1
lung disease + CHF	1	1	1.0	0	1
total	**409**	**64**	**6.4**	**30**	**34**

Baseline demographics and clinical characteristics are shown in Table 5 and were balanced between groups. Most participants had COPD (63%, n=40) or ILD (30%, n=19). 42% had mMRC Grade 3 (breathless after walking ~90 meters/few minutes on level ground) (n=27) and 58%

mMRC Grade 4 (too breathless to leave the house or when dressing) (n=37). A baseline HADs score of >15 was present for 38% of participants (n=14). 33% (n=21) were receiving opioids.

Table 5: Baseline demographic, clinical and minimisation characteristics

	Mirtazapine n=30	**Placebo n=34**
Age (years), Mean (s.d.)	72.9 (7.12)	70.6 (9.43)
Gender		
Men	24 (80.0%)	23 (67.6%)
Women	6 (20.0%)	11 (32.4%)
Main Diagnosis		
Lung Disease & Cancer	2 (6.7%)	1 (2.9%)
Lung Disease & Chronic Heart Failure	0 (0.0%)	1 (2.9%)
Cancer	0 (0.0%)	1 (2.9%)
Lung Disease	27 (90.0%)	29 (85.3%)
Chronic Heart Failure	1 (3.3%)	2 (5.9%)
Lung Disease categories *(includes lung disease + other diagnosis)*	*29 (96.7%)*	*31 (91.2%)*
COPD	*20 (69.0%)*	*20 (64.5%)*
ILD	*8 (27.6%)*	*11 (35.4%)*
COPD & ILD	*1 (3.4%)*	*0 (0.0%)*
AKPS score, Mean (s.d.)	62.0 (9.15)	63.8 (8.88)
Breathlessness at worst over 24 hours NRS / 10, Mean (s.d.)	7.6 (1.25)	8.0 (1.73)

Breathlessness on average over 24 hours NRS / 10, Mean (s.d.)	5.4 (1.36)	5.0 (1.76)
mMRC grade		
Grade 3 - breathless after walking ~90 metres/few minutes on level ground	12 (40.0%)	15 (44.1%)
Grade 4 - too breathless to leave the house or when dressing	18 (60.0%)	19 (55.9%)
HADS score		
0-14	19 (63.3%)	21 (61.8%)
15 or above	11 (36.7%)	13 (38.2%)
IPOS score / 17 items, Mean (s.d.)	21.5 (8.61)	19.7 (7.23)
EQ-5D Index, Mean (s.d)	0.53 (0.05)	0.60 (0.03)
EQ-VAS, Mean (s.d)	54.3 (17.9)	53.8 (18.0)
Total health and social care costs in the previous 3 months (£), Mean (s.d)	2220 (577)	2007 (727)
Receiving opioid medication		
Yes	11 (36.7%)	10 (29.4%)
No	19 (63.3%)	24 (70.6%)
Participant able to complete QoL measures	30 (100.0%)	34 (100.0%)
Help required to complete QoL and type		
Questions read out to participant	15 (50.0%)	16 (47.1%)
Helped to complete answers	4 (13.3%)	2 (5.9%)
Other	2 (6.7%)	1 (2.9%)

Total needing help	21/30 (70.0%)	19/34(55.9%)

8.3 Intervention and outcomes

The intervention was well tolerated during the trial with few adverse effects reported. There was only one grade 3 adverse event which was reported in the placebo arm. In total 12 serious adverse events were reported, 7 in the mirtazapine arm and 5 in the placebo arm. There was 100% completion of questionnaires at baseline and little missing data throughout the trial (Table 6). However, 63% (n=40) of participants did require some help completing the trial questionnaires.

Table 6: Missing data categorised using the MORECare classification for missing data in palliative care studies

Questionnaire/ outcome	**Baseline**	**MORECare Classification**	**Day 14**	**MORECare Classification**	**Day 28**	**MORECare Classification**
Average NRS	0/64		1/63	2 ADI	1/58	4 ADI, 2 ADD, 1AaR
Worst NRS	0/64		1/63	2 ADI	1/58	4 ADI, 2 ADD, 1AaR
CRQ dyspnoea	0/64		2/62	3 ADI, 1 missed data item	1/58	4 ADI, 2 ADD, 1AaR
CRQ fatigue	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
CRQ emotional	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
CRQ mastery	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS total	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS pain	0/64		1/62	3 ADI	2/58	4 ADI, 2 ADD, 1AaR, 1 missed data item
IPOS shortness of breath	1/64	1 missed data item	2/62	3 ADI, 1 missed data item	1/58	4 ADI, 2 ADD, 1AaR
IPOS weakness/lack of energy	2/64	2 missed data item	2/62	3 ADI, 1 missed data item	2/58	4 ADI, 2 ADD, 1AaR, 1 missed data item

IPOS nausea	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS vomiting	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS poor appetite	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS constipation	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS sore or dry mouth	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS drowsiness	0/64		1/62	3 ADI	2/58	4 ADI, 2 ADD, 1AaR, 1 missed data item
IPOS poor mobility	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS anxiety	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS family or friend worried	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS depressed	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS at peace	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS sharing feelings	1/64	1 missed data item	1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS problems addressed	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
IPOS enough information	0/64		2/62	3 ADI, 1 missed data item	1/58	4 ADI, 2 ADD, 1AaR
HADS anxiety	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
HADS depression	0/64		1/62	3 ADI	1/58	4 ADI, 2 ADD, 1AaR
GSES Total	0/64				2/58	4 ADI, 2 ADD, 1AaR, 1 missed data item
EQ5D mobility	0/64				1/58	4 ADI, 2 ADD, 1AaR
EQ5D self-care	0/64				1/58	4 ADI, 2 ADD, 1AaR
EQ5D usual activities	0/64				2/58	4 ADI, 2 ADD, 1AaR, 1 missed data item
EQ5D pain	0/64				1/58	4 ADI, 2 ADD, 1AaR

EQ5D anxiety and depression	0/64				1/58	4 ADI, 2 ADD, 1AaR
EQ5D health score	0/64				1/58	4 ADI, 2 ADD, 1AaR
SPPB Chair stand	11/64	11 ADI			9/58	12 ADI, 2 ADD, 1 AaR
SPPB Balance	16/64	11 ADI, 5 missing data item			15/58	12 ADI, 2 ADD, 1AaR, 6 missing data items
SPB Gait	11/64	11 ADI			9/58	12 ADI, 2 ADD, 1AaR
SPPB Summary	16/64	11 ADI, 5 missing data item			15/58	12 ADI, 2 ADD, 1AaR, 6 missing data items

ADI: attrition due to illness; ADD: attrition due to death; AaR: attrition at random

It became apparent during the qualitative interviews that a number of participants had requested to be prescribed mirtazapine by their General Practitioner once the trial had finished. I therefore decided to do an interim analysis for these participants to explore aspects of feasibility including acceptability of the intervention and the outcomes. For further detail see published case series in section 8.4.

8.4 Case Series

Six cases were selected for the interim analysis. Cases were chosen if they had disclosed during the qualitative interview that they had been taking mirtazapine prescribed by their GP since the trial had finished. All six cases reported a perceived benefit during the trial period, with no adverse effects. Furthermore, the fact that they had all requested to be prescribed mirtazapine when the trial finished suggests that the intervention was acceptable. At the time of the interviews, cases had been receiving mirtazapine for a variable time period of 2 weeks–5 months.

The case series also provided an opportunity to consider the feasibility of the outcome measures chosen. Minimal missing data suggests that the questionnaires were acceptable to participants and not a burden to complete. However, it is also important to be confident that the right outcomes are being measured. In the case series participants described physical (breathing, sleep, appetite, mobility), emotional (feeling frightened), and control as being

important outcomes. This supports my model of 'total breathlessness' and emphasises the importance of using outcome measures which are able to detect changes across these important domains. More detail is presented in the following paper which was published in Palliative Medicine (see accepted manuscript version below).

Use of mirtazapine in patients with chronic breathlessness: A case series'

Abstract

Background

Breathlessness remains a common and distressing symptom in people with advanced disease with few effective treatment options. Repurposing of existing medicines has been effective in other areas of palliative care, for example antidepressants to treat pain, and offers an opportunity to deliver improved symptom control in a timely manner. Previous case series have shown reduced breathlessness following the use of sertraline (a selective serotonin reuptake inhibitor) in people with chronic obstructive pulmonary disease.

Cases

Six cases where mirtazapine, a noradrenergic and specific serotonergic antidepressant, was used to treat chronic breathlessness in advanced lung disease.

Case management

All cases received mirtazapine at a starting dose of 15mg, prescribed under the care of their primary care physician. Cases had been receiving mirtazapine for a variable time period (2 weeks to 5 months) at the time of the interviews.

Case outcome

All cases reported less breathlessness and being able to do more. They described feeling more in control of their breathing, and being able to recover more quickly from episodes of breathlessness. Some cases also reported beneficial effects on anxiety, panic, appetite and sleep. No adverse effects were reported.

Discussion

Patients with chronic breathlessness in this case series reported benefits during mirtazapine treatment. To determine the effectiveness of mirtazapine in alleviating breathlessness and improving quality of life in chronic lung disease, blinded randomised trials are warranted.

Key words

Breathlessness, shortness of breath, mirtazapine, antidepressant, case series, advanced disease

Key Statements

What is already known about the topic?

- Breathlessness is a common and distressing symptom in advanced disease, with few effective treatment options
- New treatments are urgently needed
- Repurposing of existing medicines has been effective in other areas of palliative care

What this paper adds

- This case series is the first to report the use of mirtazapine in the management of chronic breathlessness
- Patients with advanced lung disease and chronic breathlessness reported mirtazapine to be of benefit to them
- Patients reported less breathlessness and being able to do more, as well as beneficial effects on anxiety, panic, appetite, and sleep

Implications for practice, theory or policy

- Mirtazapine may be beneficial in reducing breathlessness and improving quality of life in patients with chronic lung disease
- To determine the effectiveness blinded randomised trials are warranted

- Choice of outcome measures which incorporate not only breathlessness, but anxiety, panic, appetite and sleep will be important when conducting trials in breathlessness

Background

Breathlessness is a common and distressing symptom in people with advanced malignant and non-malignant disease1. Chronic breathlessness has recently been defined as breathlessness at rest or on minimal exertion that persists despite optimal treatment of the underlying disease2.

Whilst the current evidence-base for individual non-pharmacological interventions is variable, a multidisciplinary approach combining a number of components (pacing, breathing training and use of a hand-held fan) has been shown to be effective at improving confidence and control over breathing3. There are few effective pharmacological treatment options, with some evidence to support the use of opioids, but concerns regarding side effects and small effect sizes4. Whilst benzodiazepines are sometimes used to treat breathlessness related anxiety, there is no evidence that they relieve breathlessness in adults with advanced disease5. New treatments are urgently needed. Repurposing existing medicines has been effective in other areas of palliative care (for example antidepressants to treat pain) and offers a potential opportunity to deliver improved symptom control in a timely manner.

Two case series of sertraline, a selective serotonin reuptake inhibitor (SSRI), showed a subjective decrease in breathlessness in patients with chronic obstructive pulmonary disease (COPD) 6 7, and a phase III trial is ongoing to determine effectiveness to alleviate chronic breathlessness in advanced illness8. SSRI's inhibit serotonin re-uptake resulting in a rise in serotonin (5HT) which is thought to create their therapeutic effect in depression9. The mechanism of action of SSRI'S in breathlessness is not understood. Serotonin may partially modulate respiratory function, and impact on areas of the brain relating to fear and anxiety, which appear to be more active during experimentally induced breathlessness9.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), and enhances 5-HT1 receptor mediated neurotransmission resulting in increased levels of serotonin in the cortex9. Increased serotonin may be beneficial in the treatment of chronic breathlessness by inhibiting 'fear circuits' which have been shown to originate in the amygdala, and appear to be

more active during experimentally induced breathlessness9. Respiratory modulation is another possible mechanism as described above. Mirtazapine is an effective treatment for depression, with a faster onset of action when compared to SSRI's. A number of small randomised controlled trials have evaluated efficacy in anxiety disorders, with some evidence in the treatment of panic disorder10. These effects may be of additional benefit in breathlessness in chronic lung disease which has been associated with high levels of anxiety. Mirtazapine blocks 5-HT2 and 5-HT3 receptors, which can be an advantage in clinical practice by reducing the gastrointestinal effects commonly reported with SSRI's9. At lower doses mirtazapine can be quite sedating due to its high affinity for histamine H1 receptors; but at higher does the increased noradrenergic transmission counteracts this effect9. The most common side effects of mirtazapine are increased appetite, weight gain and somnolence, which may be advantageous to patients with advanced disease who frequently report poor appetite and disrupted sleep1.

Case presentation

We present a case series of 6 people who received mirtazapine for breathlessness at a starting dose of 15mg, prescribed under the care of their primary care physician. All had recently participated in a randomised controlled feasibility trial of mirtazapine for chronic breathlessness, and had requested continued compassionate use from their primary care physician. Qualitative interviews were conducted as part of the feasibility trial. Data was collected between March 2017 and February 2018. The study received ethical approval through the London Central Research Ethics Committee (REC reference 16/LO/0091). All patients entered the trial voluntarily and provided written consent for their anonymised data to be shared in scientific publications. The trial enrolled people with advanced disease and severe breathlessness, as indicated by a score of 3 or 4 on the Modified Medical Research Council Dyspnea Scale (mMRC), i.e. breathlessness after walking 100 yards or after a few minutes on level ground, or when dressing. At the time of the interviews, patients had been receiving mirtazapine for a variable time period of 2 weeks to 5 months. All patients reported an improvement in breathlessness. This was often accompanied by a reduction in anxiety, fewer episodes of panic, as well as improvements in appetite and sleep. Clinical characteristics and reported change in symptoms for all cases are shown in Table 1. Two cases are then described in detail.

Table 1: Clinical Characteristics and reported change in symptoms (+ indicating improvement in symptom)

Case Number	Age	Sex	Diagnosis	mMRC Dyspnea Scale		Australia-modified Karnofsky Performance scale	HADs	
				Breathlessness	Anxiety/ panic	Appetite		Sleep
Case 1	72	Male	Interstitial Lung Disease (ILD)	4	60	7	+	+
	+							
Case 2	68	Male	Chronic Obstructive Pulmonary Disease	4	60	27		+++
	+++	++	++					
Case 3	70	Female	Interstitial Lung Disease	3	80	8	+	+
Case 4	64	Male	Chronic Obstructive Pulmonary Disease	4	70	8		+++
	+++							
Case 5	74	Female	Chronic Obstructive Pulmonary Disease	4	60	17		++
	++	+	+					
Case 6	81	Male	Chronic Obstructive Pulmonary Disease	3	70	20		+
	+		+					

Case 1:

Case 1 is a 72 year old male who lives at home with his wife. He was diagnosed with interstitial lung disease 4 years ago, and has a past medical history of bronchiectasis, congestive heart failure and a permanent pacemaker. Prescribed medications at the time of interview included low dose modified release morphine prescribed for chronic breathlessness (5mg twice daily), spironolactone and furosemide. Renal function and liver function tests were within normal limits. His FEV1/FVC ratio was 1.01. Case 1 described experiencing breathlessness on minimal exertion, and whilst speaking in conversation. He found he often had to stop when he became breathless to recover. At baseline Case 1 scored 4 on the mMRC Dyspnea Scale and 60 on the Australia-Modified Karnofsky Performance Scale (AKPS). His 'at worst' breathlessness score on the numerical rating scale was 8, and he scored 7 on the Hospital Anxiety and Depression Scale (HADs). Case 1 was prescribed mirtazapine and was reviewed 2 weeks later. He reported improved breathing and being able to do more including walking further. He described feeling

more in control and being able to recover from episodes of breathlessness more quickly. He also noticed an improvement in his appetite. He did not report any adverse effects.

Case 2:

Case 2 is a 68 year old male who lives alone. He was diagnosed with severe COPD with emphysema 2 years ago, and is a current smoker. He has a past medical history of hypercapnic respiratory failure for which he uses home non-invasive ventilation, chronic heart failure and benign asbestos plaques. Prescribed medications at the time of assessment included Seretide, Salbutamol, Tiotropium, Spironolactone and Furosemide. Renal function and liver function tests were within normal limits. His FEV1/FVC ratio was 0.35. Case 2 reported severe breathlessness with episodes of panic causing him to regularly attend his local Accident & Emergency department. He described feeling frightened to get out of bed in the morning for fear of triggering breathlessness, and said he didn't often leave the house. At baseline he scored 4 on the mMRC Dyspnea Scale and 60 on the Australia-Modified Karnofsky Performance Scale (AKPS). His 'at worst' breathlessness score on the numerical rating scale was 8, and he scored 27 on the Hospital Anxiety and Depression Scale. Case 2 was prescribed mirtazapine and was reviewed 5 months later. He described feeling less breathless and being able to walk further. He also described sleeping better which he felt impacted positively on his breathing. Case 2 reported no presentations to hospital with breathlessness. He reported no adverse effects but an increased appetite.

Discussion/ Conclusion

This case series is the first to report the use of mirtazapine in the management of chronic breathlessness. Patients with advanced lung disease (COPD and ILD) and chronic breathlessness report mirtazapine to be of benefit to them.

All cases reported less breathlessness and being able to do more. They described feeling more in control of their breathing, and being able to recover more quickly from episodes of breathlessness. Some cases also reported beneficial effects on anxiety, panic, appetite and sleep (as shown in Table 1). No adverse effects were reported despite patients taking mirtazapine for up to 5 months. Given the safety concerns associated with long-term use of

other pharmacological treatments in breathlessness such as opioids, data on mirtazapine use for up to 5 months is helpful and contributes towards ongoing pharmacovigilance.

To determine the effectiveness of mirtazapine in alleviating breathlessness and improving quality of life in chronic lung disease, blinded randomised trials are warranted. On the basis of this case series, it appears that 'improved breathing' and 'being able to do more' are important outcomes. Sleep, appetite, feeling less frightened and being more in control may also be important. Future work should aim to unpick how these domains relate and provide a better understanding of the mechanism of effect of mirtazapine in chronic breathlessness.

Acknowledgements

This work is independent research funded by Marie Curie, Cicely Saunders International and The Atlantic Philanthropies in the Cicely Saunders Institute Fellowship Programme. NL is completing a training fellowship funded by Cicely Saunders International and Marie Curie (Grant Number A18859). MM is supported by an NIHR Career Development Fellowship (CDF-2017-10-009) and NIHR Health Services & Delivery Research grant (HSDR 16/02/18) and NIHR CLARHC South London. IJH is an NIHR Emeritus Senior Investigator and is supported by NIHR CLARHC South London. This research was supported by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, which is part of the National Institute for Health Research (NIHR), and is a partnership between King's Health Partners, St. George's, University London and St George's Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of Interest statement:

The authors declare that they have no conflict of interest

References

1. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. BMC Palliative Care 2011;10:15-15. doi: 10.1186/1472-684X-10-15

2. Johnson MJ, Yorke J, Hansen-Flaschen J, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. European Respiratory Journal 2017;49(5) doi: 10.1183/13993003.02277-2016

3. Bausewein C, Booth S, Gysels M, et al. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. The Cochrane database of systematic reviews 2008(2):Cd005623. doi: 10.1002/14651858.CD005623.pub2 [published Online First: 2008/04/22]

4. Barnes H, McDonald J, Smallwood N, et al. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. The Cochrane database of systematic reviews 2016;3:Cd011008. doi: 10.1002/14651858.CD011008.pub2 [published Online First: 2016/04/01]

5. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. The Cochrane database of systematic reviews 2016;10:Cd007354. doi: 10.1002/14651858.CD007354.pub3 [published Online First: 2016/11/02]

6. Papp LA, Weiss JR, Greenberg HE, et al. Sertraline for chronic obstructive pulmonary disease and comorbid anxiety and mood disorders. The American journal of psychiatry 1995;152(10):1531. [published Online First: 1995/10/01]

7. Smoller JW, Pollack MH, Systrom D, et al. Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics 1998;39(1):24-9. doi: 10.1016/s0033-3182(98)71377-5 [published Online First: 1998/04/16]

8. Watts GJ, Clark K, Agar M, et al. Study protocol: a phase III randomised, double-blind, parallel arm, stratified, block randomised, placebo-controlled trial investigating the clinical effect and cost-effectiveness of sertraline for the palliative relief of breathlessness in people with chronic breathlessness. BMJ Open 2016;6(11) doi: 10.1136/bmjopen-2016-013177

9. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications: Cambridge university press 2013.

10. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas 2001;34(10):1303-7. [published Online First: 2001/10/11]

8.5 What influenced people to take part and remain in the trial?

The second part of objective 3 was to explore what influences people to take part and remain in a drug trial for chronic or refractory breathlessness. Thematic analysis of in-depth qualitative interviews was undertaken; the findings are presented in the following paper, accepted for publication in *Trials* (Appendix 9).

A key finding was the importance of a person-centred approach which appeared to support recruitment and retention in the BETTER-B (Feasibility) trial. Prioritisation of the relationship between the patient and professional; person-centred processes including home visits, assistance with questionnaires, and involvement of the carer; and enabling people to participate by having processes in line with individual capabilities all influenced the decision to participate and remain in the trial.

What influenced people with chronic or refractory breathlessness and advanced disease to take part and remain in a drug trial? A qualitative study.

Lovell N[1], Etkind SN[1], Bajwah S[1], Maddocks M[1], Higginson IJ[1]

1. Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, King's College London, Bessemer Road, London SE5 9PJ, United Kingdom

*Corresponding Author Details:

Natasha Lovell. Email: Natasha.lovell@kcl.ac.uk. Tel: +44 (0)20 7848 5773.

Abstract

Background

Recruitment and retention in clinical trials remains an important challenge, particularly in the context of advanced disease. It is important to understand what affects retention to improve trial quality, minimise attrition and reduce missing data. We conducted a qualitative study embedded within a randomised feasibility trial and explored what influenced people to take part and remain in the trial.

Methods

Qualitative study embedded within a double blind randomised trial (BETTER-B(Feasibility): BETter TreatmEnts for Refractory Breathlessness) designed using a person-centred approach. Participants with cancer, Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), or Chronic Heart Failure (CHF), with a Modified Medical Research Council Dyspnoea Scale grade 3/4 were recruited from three UK sites. A convenience subsample completed qualitative interviews after the trial. Interviews were analysed using thematic analysis. Results were considered in relation to the core elements of person-centred care and our model of the person-centred trial.

Results

In the feasibility trial 409 people were screened for eligibility and 64 randomised. No participant was lost to follow up. 22 participants took part in a qualitative interview. 11 had a diagnosis of COPD, 8 ILD, 2 CHF, and 1 lung cancer. Median age was 71 years (56-84). 16 were male. 20 had completed the trial, 2 withdrew due to adverse effects. The relationship between patient and professional, potential for benefit, trial processes and the intervention all influenced the decision to participate in the trial. The relationship with the research team and continuity, perceived benefit, and aspects relating to trial processes and the intervention influenced the decision to remain in the trial.

Conclusions

In this feasibility trial recruitment targets were met, attrition levels were low, and aspects of the person-centred approach were viewed positively by trial participants. Prioritisation of the relationship between the patient and professional; person-centred processes including home visits, assistance with questionnaires, and involvement of the carer; and enabling people to participate by having processes in line with individual capabilities appears to support recruitment and retention in clinical trials in advanced disease. We would recommend the integration of a person-centred approach in all clinical trials.

Trial registration

Registry name: ISRCTN

Registration number: ISRCTN32236160

Title: BETTER-B(Feasibility): BETter TreatmEnts for Refractory Breathlessness

Date of registration: 13/06/2016

Key words:

qualitative

randomised controlled trial

palliative care

breathlessness

recruitment

retention

person centred care

Background

Recruitment and retention in clinical trials remains an important challenge which can impact on the validity of results by introducing bias and reducing power. Of 151 randomised control trials (RCTs) funded and published by the UK's National Institute for Health Research (NIHR), the target sample size was only achieved in 56% (1). Recruitment to clinical trials in people with advanced disease or in palliative care can be particularly challenging. For example, a recent systematic review found the target sample size was only achieved in 36.8% of trials assessing a therapeutic intervention (2). Eligibility can be a major limiting factor affecting recruitment in advanced disease. Trials often need to screen 10-15 patients to recruit one, and strategies to improve recruitment have had variable success (3-11). To advance the evidence base in palliative care we need high quality clinical trials, including Clinical Trials of an Investigational Medicinal Product (CTIMP), of which there are few, in part due to these challenges (12).

Retention in clinical trials is perhaps even more important, and has recently been identified as a top priority (13-15), with high levels of attrition a well-recognised problem. A review of clinical trials in advanced cancer identified a median attrition of 26% at the primary end point, increasing to 44% at the end of the study (16). Reasons for attrition included a high symptom burden (21%), patient preference (15%), hospitalisation (10%), and death (6%)(16). Attrition can lead to high levels of missing data, the level of which, in a recent systematic review of palliative care trials, was associated with study duration and an increasing number of study questionnaires and/ or tests (17). However, even for palliative care drug trials of short duration (4 weeks) attrition has been shown to be high, with only 40% of participants achieving the primary end point in a trial of pregabalin for cancer induced bone pain (5). A review of 108 randomised controlled trials of palliative care interventions found that the reason for missing data was unclassified in 53%, recorded as loss to follow up or withdrawal with no further details of the underlying reason (18). Meta-ethnographic review has identified five themes which may influence non retention in trials: 1) aspects of the trial did not fit with sense of self, 2) the trial design was not individualised, 3) trial processes were not in line with individual capabilities, 4) concerns about the trial medication, and 5) the extent to which trial participation could be appropriately accommodated into individuals' broader lives (19).

Research within Clinical Trials Units (CTUs) has considered methods that may improve recruitment and retention, identifying the importance of support and training for researchers and clinicians, and choice of appropriate outcome measures (14, 20). However, strategies to improve recruitment into trials have had variable success (3). There is an increasing literature around person centeredness in trials with growing evidence that involving patients at the research design stage can direct recruitment and retention strategies and improve enrolment (21-23). Patient and public involvement (PPI) is one method of applying person centeredness to trials, and can help to ensure that the research process is participant friendly and trial information is relevant, readable and understandable (24, 25). While studies evaluating person-centred care in trials remain limited, Chhatre et al applied a conceptual model of patient-centred recruitment and retention to a RCT of patients with newly diagnosed prostate cancer (26). The study identified strategies which may aid recruitment and retention. However, limitations due to time and resource constraints were acknowledged, and attrition was 26% at one of the three sites (26).

As more people approach the end of their lives with chronic and complex conditions, the need for robust research and evidence has never been greater. However, clinical trials in palliative care remain sparse, often limited by poor funding and methodological weaknesses (2, 27, 28). It is therefore important to understand what affects retention so that we can minimise attrition and ensure high quality clinical trials of palliative care interventions in the future. We conducted a qualitative study embedded within a randomised feasibility designed using a person-centred approach. The study aimed to explore what influenced participants to take part and remain in the trial.

Methods

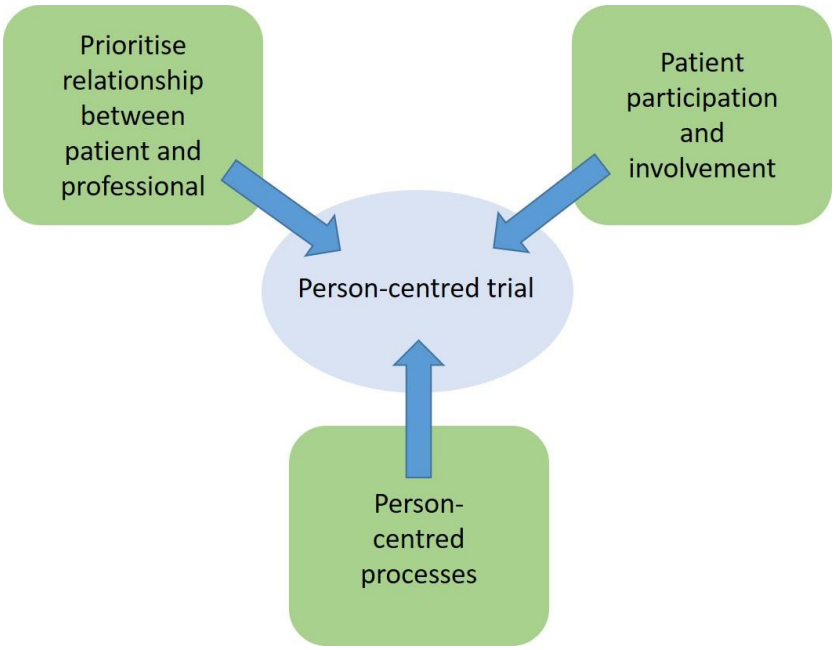
Design

We conducted a qualitative study embedded within a randomised trial of mirtazapine for chronic or refractory breathlessness (BETTER-B(Feasibility): BETter TreatmEnts for Refractory Breathlessness). The trial design aimed to optimise recruitment and retention through the use of a person-centred approach, which has been shown to enable engagement and improve patient outcomes in advanced disease (29-31).

Based on the core concepts of person-centred care described by Kitson (32) and following feedback from PPI representatives we developed the model of a person-centred trial (figure 1).

Our design aimed to put the patient at the centre of the trial and minimise study burden, therefore enabling participants to be actively involved and able to participate. The design focused on developing a genuine relationship between the researcher and participant, with emphasis on continuity. Burden from the trial was minimised by offering home visits and helping participants to complete trial related questionnaires to ensure a supportive system. PPI contributed to all stages of the trial, from design to analysis with representatives on the Trial Management Group (TMG) and the Trial Steering Committee (TSC). Trial burden was highlighted as important, and changes were made to the patient information sheet to ensure a clearer explanation of trial processes including the concept of randomisation.

Figure 1: The Person-centred trial



In depth interviews were conducted with patients who had taken part in a double-blind randomised feasibility trial of mirtazapine for chronic or refractory breathlessness. Ethical approval was received from the UK Health Research Authority (16/LO/0091) and the trial was prospectively registered (ISRCTN 32236160).The study is reported in accordance with the consolidated criteria for reporting qualitative research (COREQ) (33).

Setting

Participants were recruited from three UK sites; King's College Hospital, Nottingham City Hospital NHS Trust, and Castle Hill Hospital. Potential participants were identified through inpatient clinical teams, multi-disciplinary team meetings, hospital clinic lists, and hospital databases. At each site there was a small dedicated research team who were involved in both the recruitment and follow up data collection across all time points of the trial.

Study participants and sampling

Those eligible for the feasibility trial were adults with cancer, Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), or Chronic Heart Failure (CHF), with a Modified Medical Research Council (mMRC) Dyspnoea Scale grade 3 ("I stop for breath after walking about 100 yards or after a few minutes on the level") or 4 ("I am too breathless to leave the house" or "I am breathless when dressing"), with no current diagnosis of severe depression, not currently prescribed an antidepressant medication. For full eligibility criteria see Appendix one. A sampling frame was agreed which included characteristics considered to be important including; gender, diagnosis, trial completion/ non completion, and age (<65 years / >65 years). However, due to the limited pool of participants we decided to take a pragmatic approach and used convenience sampling, offering each trial participant the opportunity to participate in a qualitative interview. Participants were approached by telephone or in-person to arrange an interview. All participants provided written informed consent prior to their interview.

Trial schedule

Patients and carers were approached by their usual clinician and provided with some initial information about the trial. If they were in agreement they were then contacted by a researcher who was able to provide more detailed information including; the rationale for doing the study, the trial design, and what it would mean if they agreed to take part in terms of the intervention and study assessments. All members of the research team had training and experience of working with people living with advanced disease. Patients were given a minimum of 24 hours to consider the trial and discuss with friends and family. Participants then provided written informed consent, and a more detailed eligibility assessment followed. After randomisation the medication was provided along with a diary to complete, details of who to contact with any questions or concerns, and emergency contact details for out of

hours. Participants received 28 days of trial treatment (either oral mirtazapine or placebo capsules). They were assessed face to face on day 0, day 14 and day 28, and via telephone on day 7, day 21, and day 35. Assessments were organised at a time which was convenient for the participant with some flexibility (+/-1 day). Participants were offered to be visited at home and assistance was provided with completing the trial-based questionnaires. Continuity of the researcher was prioritised where possible.

Data collection

Qualitative interviews were conducted at the end of the trial. Interviews were conducted in a place of the participants choosing. This was usually their own home, but some interviews were conducted in hospital. The topic guide (Appendix two) was developed using existing literature and refined following feedback from PPI representatives and the Trial Management Group (1-6). The interview schedule included questions about experience of recruitment to the trial, why they had decided to take part, expectations of the trial, and experience of trial processes (taking the trial medication, experience of trial visits, and experience of completing the trial questionnaires). Interviews were digitally audio recorded and transcribed verbatim. A distress protocol was used to minimise the risk of potential harm. All interviews were conducted by one female researcher (NL) with a medical background, who had completed training in in-depth interviewing. Interviews took place between January 2017 and December 2017.

Analysis

The qualitative interviews were analysed using Braun and Clarke's framework for thematic analysis [29] using NVIVO version 10 (QSR International (UK) Ltd.). Transcripts were read and re-read and then coded inductively for themes relating to; reasons to participate in the trial, reasons not to participate in the trial, reasons to remain in the trial and reasons to discontinue the trial. Results were considered in relation to the core elements of person-centred care and our model of the person-centred trial (figure 1) (32). Three transcripts were double coded by another researcher (SE) who produced their own coding frame. Areas of agreement and disagreement were then discussed until consensus was achieved.

Results

The feasibility trial was open to recruitment between August 2016 and November 2017. Each centre was open for a total of 12 months. 409 patients were screened, 150 were eligible, and 64 randomised. No participants were lost to follow up. 12 participants discontinued treatment prior to day 28, five of whom withdrew from data collection. 63% (n=40) of participants required some help competing the trial questionnaires.

The qualitative interviews were conducted between January 2017 and December 2017. The median time between trial completion and qualitative interview was 83 days (range 1-252). 22 participants were interviewed. 11 had a diagnosis of COPD, 8 ILD, 2 CHF, and 1 lung cancer. The median age was 71 years (range 56-84). 16 were male. 20 had completed the trial, whilst 2 withdrew due to reported adverse effects of the trial medication. The mean interview duration was 33 minutes (range 15-104). Despite the use of convenience sampling, variation was achieved, and we interviewed participants from all 3 research sites, all disease groups, both age and gender categories, with 2 non-completers also participating in interviews. No trial decliners agreed to complete a qualitative interview.

Table 1: Characteristics of participants

	Male	Female
ILD		
<65 years old	1	
>65 years old	5	3*
COPD		
<65 years old	2	1
>65 years old	5	1
CHF		
<65 years old		
>65 years old	2*	
Cancer		
<65 years old		
>65 years old	1	1

*1 did not complete trial

The relationship between patient and professional, potential for benefit, trial processes and the intervention all influenced the decision to participate in the trial. The relationship and continuity with the research team, perceived benefit, and aspects relating to trial processes and the intervention influenced the decision to remain in the trial.

What influenced people to take part in the trial

Approach

The way in which potential participants were approached was important when considering whether to take part in the trial. Many chose to participate because of their relationship with their usual clinician. Being approached by someone familiar appeared to validate the authenticity of the trial. A genuine patient-professional relationship based on open communication, knowledge and skills was valued, and made patients more likely to agree to be contacted by a researcher.

'It came through when I was at the IPF meeting and my consultant was there that day giving a talk so I figured it was bona fide' 1010, Female with ILD >65 years old

'My doctor said 'well try it, anything's worth a try'. Its our GP… we've known him for a while… he's a doctor that listens to you… he's very good like' 1022, Male with COPD >65 years old

The initial encounter with the researcher was key. Clear communication of trial related material established confidence in the research team. Despite some participants having concerns about the expectation that might be placed on them, they felt reassured when the initial assessment was tailored and focused to their individual needs (for example by ensuring that the participant did not feel rushed, and helping them to complete the trial questionnaires). Fundamental was the ability of the researcher to assess and meet these individual needs:

'The interviewers were very pleasant, very helpful, they explained everything to me, and I agreed to it' 1001, Male with COPD >65 years old

'I thought, I hope they're not going to push me too much… but everything was fine, you know, spot on. They understood my needs. People took the time and they listen to you'. 1014, Male with COPD <65 years old

Motivations to take part

The possibility of potential benefit was a large contributing factor when deciding whether to participate in the trial. Most commonly participants described hoping for an improvement in symptoms, above all their breathing. Many viewed the trial as an opportunity to have extra input from clinical services, including additional assessments prior to enrolment, regular monitoring throughout the trial, and being seen by a specialist.

'I was prepared to try anything that would help with me breathing' 1015, Female with COPD >65 years old

'I had a full medical before I started on the course, which was good, it eased my mind' 1015, Female with COPD >65 years old

'They just told us that we would be regularly monitored', 1010, Female with ILD >65 years old

'It opens doors at the hospitals for you, like I've got to see a specialist through it' 1022, Male with COPD >65 years old

For many, living with chronic or refractory breathlessness can be an isolating experience, and therefore the social aspect of participating in the trial was perceived as a potential benefit, with the trial providing an opportunity to meet other people who were in a similar position.

'I was gonna gain in that I would be meeting a few more people' 1009, Male with COPD >65 years old

Participants appeared to understand the concept of randomisation and were mostly accepting of the fact that they may not receive the active medication. However, some participants did express concerns about receiving the placebo medication and missing out on a potential benefit from the active medication.

'I just sort of tried to take it in my stride, whichever I get, I get, cause there's not a lot you can do about it' 1001, Male with ILD >65 years old

'Only if it wasn't the drug… then there might not be a chance of it working' 1008, Male with ILD <65 years old

Altruism was also commonly described, and people wanted to participate to help others, regardless of whether they would experience a direct benefit. One man with COPD explained that he did not expect the trial to help him but hoped it might benefit others in the future. Participants also talked about their individual experience of receiving healthcare, often over a number of years, and many felt that the trial was an opportunity to be involved and give something back to the health service. Some people recognised the importance of clinical trials in the context of research, and wanted to participate to advance science, and help to develop new treatments.

'It won't do me any good but it might help other people in the future, you know. So, my expectations are in the ways that it'll help other people in the future, you know, by me taking a part in these trials' 1014, Male with COPD <65 years old

'I have had some wonderful service from the NHS (National Health Service), and I thought well this is a chance to pay something back by taking part' 1004, Male with COPD >65 years old

'People need to know about these things… if it is going to help then I'll take part in these trials. To, you know, help, help science' 1005, Male with ILD >65 years old

Trial design and the intervention

The trial design was important when deciding whether to participate and attempts to minimise burden were viewed favourably by participants. The opportunity to be visited at home instead of going into hospital was a positive influence and made people more likely to participate in the trial.

'I didn't have to go to the hospital… you do home visits, and that, that made my mind up even more to do it. Because of the struggling to walk and everything else, so I was more than happy' 1003, Male with COPD >65 years old

The intervention was perceived as simple and low risk, and for some it was important that they could continue other disease specific medications but still be part of the trial.

'The taking of the medication was simple, I didn't forget it once.' 1004, Male with COPD >65 years old

'I rang up the hospital and asked, and they said, 'yeah, you'll be ok, ones for your brain and ones for your lungs'' 1010, Female with ILD >65 years old

Whilst some participants expressed concerns about taking an antidepressant medication, this was mostly offset by implicit trust in the clinicians and researchers, and a belief that they wouldn't be given anything which could cause harm.

'That was my thought when they first said antidepressant 'oh, do I want to be taking something like that?' but at the end of the day, they're not going to do anything that's going to put you at any risk' 1020, Male with COPD <65 years old

Although we only interviewed people who had participated in the trial, the interviews did highlight some concerns relating to the intervention. One participant who experienced adverse effects and later withdrew from the trial felt that more information could have been provided about the trial medication.

'It wasn't a great deal of information about the actual drug, to be honest' 1016, Male with heart failure >65 years old

What influenced people to remain in the trial

Importance of the relationship and continuity of care

The importance of the relationship between the participant and the researcher was identified across all interviews and was substantial when considering the reasons why people remained in the trial. Attempts by the researcher to minimise burden and ensure a calm environment were recognised and appreciated by participants. The personal attributes of the researcher were also central to remaining in the trial. Participants described the importance of effective communication, being treated with respect, and not feeling rushed during trial visits.

'I found the people extremely helpful; nothing was too much trouble. Everything was explained in meticulous detail really, it was so easy, everything was done for you, the drugs were all measured out you had the right number for the right days. All I had to do was wake up and pop

the pill, you know. The people were lovely, it was a very very rewarding experience in a lot of ways.' 1020, Male with COPD <65 years old

*'Like *** (research nurse) said, if there's any problems and you can't make it, just give us a ring or anything like that, there's no, you must arrive or that sort of thing. And it's a relaxing place, when you go there, there's no hustle and bustle.' 1013, Male with COPD >65 years old*

'The (research nurses) are absolutely brilliant, and that does make a difference, you know that you're going to walk in… they explain things so well don't they, and they're so patient and you know' 1012, Male with ILD >65 years old

'They ask you a question, but they listen to you, they didn't jump in and try to answer for you. I was number one, you know what I mean' 1014, Male with COPD <65 years old

Continuity was important and enabled participants to build up a relationship with the research team. One participant explained that while they didn't always see the same member of the research team, someone they had met before always made an effort to come and say hello when they arrived.

*'I'd go in and sit down, they'd maybe make me a cup of tea if I was waiting and whatever, then they'd come through. It wasn't always the same person, but *** (research nurse) would pop in and say hello and she'd say so-and-so's seeing you today'. 1020, Male with COPD <65 years old*

In contrast not being given clear trial related information and feeling rushed by members of the research team was reported by one participant who chose to withdraw from the trial. While the participant chose to withdraw due to adverse effects of the trial medication, these other factors may have contributed to this decision.

'It was a bit rushed wasn't it' 1016, Male with HF >65 years old

Perceived benefits

Perceived benefits from the trial medication motivated people to remain in the trial. Participants described improved breathing, but also beneficial effects on sleep, fatigue and appetite, which for some led to increased confidence and an ability to be more active.

Participants also perceived the regular monitoring they received during the trial to be beneficial and describing feeling 'taken care of' during the trial period.

'Everything was so much better. I would sleep better, so if I sleep better that means by breathing is better when I wake up in the morning, which it never was before. Everything has just changed for the better.' 1003, Male with COPD >65 years old

'The follow up has been very good. I was seen at weekly intervals to see how things were progressing, and if there were any problems, so I felt I was being taken care of in terms of the trial' 1017, Male with ILD >65 years old

The social aspect was an additional benefit for many participants and provided an interruption to an otherwise sometimes isolating existence. This was described by participants visited at home but also those who were reviewed in the Clinical Trials Unit.

'I quite enjoyed the experience of having somebody to come in and talk to me' 1001, Male with ILD >65 years old, visited at home

'They could've come to my home, but I prefer to come here cause it gets me out the house for an hour or two… its nice just to come somewhere and as I say, meet different people, see different people, which is half the battle when you, you know' 1014, Male with COPD <65 years old, attended the trials unit

It was important that participants felt actively involved and as though they were contributing to the trial. Knowing that the trial may benefit patients in the future, as well as providing an opportunity for individuals to give back were motivating factors for completing the trial. Several participants described how they found the trial process rewarding on an individual level.

'I just felt as though I was doing some good. It was personally rewarding for me, because I felt as though I was contributing, you know' 1020, Male with COPD <65 years old

Trial processes and the intervention

Aspects relating to the trial design and intervention were also important when considering the reasons why participants remained in the trial. The offer of home visits reduced the burden of participating, and while participants described the questionnaires as straight forward, they were grateful when help was provided.

Being at home was perfect, they were always on time, and prompt. Oh the home visits are quite good you know. Saved me a lot of bother not going to the hospital' 1002, Male with COPD >65 years old

'If there were any problems then they would run me through the questions'. 1020, Male with COPD <65 years old

The intervention was simple and well tolerated and participants found the chart provided a useful reminder. Trial duration was also important with a shorter duration felt to be more manageable.

'It was tablets and I took them every day as I was asked to, um we made a note of them in a chart to make sure I had taken them, it was no problem at all' 1001, Male with ILD >65 years old

'I thought that as it was also only over a 28-day period I thought yeah, I'd, I'd be quite happy to try.' 1010, Female with ILD >65 years old

Adverse effects of the intervention were an important influence for participants discontinuing the trial and were reported by both participants who were interviewed after withdrawing from the trial.

'I just sat up in bed looking at the tablets and thinking, should I chance it tonight or not, because I knew how I might feel a bit groggy the next day, so it put you off taking the tablet' 1019, Female with ILD >65 years old

Discussion

This study identifies important considerations which may influence recruitment and retention in clinical trials. We found that the relationship between patient and professional, potential for

benefit, trial processes and the intervention all influenced the decision to participate in the trial. The relationship with the research team and continuity, perceived benefit, and aspects relating to trial processes and the intervention influenced the decision to remain in the trial. In this trial recruitment targets were met and attrition levels were low, suggesting that a person-centred approach can support successful recruitment and retention.

What influences potential participants to take part in a clinical trial (or not) is recognised to be a complex multifactorial process (34-39). In this study we found that the initial approach by both clinician and researcher was key in developing a genuine relationship built on trust, a concept which has been identified as important when deciding whether to participate in a clinical trial (34, 35, 40). In this study participants described the potential benefit to self and others as a motivating factor, comparable to the findings of previous qualitative research conducted in the palliative care setting (37). While concerns about randomisation and the potential for side effects can be deterrents to participating in a clinical trial (36), this was not a major influencing factor for the participants we interviewed. The trial design was important and attempts to minimise burden were viewed favourably by participants. This is an important consideration as missing data in trials has been shown to increase with the number of questionnaires/ tests (17).

In this study the relationship between the patient and professional was crucial, and particularly important when considering what influenced people to remain in the trial. Feeling listened to, being treated with respect, and having their needs understood were important influences supporting retention. The continuity of the research team was also important, and enabled participants to build up a trusting relationship over the trial duration; one participant referred to this as 'feeling like part of the family'. In addition, participants praised the research team for the extra time taken during trial visits. This ensured that individuals did not feel rushed and allowed assessments to be completed in the participant's own time. These finding have implications for the set-up of research teams across trials. While our results highlight the importance of developing a genuine patient professional relationship, this needs to be balanced so that patients do not feel coerced to take part or remain in a trial. Training and the use of standard operating procedures are also crucial to ensure that assistance with questionnaires is applied in a consistent manner. Although there are often concerns about including people with advanced disease in studies, research suggests that those living with advanced disease want the opportunity to be involved in research, and report it to be a positive experience from which they benefit (41).

The design of the trial and trial processes were also important considerations, particularly for trial retention. It has been suggested that an individualised design, based around individual capabilities, which enables participation alongside the other challenges in life may impact positively on trial retention (19). We applied a person-centred approach by providing clear trial related information, offering home visits, involving the carer, and assisting with trial related questionnaires. PPI was crucial and feedback from representatives ensured that that the trial worked around the patient, and not the other way around.

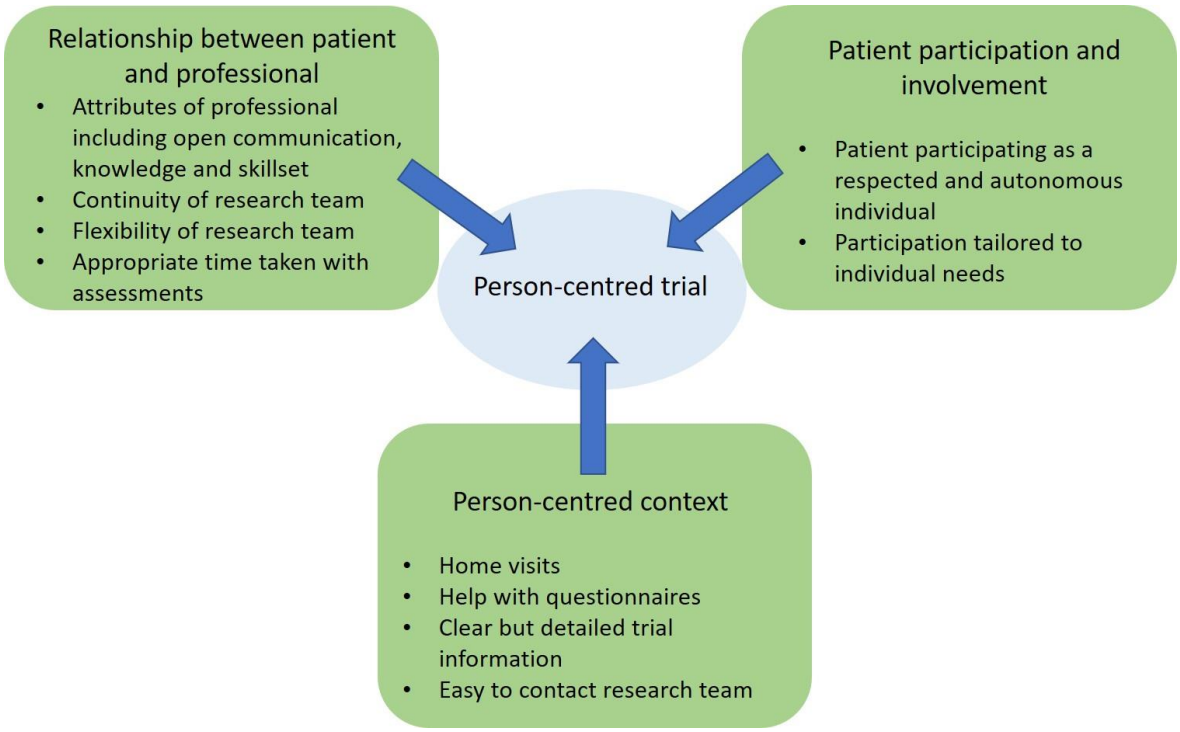
The results of this study have important implications for policy and funding. In our trial a small dedicated research team facilitated a genuine relationship based on open communication, knowledge and the perceived skillset of the researcher. Home visits and spending time with the participant, often helping them to complete trial questionnaires (63% of participants in this trial) was important. Time and resource constraints have been acknowledged as a limitation in other studies and if we are to improve retention within trials we need to ensure that funding allows adequate resource allocation to spend time supporting participants with trial processes (26). While our study suggests a benefit to having the same researchers working across all stages of a trial, current funding models in the UK focus specifically on recruitment and not on retention and therefore the funding for follow-up often needs to be pooled from other budgets (42). In practice, continuity of research staff is not a commonly reported outcome and so it is difficult to know the impact of this across different specialties, and for larger trials. To ensure that the same researchers are able to work across trials funding models need to be revised to rebalance of emphasis of recruitment and retention (43).

It is important to acknowledge that the researchers in our trial all had training and experience working with people living with advanced disease. Participants valued the personal attributes of the professional, a quality which has been identified as critical in person-centred care (32). Characteristics which have previously been identified as important for Palliative Care Professionals include: interpersonal skills, a willingness to listen, being someone the patient feels able to talk to, demonstrating an interest in knowing patients' as people, and recognising that patients may need to feel in control (32, 44). Therefore the attributes of professionals delivering PCC and Palliative Care are closely aligned (45). Increased opportunities for the training of research staff has been highlighted as important if we are to improve retention in clinical trials in the future (20, 43).

So how can PCC be applied to clinical trials in practice?

To improve retention clinical trials need to be individualised, with processes in line with individual capabilities, and considered alongside the other challenges in life (19). We propose that implementing a person-centred approach can support recruitment and retention. Our model focuses on three key areas: development of a genuine relationship between the participant and professional, enabling participation, and ensuring trial processes are person-centred (figure 2). Education and training can help to provide professionals with the required knowledge and skillset and ensure that trial assessments are tailored to the holistic needs of the individual. Continuity of research team provides an opportunity for the researcher and participant to build a genuine relationship during the trial period. Person-centred trial processes such as home visits and helping participants to complete trial related questionnaires helps to minimise the burden for participants.

Figure 2: The Person-centred trial in practice



Strengths and limitations

To our knowledge this is the first study to consider what influences people to take part and more importantly remain in a clinical trial in the context of advanced disease. The study used in depth interviews and despite the use of convenience sampling achieved variation with participants across all characteristics identified to be important. While a single researcher conducted all of the interviews, interpretation bias was minimised by use of a reflexive diary, double coding of a subset of transcripts, and discussion of findings within the research team.

The study was limited by one female researcher (NL) with a medical background conducting all of the interviews. In addition some of the interviewees had met this researcher during the feasibility trial, therefore increasing the risk of social desirability bias, and participants may have been reluctant to offer criticisms about the trial intervention and/ or processes. The time period between the trial ending and a qualitative interview being conducted varied, and this may have increased the risk of recall bias in the qualitative interviews. Some interviews were conducted with a carer present which may have impacted on the answers given. Although we achieved a varied sample of trial participants, we only interviewed two participants who did not complete the trial, and were not able to interview anyone who declined to participate in the trial.

The trial itself was of short duration with an arguably simple intervention and may therefore be perceived as easier in terms of recruitment and retention when compared to a longer trial or one of a complex intervention. However, challenges with recruitment (in part due to eligibility) and high attrition levels have previously been demonstrated in short duration drug trials conducted in people with advanced disease (5). 16 of the interviews were conducted with male patients which is reflective of the main trial participants. This is similar to other trials (46) and may reflect that fact that chronic lung disease has previously been considered to be a condition predominantly affecting men (47). It has however recently been acknowledged that women remain underrepresented in chronic lung disease trials and this should be addressed in future research (48). With an aging population, an increasing number of people are living with chronic and complex conditions and multimorbidity. The findings from our study are therefore relevant and important for clinical trials in the future.

Conclusions

This study identifies important considerations which influenced the decision to participate and remain in a feasibility trial of mirtazapine for chronic or refractory breathlessness. Results

should be considered within the context of the existing literature which suggests an increasing role for a person-centred approach in trials. Patient and public involvement can help to identify how aspects of a trial can be more person-centred and should be incorporated at all stages of trial design. We propose that prioritisation of the relationship between the patient and the professional, ensuring the trial design is as person-centred as possible, and enabling people to participate with processes in line with individual capabilities may improve recruitment and retention in clinical trials in advanced disease. The results of this study have potential implications for the future funding of trials, and highlight the importance of having a dedicated research team who are able to build a genuine relationship with participants throughout the duration of a trial. Our model of the person-centred trial should be considered when designing a clinical trial, ideally at the prefunding stage and involving PPI representatives across all stages of trial development and analysis. Future work should aim to evaluate the application of a person-centred approach to clinical trials in different settings.

Declarations

Abbreviations

Clinical trials unit	CTU
Criteria for reporting qualitative research	COREQ
Chronic Heart Failure	CHF
Chronic Obstructive Pulmonary Disease	COPD
Clinical Trials of an Investigational Medicinal Product	CTIMP
Interstitial Lung Disease	ILD
Modified Medical Research Council Dyspnoea Scale	mMRC
National Institute for Health Research	NIHR
National Institute for Health and Care Excellence	NICE
Patient and Public Involvement	PPI
Person-centred care	PCC
Randomised Controlled Trial	RCT

Ethics approval and consent to participate

Ethical approval was received from the UK Health Research Authority (16/LO/0091). All participants provided written informed consent.

Consent for publication

Not Applicable.

Availability of data and material

Requests for data should be made to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

Funding

This work is independent research funded by Marie Curie, Cicely Saunders International and The Atlantic Philanthropies in the Cicely Saunders Institute Fellowship Programme. NL is completing a training fellowship funded by Cicely Saunders International and Marie Curie (Grant Number A18859). MM is supported by an NIHR Career Development Fellowship (CDF-2017-10-009) and NIHR CLARHC South London. IJH is an NIHR Emeritus Senior Investigator and is supported by NIHR CLARHC South London. This research was supported by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) South London, which is part of the National Institute for Health Research (NIHR), and is a partnership between King's Health Partners, St. George's, University London and St George's Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funding body had no role in the design of the study and collection, analysis and interpretations of data and in writing the manuscript.

Authors' contributions

Concept and development: NL, SE, SB, MM, IJH

Drafting: NL, SE, SB, MM, IJH

Review and approval of final draft: NL, SE, SB, MM, IJH

Acknowledgements

BETTER-B Feasibility is supported by Marie Curie, Cicely Saunders International (CSI) and The Atlantic Philanthropies, led by King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilitation, UK.
Chief Investigator: Professor Irene Higginson
Co-investigators: Dr Vincent Crosby, Dr Simon Hart, Dr Sarah Brown, Dr Louise Flanagan, Professor Surinder Birring, Professor Julia Brown, Professor Miriam Johnson, Professor David Currow, Professor Trevor Sheldon
Centre Principle Investigators: Sabrina Bajwah (London), Simon Hart (Hull), Dr Andrew Wilcock (Nottingham)

We thank all collaborators & advisors including service-users. BETTER-B Feasibility Trial Group members:
Research Nurses/ Clinical Trial Managers: Cathann Manderson, Sarah Farnan, Paramjote Kaler, Caty Pannell, Evelyne Burssens, Kayleigh Brindle, Caroline Wright
Researcher and Lead Qualitative Researcher: Dr Natasha Lovell
Health economist: Dr DeokHee Yi
Statisticians: Hannah Buckley, Sarah Brown
Clinical Trials Research Unit (Leeds): Heather Poad, Emma Best, Victoria Hiley, Heather Cook, Helen Howard
Collaborators: Dr Rohit Lal, Dr Charles Reilly, Dr Anna Gerratt, Dr Frank McCaughan, Dr Matthew Maddocks, Dr Rachael Barton
Main Recruiting Clinicians: Dr Irem Patel, Dr Birring, Dr West, Wai Lam, King's Palliative Care Team/ GSTT Palliative Care Team
PPI members: Mandy Paine, Colleen Ewart, Gerry Bennison, Sylvia Bailey

Pharmacy (King's College Hospital): Stuart Chandler

Research project co-ordinators: Deborah Tonkin, Anna Johnston

References

1. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ open. 2017;7(3):e015276.

2. Bouca-Machado R, Rosario M, Alarcao J, Correia-Guedes L, Abreu D, Ferreira JJ. Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. BMC Palliat Care. 2017;16(1):10.

3. Boland J, Currow DC, Wilcock A, Tieman J, Hussain JA, Pitsillides C, et al. A systematic review of strategies used to increase recruitment of people with cancer or organ failure into clinical trials: implications for palliative care research. Journal of pain and symptom management. 2015;49(4):762-72.e5.

4. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(5):778-88.

5. Fallon M, Hoskin PJ, Colvin LA, Fleetwood-Walker SM, Adamson D, Byrne A, et al. Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(6):550-6.

6. Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. BMJ supportive & palliative care. 2013;3(3):318-23.

7. Rinck GC, van den Bos GA, Kleijnen J, de Haes HJ, Schade E, Veenhof CH. Methodologic issues in effectiveness research on palliative cancer care: a systematic review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1997;15(4):1697-707.

8. Hanson LC, Bull J, Wessell K, Massie L, Bennett RE, Kutner JS, et al. Strategies to support recruitment of patients with life-limiting illness for research: the Palliative Care Research Cooperative Group. Journal of pain and symptom management. 2014;48(6):1021-30.

9. Ewing G, Rogers M, Barclay S, McCabe J, Martin A, Todd C. Recruiting patients into a primary care based study of palliative care: why is it so difficult? Palliative medicine. 2004;18(5):452-9.

10. McWhinney IR, Bass MJ, Donner A. Evaluation of a palliative care service: problems and pitfalls. BMJ (Clinical research ed). 1994;309(6965):1340-2.

11. Jordhoy MS, Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. Palliative medicine. 1999;13(4):299-310.

12. Bajwah S, Ross JR, Peacock JL, Higginson IJ, Wells AU, Patel AS, et al. Interventions to improve symptoms and quality of life of patients with fibrotic interstitial lung disease: a systematic review of the literature. Thorax. 2013;68(9):867-79.

13. Kearney A, Daykin A, Shaw ARG, Lane AJ, Blazeby JM, Clarke M, et al. Identifying research priorities for effective retention strategies in clinical trials. Trials. 2017;18(1):406.

14. Tudur Smith C, Hickey H, Clarke M, Blazeby J, Williamson P. The trials methodological research agenda: results from a priority setting exercise. Trials. 2014;15:32.

15. Brunsdon D, Biesty L, Brocklehurst P, Brueton V, Devane D, Elliott J, et al. What are the most important unanswered research questions in trial retention? A James Lind Alliance Priority Setting Partnership – The PRioRiTy II (Prioritising Retention in Randomised Trials) Study. PREPRINT (Version 1) available at Research Square [+https://doiorg/1021203/rs2439/v1+]. 2019.

16. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer. 2013;119(5):1098-105.

17. Hussain JA, White IR, Langan D, Johnson MJ, Currow DC, Torgerson DJ, et al. Missing data in randomized controlled trials testing palliative interventions pose a significant risk of bias and loss of power: a systematic review and meta-analyses. Journal of clinical epidemiology. 2016;74:57-65.

18. Hussain JA, Bland M, Langan D, Johnson MJ, Currow DC, White IR. Quality of missing data reporting and handling in palliative care trials demonstrates that further development of the CONSORT statement is required: a systematic review. Journal of clinical epidemiology. 2017;88:81-91.

19. Skea ZC, Newlands R, Gillies K. Exploring non-retention in clinical trials: a meta-ethnographic synthesis of studies reporting participant reasons for drop out. BMJ open. 2019;9(6):e021959.

20. Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. Trials. 2014;15:399.

21. Mullins CD, Vandigo J, Zheng Z, Wicks P. Patient-centeredness in the design of clinical trials. Value Health. 2014;17(4):471-5.

22. Crocker JC, Ricci-Cabello I, Parker A, Hirst JA, Chant A, Petit-Zeman S, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. BMJ (Clinical research ed). 2018;363:k4738.

23. Sidani S, Fox M, Collins L. Towards Patient-Centered Clinical Trial Designs. European Journal for Person Centered Healthcare. 2017;5(3):300-7.

24. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, et al. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials - a work in progress. Res Involv Engagem. 2016;2:15.

25. Nilsen ES, Myrhaug HT, Johansen M, Oliver S, Oxman AD. Methods of consumer involvement in developing healthcare policy and research, clinical practice guidelines and patient information material. Cochrane Database Syst Rev. 2006(3):Cd004563.

26. Chhatre S, Jefferson A, Cook R, Meeker CR, Kim JH, Hartz KM, et al. Patient-centered recruitment and retention for a randomized controlled study. Trials. 2018;19(1):205.

27. Higginson IJ. Research challenges in palliative and end of life care. BMJ Supportive & Palliative Care. 2016;6(1):2-4.

28. Visser C, Hadley G, Wee B. Reality of evidence-based practice in palliative care. Cancer Biol Med. 2015;12(3):193-200.

29. Kane PM, Murtagh FE, Ryan K, Mahon NG, McAdam B, McQuillan R, et al. The gap between policy and practice: a systematic review of patient-centred care interventions in chronic heart failure. Heart failure reviews. 2015;20(6):673-87.

30. Burton CD, Entwistle VA, Elliott AM, Krucien N, Porteous T, Ryan M. The value of different aspects of person-centred care: a series of discrete choice experiments in people with long-term conditions. BMJ open. 2017;7(4):e015689.

31. Chenoweth L, Forbes I, Fleming R, King MT, Stein-Parbury J, Luscombe G, et al. PerCEN: a cluster randomized controlled trial of person-centered residential care and environment for people with dementia. International psychogeriatrics. 2014;26(7):1147-60.

32. Kitson A, Marshall A, Bassett K, Zeitz K. What are the core elements of patient-centred care? A narrative review and synthesis of the literature from health policy, medicine and nursing. Journal of advanced nursing. 2013;69(1):4-15.

33. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2007;19(6):349-57.

34. Biedrzycki BA. Decision making for cancer clinical trial participation: a systematic review. Oncology nursing forum. 2010;37(6):E387-99.

35. Biedrzycki BA. Factors and outcomes of decision making for cancer clinical trial participation. Oncology nursing forum. 2011;38(5):542-52.

36. White CD, Hardy JR, Gilshenan KS, Charles MA, Pinkerton CR. Randomised controlled trials of palliative care - a survey of the views of advanced cancer patients and their relatives. European journal of cancer (Oxford, England : 1990). 2008;44(13):1820-8.

37. Gysels M, Shipman C, Higginson IJ. "I will do it if it will help others:" motivations among patients taking part in qualitative studies in palliative care. Journal of pain and symptom management. 2008;35(4):347-55.

38. Ulrich CM, Ratcliffe SJ, Wallen GR, Zhou QP, Knafl K, Grady C. Cancer clinical trial participants' assessment of risk and benefit. AJOB empirical bioethics. 2016;7(1):8-16.

39. Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Quality in health care : QHC. 2001;10 Suppl 1:i2-8.

40. Bayly J, Edwards BM, Peat N, Warwick G, Hennig IM, Arora A, et al. Developing an integrated rehabilitation model for thoracic cancer services: views of patients, informal carers and clinicians. Pilot Feasibility Stud. 2018;4:160.

41. Gysels MH, Evans C, Higginson IJ. Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. BMC Medical Research Methodology. 2012;12(1):123.

42. Department of Health. Attributing the costs of health and social care Research & Development (AcoRD). 2012.

43. Daykin A, Clement C, Gamble C, Kearney A, Blazeby J, Clarke M, et al. 'Recruitment, recruitment, recruitment' - the need for more focus on retention: a qualitative study of five trials. Trials. 2018;19(1):76.

44. Johnston B, Smith LN. Nurses' and patients' perceptions of expert palliative nursing care. Journal of advanced nursing. 2006;54(6):700-9.

45. Saunders DC. Social work and palliative care—the early history. The British Journal of Social Work. 2001;31(5):791-9.

46. Currow DC, Ekstrom M, Louw S, Hill J, Fazekas B, Clark K, et al. Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial. Eur Respir J. 2019;53(1).

47. Barnes PJ. Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms. Am J Respir Crit Care Med. 2016;193(8):813-4.

48. Gut-Gobert C, Cavailles A, Dixmier A, Guillot S, Jouneau S, Leroyer C, et al. Women and COPD: do we need more evidence? Eur Respir Rev. 2019;28(151).

Chapter 9 –Discussion

9.1 Main findings

This thesis aimed to explore the feasibility of, and ways to optimise recruitment, retention, and outcome measures in a double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness. The thesis found that a person-centred approach was recognised and valued by participants and appeared to support trial recruitment and retention. Key aspects of the person-centred trial included: prioritisation of the relationship between the patient and professional; person-centred processes including home visits, assistance with questionnaires, and involvement of the carer; and enabling people to participate by having processes in line with individual capabilities. The results from my mixed-methods study found that change in experience of breathlessness was commonly captured by the NRS worst, NRS average and CRQ. The NRS worst appeared to capture change most frequently out of all the measures. A key finding was that the NRS worst appeared to capture changes across multiple domains suggesting that although it is a single item measure, it is possible that is measures more than one construct. Future work should ensure the validity of this specific format of question, however, from this study the NRS worst appears to be the most useful outcome measure in this type of trial, and for this type of intervention.

This is important because chronic or refractory breathlessness is common, distressing, under researched, and lacking effective treatments (5-7, 12, 16, 27). New treatments are needed, but to evaluate these successfully we need to be able to deliver trials and have the right outcome measures (71, 72, 131). Although a number of PROMs have been validated to assess breathlessness there remains little consensus about which to use and when (71, 131, 132). There is also uncertainty about the extent of which currently used outcome measures capture the changes which are important to people. To determine the effectiveness of new treatments clinical trials are needed, which involves recruiting and retaining people. Conducting research among people with advanced disease presents challenges, including; difficulty recruiting participants, high attrition rates, and unpredictable disease trajectories (22, 23, 89, 90, 99, 100, 116, 133). This thesis aimed to fill this evidence gap and provide recommendations on how to optimise recruitment, retention and the selected outcome measures in a randomised controlled drug trial for chronic or refractory breathlessness.

9.2 How the concerns of people living with breathlessness inform outcome measurement

9.2.1 The main concerns of people living with breathlessness

A first key step in the thesis was to understand what the concerns of people living with breathlessness are and how important changes might be captured using outcome measures. The choice of outcome measure in a randomised controlled drug trial for chronic or refractory breathlessness is key and needs to capture the concerns that matter to those experiencing it, but also be able to detect any effect of the intervention. Previous qualitative studies have explored the experience of living with breathlessness, often with the purpose of identifying unmet need (80-82), exploring experience of care and access to services (83-85), and understanding the impact on carers (16, 86).

I conducted a thematic synthesis of the concerns of people living with advanced disease and experiencing breathlessness with the aim of informing outcome measurement. During my systematic search I did not identify any studies which had previously attempted to do this. Therefore, my review made an original contribution to the field. Thirty-eight studies were included with a total of 672 participants. My systematic review found that people with advanced disease living with breathlessness have concerns across six domains; 1) the physical symptoms of breathlessness and subsequent effect on function; 2) the emotional impact; 3) the spiritual distress experienced; 4) the social impact of breathlessness; 5) concerns relating to aspects of control; and 6) the context of breathlessness (acute episode or chronic). The main concerns were comprehensive and wide ranging extending far beyond a single episode of breathlessness and impacting significantly on those around them.

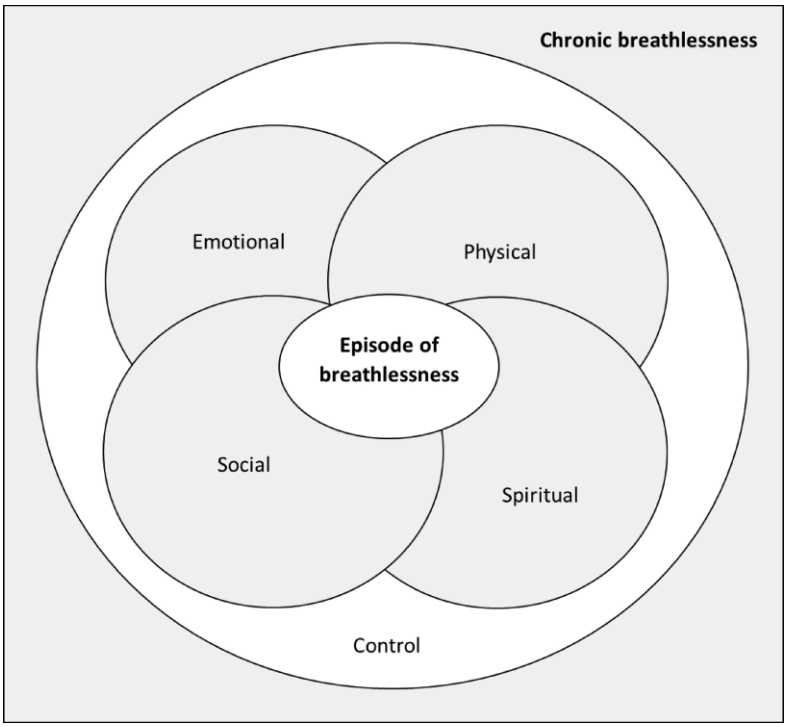
9.2.2 Model of total breathlessness

While conducting the thematic synthesis I considered how concerns mapped onto existing models of breathlessness. The model of 'total dyspnoea' was proposed by Abernethy and Wheeler in 2008 and based on the concept of 'total pain' (134, 135). The model considers the experience of breathlessness across physical, psychological, social and spiritual domains but was not based on any published breathlessness literature. During the process of thematic analysis themes were generated, many of which appeared to fit within the model of 'total

dyspnoea'. However, I also identified important themes which did not fit within this model. I therefore decided to further develop the model, based on that of 'total dypsnoea' but incorporating the additional findings.

This final model of 'total breathlessness' included six domains; physical, emotional, spiritual, social, control, and context (Figure 4)(87). Psychological was changed to emotional to reflect the significance of emotions as part of the experience of breathlessness in the qualitative data. Control and context were also added as new domains. Participants described the importance of control during an immediate episode of breathlessness where a lack of control often resulted in crisis help-seeking. Control was also described in the wider context of a person's life, in particular the unpredictability of breathlessness made it difficult to make definitive plans or be spontaneous. Context was also added as a domain. Participants described concerns relating to an episode of breathlessness and also in the wider context of living with chronic or refractory breathlessness. The context of a concern was important and could shape an individual's response. If clinicians understand the context within which a concern is positioned, they may be more able to tailor management strategies, and enhance coping for patients. While concerns can be described within a single-domain, most are not exclusive to one, and there is a considerable overlap between domains as demonstrated in the model.

Figure 4: Model of 'total breathlessness'(87)



9.3 Similarities and differences between thematic synthesis and mixed methods study: Implications for outcome measurement

My thematic synthesis identified that people with advanced illness experiencing breathlessness describe concerns across multiple-domains (87). To meet the aim and objectives of this thesis it was next important to explore what outcomes are important to participants in a drug trial for chronic or refractory breathlessness and to what extent these are captured using standard measures. If we accept that breathlessness is a multidimensional experience, and people experiencing breathlessness describe concerns across multiple-domains, then a multiple-domain outcome measure may be most likely to capture this range of concerns. Patient report is considered the gold standard for assessing breathlessness and therefore a mixed methods study was considered the most appropriate method to test this hypothesis (136).

I conducted a mixed methods study embedded within a randomised trial comprising qualitative interviews conducted at the end of the trial, and outcome measure data collected pre and post intervention. Participants were asked about whether they had perceived a change during the trial period, and if so what had changed. Change in patient experience of breathlessness in the qualitative interviews was then compared at an individual level to the change score for three commonly used outcome measures; the CRQ (a multiple-domain measure); the NRS worst and the NRS average (both single domain measures). These measures were chosen based on current guidance which recommends combining a single-domain measure with a multiple-domain measure in breathlessness research (71, 72).

Participants described important changes in their experience of breathlessness across multiple domains during the trial supporting the model of 'total breathlessness'. Changes in the qualitative data were commonly captured in all three outcome measures. There was agreement between the qualitative data and the CRQ in 15 of 21 cases, the NRS average in 16 of 21 cases, and the NRS worst in 18 of 21 cases. These findings were slightly unexpected considering the findings of my thematic synthesis which appeared to suggest that a multidimensional measure would be most likely to capture concerns across the multiple domains of 'total breathlessness'. In fact, both NRS measures did well, and the NRS worst appeared to capture change most frequently out of all the measures.

It is helpful to consider why this might be. Although our model of 'total breathlessness' could be incorrect, previous research describes breathlessness as being 'derived from interactions between physiological, psychological, social, and environmental factors' which would support the domains of our model (1). Also, in the qualitative interviews trial participants described important changes in their experience of breathlessness across the six domains of 'total breathlessness'. We should also consider whether the questions asked in the qualitative interviews were the right ones, and whether this may have impacted on the results. Within our topic guide participants were asked to describe if the drug had changed how they felt. Participants were then sometimes prompted with questions about their breathing, sleep, appetite or drowsiness. However, no specific questions were asked which related to the six domains of 'total breathlessness' so it seems unlikely the questions impacted on our results. I will now consider the results for each of the measures.

9.3.1 Chronic Respiratory Questionnaire

The CRQ is a twenty-item health-related quality of life questionnaire originally validated through a series of studies spanning item development, reproducibility, and responsiveness (77, 137). In this trial the CRQ was completed at baseline, day 14 and day 28, and a change score was calculated from baseline to day 28. Results from my mixed-methods study found that change in experience in the qualitative data was captured in at least one domain of the CRQ for 15 of the 22 participants, most commonly the emotion or mastery domain, and least commonly the dyspnoea domain.

When a change was perceived in the qualitative data, a clinically important change score was most commonly seen in the emotion or mastery domain of the CRQ. This could be because the intervention for the trial was an antidepressant medication, and therefore the mechanism of action may have led to changes across these domains. Change in patient experience was less commonly captured in the dyspnea domain. This section of the questionnaire asks participants to identify five important activities and saw how short of breath each activity makes them feel. Our trial recruited people severely affected by breathlessness with an mMRC score grade 3 or 4. This equates to 'I stop for breath after walking 100 yards or a few minutes on the level', or 'I am too breathless to leave the house or become breathless while dressing'. It is therefore possible that despite an improvement in their experience of breathlessness, the activities in the dyspnea domain continued to cause severe shortness of breath, and therefore scores for

this domain did not reflect a clinically important change. It is therefore important to consider the validity of the measure for this population and in this type of trial.

9.3.2 Numerical Rating Scale

Some validity of the NRS as a measure of breathlessness was first proposed in 1998 in a study published by Gift et al. (73). In this study the scale was anchored with 0=no shortness of breath, and 10=shortness of breath as bad as can be, accompanied with the statement: 'Indicate how much shortness of breath you are having right now'. The validation was based on correlation of NRS scores in comparison to Visual Analog Dyspnea Scale scores in patients with COPD at rest and following exercise. The validation was limited with no test of content validity or reliability. Increasingly the NRS is adopted as a primary outcome measure in breathlessness trials, but often accompanied by a different statement or question (Appendix 10: Wording of NRS Across Studies). Two common iterations are the NRS average accompanied by the question 'How has your breathlessness been over the last 24 hours on average?', and the NRS worst accompanied by the question 'What is the worst your breathlessness has been over the last 24 hours?'. Yet based on a search of the literature up until December 2019 neither of these iterations of the NRS have been subjected to rigorous psychometric testing (138).

Results from my mixed-methods study found that change in experience in the qualitative data was captured in the NRS average in 16 of 21 cases, and the NRS worst in 18 of 21 cases. In this study the NRS average appeared to capture changes in the physical domain consistently. In comparison the NRS worst appeared to capture changes across multiple-domains including physical, emotional, spiritual, social, and control. It is therefore possible that the NRS worst is measuring more than one construct despite being a single-item outcome measure. These findings also suggest that the statement/ question which accompanies the NRS 0-10 scale might impact on what construct is being measured.

9.3.3 Use of the numerical rating scale in pain and how might this inform use in breathlessness

Given that the NRS is commonly used in breathlessness research it is helpful to consider the wider use of it. Numerical rating scales are increasingly used to assess symptoms and are the most common outcome measure in pain research (139). However, a systematic review of studies assessing pain intensity identified similar discrepancies in how numerical rating scales

are used, often varying in length, the time period asked about, number of response options and verbal descriptors (140). The review highlights the importance of psychometric testing, and suggests that consistency of wording, time frame, and format is important, particularly if comparisons are to be made (140).

The Brief Pain Inventory (BPI) is perhaps the most commonly used outcome measure in pain research, shown to capture three dimensions of pain; severity, activity interference, and affect interference (141). All statements use a 0-10 numerical rating scale, the severity questions anchored with 0 = no pain and 10 = pain as bad as you can imagine it, and the interference questions anchored with 0 = does not interfere and 10 =completely interferes. The measure includes four severity items and seven interference items, and has undergone extensive psychometric testing including; content, criterion, and construct validity; internal consistency, and test-retest reliability (142-144). While the three dimensions have been shown to be interpretable across different levels of pain severity in psychometric testing (mild, moderate and severe), they were prominent and interfered with most when pain was severe (143). In addition, the 'pain at its worst' item of the BPI has been shown to correlate best with functional interference score (145).

This suggests that outcome measures which ask about 'worst' or 'most severe' pain incorporate several dimensions of pain and not just severity. This is supported by research conducted in patients with mesothelioma who were asked about the concept of worst pain (146). One participant stated I 'would mark 10 if the pain was so intense that I was unable to essentially perform the tasks in my life' (146). In another study nursing students described worst pain to include emotion and existential distress, and represent more than just pain (147).

The results from my mixed methods study support a similar pattern in breathlessness and suggest that when we ask people about their worst breathlessness this encompasses more than just breathlessness severity. This could be because breathlessness is subjective and the experience for one individual is different to another. Therefore 'worst breathlessness' for one person may focus predominantly on the physical limitations, but for someone else it may be the emotions experienced, or the social impact which are the distinguishing elements. Therefore, asking about 'worst pain' or 'worst breathlessness' might be interpreted individually based on what is important to the person. The results of this study suggest that the NRS worst using the question ''How bad has your breathlessness felt at its worst over the past 24 hours?'' is able to capture change in patients' experience of breathlessness across

domains known to be important to patients, and support its use as a primary outcome measure for this type of trial and this type of intervention.

9.3.4 Implications for outcome measures in breathlessness

The results from my mixed methods study has identified important questions about the terminology used to describe outcome measures in breathlessness, and how these measures are validated. As discussed in chapter 3, while many measures have been developed to assess and measure breathlessness, there remains little guidance about which to use and when (71, 72, 131). The terminology used to describe these measures remains inconsistent and measures like the NRS have been described as single item, single domain and unidimensional in the literature (1, 71). The results of my mixed methods study suggest that while the NRS is a single item measure, it is most likely capturing more than one construct, and should therefore not be described as a single domain or unidimensional measure.

The results of my mixed methods study also raise questions about how outcome measures in breathlessness are validated. While the NRS is increasingly adopted as a primary outcome measure in breathlessness trials, the original validation work was solely based on correlation of score to the Visual Analog Dyspnea Scale and included no test of content validity or reliability (73). Ideally the psychometric evaluation of a measure will include an assessment of validity, internal consistency, reliability, responsiveness, and interpretability. However, systematic review shows that many measures have not been adequately evaluated (148). To determine the effectiveness of breathlessness interventions we need to have valid measures, but more importantly we need to know what we are measuring. While the NRS worst appears to be the most useful outcome measure in this type of trial and for this type of intervention future work should aim to determine the psychometric properties of this measure.

9.4 Feasibility of a randomised controlled trial for chronic or refractory breathlessness in advanced disease

This thesis also aimed to explore the experience and feasibility of trial processes and what influences participants to take part and remain in a drug trial for chronic or refractory breathlessness. Feasibility of the trial was considered using screening and recruitment data as well as results from my qualitative interview study conducted at the end of the trial. I first discuss the findings from the screening and recruitment data. I then discuss the results from

my qualitative study including what influenced participants to take part and remain in our trial of mirtazapine for chronic or refractory breathlessness.

9.4.1 Screening and recruitment

The screening to recruitment ratio for our trial was 6.4 to 1, which is favourable compared to other randomised controlled trials in palliative care, some of which report a screening to recruitment ratio as high as 15 to 1 (128, 129). It is interesting to consider why this might be. One key difference in the screening and recruitment data in our trial compared to others also conducted in advanced disease is the proportion of ineligible patients at the screening stage. In our trial the number of ineligible patients screened was quite low, only 259 people out of a total of 409. Guidance for the reporting of randomised controlled trials in palliative care states that all potential cases should be identified and reported (91). However, in our trial it was unrealistic for the research team to screen every patient in every clinic or on every hospital ward due to limited resources. Therefore, screening data relied on the clinicians based in each individual setting. It is therefore possible that some potential participants were not identified and/ or referred into the trial. It is also possible that clinicians pre-screened patients and only referred in those they considered to be eligible.

The reporting of screening and recruitment data in randomised controlled trials is inconsistent despite CONSORT stating that the number of people assessed for eligibility in a trial should be reported (149). In a recently published double blind randomised controlled trial of sertraline for symptomatic chronic breathlessness, it was reported that out of 249 people screened 223 were randomised. This is a very low screening to recruitment ratio particularly for this population, and I would expect there was a pre-screening stage which has not been reported for this study (64). The SEAR (Screening, Eligibility, Approach and Randomisation) framework was developed with the aim of standardising what is recorded during the recruitment process (150).

Randomised controlled trials often have strict inclusion and exclusion criteria and it can be challenging to identify eligible participants to recruit. However, if the inclusion and exclusion criteria is not specific enough, the population can become too heterogeneous for the question being asked. A recently reported double blind randomised placebo-controlled trial of sustained-release morphine describes making changes to their eligibility criteria due to insufficient recruitment. The trial has originally planned to recruit people with an mMRC score

of 3 or more, however, due to insufficient recruitment this was changed to include those with a score of 2. The trial found no difference between the two arms, however people with COPD and an mMRC score of 3 or 4 had a statistically and clinically significant reduction in their worst breathlessness score (151-153). This supports other research which found that it is those most severely affected by breathlessness who are most likely to benefit from opioids (61). These findings demonstrate the importance of selecting the right population when designing a clinical trial (151-153).

Most of the participants in our trial were recruited from outpatient clinics or through database screening and not from inpatient wards. This is different to previous studies in advanced disease which have reported the highest recruitment from hospital inpatients and lowest from the community (95). To be eligible for our trial participants were required to be clinically stable with no changes to the management of their underlying condition within the last week. Therefore, it is not that surprising that we did not recruit many participants from acute hospital wards. We focused on attending outpatient clinics which were more likely to have stable and therefore eligible participants, having a presence in the clinic setting is a strategy which has been shown to lead to higher levels of recruitment (95).

Recruitment from the oncology setting proved particularly difficult and most of the participants in our trial had a diagnosis of chronic lung disease, either COPD or ILD. There appeared to be several reasons for the low intake of participants with a cancer diagnosis in our trial. Firstly, there seemed to be reluctance from the oncology clinicians to refer patients into the trial. Informal feedback suggested that clinicians felt their patients 'weren't ready' for a palliative care trial and that by referring them they would somehow be 'giving up on them'. This is supported by the findings of other trials in advanced disease, in which gatekeeping has been identified as a significant issue which can affect accrual rates (90, 154-156). It also seemed that this group of patients were focused on different priorities at this time (for example getting well enough so that they could be given an anticancer treatment).

Finally, patients were only eligible for the trial if they were not currently receiving any anticancer treatment. Recruitment at the London site was from a tertiary cancer centre, and therefore it was unlikely to identify patients not currently receiving anticancer treatments. Ineligibility due to concurrent anticancer therapy was the commonest reason for ineligibility in a large observational multicentre palliative care study recently conducted (90). These findings could reflect advancements in cancer treatments, and the development of oral treatments, which may therefore continue until much later in the disease process.

9.4.2 What influences participants to take part and remain in a drug trial for chronic or refractory breathlessness

I also wanted to understand what influences participants to take part and remain in a in a drug trial for chronic or refractory breathlessness. As discussed in chapter 3 recruitment and retention in clinicals trials remains an important challenge which can impact on the validity of results by introducing bias and reducing power. What influences people to take part in a clinician trial (or not) is recognised to be a complex and multifactorial process (157-161). Retention is also important, although far less researched, and has been identified to be a top priority (96-98), with high levels of attrition a well-recognised problem (23, 99, 116). To meet this objective, I conducted a qualitative study at the end of the trial. My qualitative study identified important considerations which may have influenced recruitment and retention in our trial. Prioritisation of the relationship between the patient and professional, ensuring a person-centred trial design, and enabling people to participate by having processes in line with individual capabilities appeared to successfully support recruitment and retention. These results are now discussed in the context of the wider literature.

9.4.3 Influences on recruitment

My qualitative study found that the relationship between the patient and professional, potential for benefit, trial processes, and the intervention all influenced the decision to participate in the trial. The relationship between the patient and professional was important and trial participants described how being approached by their usual clinician appeared to validate the authenticity of the trial. The initial encounter and subsequent relationship with the research team was also important, and clear communication of trial related material established confidence in the research team. Trust in healthcare professionals and the quality of information provided are both identified in the literature as being important factors that influence trial participation (157, 158). In this study participants described the value of having clear yet detailed trial related information. Previous research has shown that the communication of complex trial related information is crucial to participation (159), and that participants value having additional written information which is accessible and they can revisit easily (161). This does however, need to be balanced alongside findings that lengthy information sheets can cause distress (88).

The possibility of potential benefit was a large contributing factor when deciding whether to participate in our trial. Some participants described being prepared to 'try anything' to help with their breathing, reinforcing quite how distressing it can be to live with chronic or refractory breathlessness. This is similar to findings from a questionnaire study of patients approached about participation in a clinical trial, which identified that motivations for trial participation included potential personal benefit and belief that the trial offered the best treatment available (162). Our trial was viewed by some as an opportunity to receive additional clinical input, with increased monitoring and the opportunity to be reviewed by a specialist. This supports findings from a questionnaire study conducted with women with breast cancer, in which participants described the perceived benefits of having extra scans and blood tests as part of the trial (161).

For many, living with chronic or refractory breathlessness can be an isolating experience, and therefore the social aspect of participating in the trial was perceived as a potential benefit, with the trial providing an opportunity to meet other people including those who were in a similar position (for those attending the trials unit). Those living with advanced disease have previously described 'having someone to talk to' as a motivation to take part in research (160). Participants in this qualitative study also talked about their individual experience of receiving healthcare, and many felt that the trial was an opportunity to be involved, give something back to the health service, and advance science. This supports previous work in which altruism has been identified as a key motivator for trial participation (159-161).

Trial processes and the intervention were also important influences for participation in our trial. The opportunity to be visited at home made people more likely to take part in the trial by minimising the burden of needing to travel. The trial design enabled patients to continue disease specific drugs which was a positive influence on trial participation. Interestingly the concept of randomisation was not described as a deterrent to participating as it has been in previous studies (159). In our study the intervention was perceived as simple and low risk, particularly because the trial drug was an already established medication licensed for the treatment of depression. Some participants described initial concerns about taking an antidepressant medication, however, this was mostly offset by implicit trust in the clinicians and researchers, and a belief that they wouldn't be given anything which could cause harm. In our study there was a perceived low risk of harm or side effects from the trial medication, which is important, as invasiveness of an intervention and potential for side effects have both been shown to be deterrents to participating in randomised trials (159, 161).

9.4.4 Influences on retention

The relationship and continuity of the research team, perceived benefit, and aspects relating to trial processes and the intervention all influenced the decision to remain in the trial. The importance of the relationship between the participant and the researcher was identified across all interviews in my study and was substantial when considering the reasons why people remained in the trial. The personal attributes of the researcher were key, and participants described the importance of effective communication, being treated with respect, and not feeling rushed during trial visits. Continuity was also important and enabled participants to build up a stronger participant-professional relationship.

My findings support those from a study conducted across clinical trials units in the UK, which aimed to assess current practice of interventions to improve recruitment and retention and identify future priorities (163). The study comprised a survey and workshop with staff members, and the findings highlight perceived importance of building and maintaining relationships with patients to improve retention within trials. Additionally the study recommends training for staff as a priority, particularly focusing on communication skills and identification of patient priorities (163). All of the researchers in our trial had training and experience working in palliative care and with people living with advanced disease. Characteristics which have previously been identified as important for palliative care professionals include: interpersonal skills, a willingness to listen, being someone the patient feels able to talk to, demonstrating an interest in knowing patients' as people, and recognising that patients may need to feel in control (164). It is therefore possible that previous training in communication skills and the personal attributes of our research team improved retention in our trial.

Perceived benefits from the trial medication motivated people to remain in the trial. Participants described improved breathing, but also beneficial effects on sleep, fatigue and appetite, which for some led to increased confidence and an ability to be more active. Participants also perceived the regular monitoring they received during the trial to be beneficial and describing feeling 'taken care of' during the trial period. Research has shown how the perceived benefits of additional monitoring can influence recruitment into clinical trials (161), and while I cannot find any evidence that this also supports trial retention it seems a logical consideration.

Aspects of the trial design and intervention were also important when considering whether to remain in the trial. Participants described the importance of assessments being tailored and focused to their individual needs. The options for home visits and assistance with trial related questionnaires minimised the burden and were valued by participants. The intervention was perceived as being simple, well tolerated and participants found the chart provided a useful reminder. Trial duration was also important with a shorter duration felt to be more manageable. These findings supports those from a meta ethnographic synthesis of qualitative data in trials, and proposes that an individualised design, based around individual capabilities, which enables participation alongside the other challenges in life may impact positively on trial retention (100).

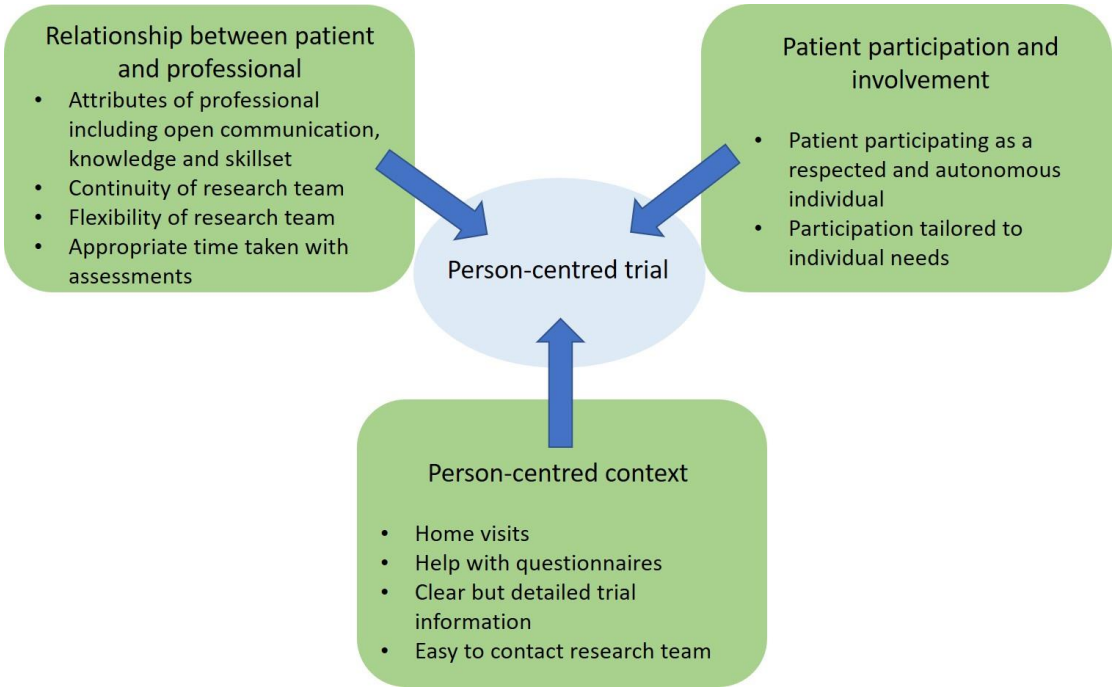
These findings have important implications for policy and funding. In our trial a small dedicated research team facilitated a genuine relationship with trial participants based on open communication. Home visits and spending time with the participant, often helping them to complete trial questionnaires was important. Time and resource constraints have been acknowledged as a limitation in other studies and if we are to improve retention within trials we need to ensure that funding allows adequate resource allocation to spend time supporting participants with trial processes (165). Our study suggests a benefit to having the same researchers working across all stages of a trial, however, current infrastructure funding models in the UK (Clinical Research Networks) focus specifically on recruitment and not on retention and therefore the funding for follow-up often needs to be pooled from other budgets (166). To ensure that the same researchers are able to work across clinical trials funding models need to be revised to rebalance of emphasis of recruitment and retention (167).

It is important to note that while there is an increasing literature around retention in clinical trials, the majority is review work which focuses on strategies to improve retention in questionnaire studies, for example though monetary incentives (168). Some primary studies have been conducted with staff from clinical trials units, however, there remains an absence of primary research focusing on trial retention with patients or trial participants themselves. To improve retention in clinical trials there is an urgent need for good quality primary studies which explore the barriers and enablers to trial retention from the participants perspective (100).

9.4.5 A person-centred care approach to recruitment and retention

Our trial design aimed to optimise recruitment and retention by using a person-centred approach (Figure 5), which has been shown to enable engagement and improve patient outcomes in advanced disease (169-171) The design aimed to put the patient at the centre of the trial, and minimise study burden, therefore enabling participants to be actively involved and able to participate. We focused on developing a genuine relationship between the researcher and participant, with emphasis on continuity. All members of the research team had experience of working with participants with advanced disease. Burden from the trial was minimised by offering home visits and helping participants to complete trial related questionnaires to ensure a supportive system. In this trial recruitment targets were met and attrition levels were low, suggesting that a person-centred approach can support successful recruitment and retention.

Figure 5: The person-centred trial, Lovell et al. 2020



9.4.6 The intervention

The findings from my qualitative data indicate that the trial medication was straight forward to take and well tolerated with few perceived adverse effects. One participant, however, did express concerns about the size and colour of the over encapsulated capsule, which was red, a colour they associated with danger. While over-encapsulation is commonly used in blinded

clinical trials, it does increase the size of the original dosage form, potentially making administration more difficult (172). The findings from this feasibility trial have recently contributed to a successful funding application for a full-scale trial. One of the changes in the full trial is that the placebo capsules will match the appearance of mirtazapine and not be over encapsulated, and therefore no larger in size or a different colour.

We anticipated that some people might have concerns about taking an antidepressant medication. Qualitative interviews have identified a number of concerns for those being commenced on antidepressant medications including: the stigma around being diagnosed with depression and what others might think, concerns about taking a mind altering drug, the risk of side effects, and worries about addition and dependency (173). However, of the 83 people who declined to participate in the trial only 11 (13%) gave the reason that they did not like the thought of an antidepressant. While I only interviewed people who took part in the trial, some participants did express feeling apprehensive about the trial drug being an antidepressant medication. Some participants stated that they did not feel depressed, and therefore queried whether they should take an antidepressant. Others were concerned about potential side effects. These concerns were generally offset by trust in the clinicians and researchers, and a belief that they wouldn't be given anything which could cause harm.

The repurposing of existing inexpensive medications that are off patent and therefore widely available is an attractive option and has been effective in other areas of palliative care, for example antidepressants to treat pain (174). It offers an opportunity to deliver improved symptom control in a timely manner. As discussed in chapter 2 the mechanism of action of mirtazapine means it may be able to improve chronic or refractory breathlessness by modifying the processing and perception of afferent information in the brain (175). However mirtazapine is also being considered as a treatment for other symptoms in people with cancer including: nausea, pain, anxiety and sleep disorders (Appendix 11) (176). It is important to acknowledge that we do not currently have the evidence to support the use of mirtazapine in the treatment of chronic or refractory breathlessness, and patients should not be given medications which are ineffective and could cause harm. However sometimes even without definitive evidence, medications are prescribed off label, often for an unapproved indication, age group, dose, or route of administration, and a study of an inpatient palliative care unit identified that one third of prescriptions were done off label (177). Blinded randomised controlled trials are therefore urgently needed to provide appropriate evidence on the effectiveness of mirtazapine in reducing chronic of refractory breathlessness.

9.4.7 The changing terminology of breathlessness

The terminology used to describe breathlessness is evolving and remains inconsistent in the literature as the debate continues. The ATS definition of 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity' is perhaps most commonly referred to and includes all experiences of breathlessness(1). The terms intractable or refractory breathlessness were introduced to describe a more specific experience, where breathlessness persists despite treatment of the underlying disease (2, 30, 35). When I initially started working on this thesis intractable or refractory breathlessness were commonly referred to in the literature, and this is reflected in the title for our feasibility trial, 'Better Treatments for Refractory Breathlessness'. Around the same time the word chronic was also introduced into the literature and used to describe breathlessness lasting a specified period, commonly three months (32). However, in 2013 Simon et al described a new classification of breathlessness during which a person experiences a severe worsening of breathlessness intensity beyond the usual fluctuations in their perception (34).

The term 'chronic breathlessness syndrome' has recently been proposed following a Delphi exercise and aims to create a common language across research and clinical disciplines (3). The agreed definition is 'breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient' and acknowledges that the syndrome is often accompanied by episodes of more intense breathlessness and panic. These episodes have now also been defined as 'episodic breathlessness' following a Delphi survey (18). This is reflected in the publications incorporated in this thesis which use the term 'chronic breathlessness'. For clarity I used the term chronic or refractory breathlessness in the main text of this thesis.

But is there a value in defining breathlessness? We know that the experience of breathlessness is subjective and varies considerably between individuals (178). We also know that breathlessness is more than just a sensory experience and has considerable psychological, social, and spiritual impacts for individuals and their families. It is difficulty to consider how this complex experience can be condensed into one term. However, there are benefits to using established terminology. Breathlessness which persists despite optimal treatment is often described by patients as invisible and neglected by healthcare professionals. By giving this experience a common term we may be able to improve recognisability among healthcare professionals, and this is a first step towards improving the assessment and management or

chronic or refractory breathlessness. Additionally, a common term may also help to develop new clinical services and increase research in this challenging area. The terminology of breathlessness will likely continue to evolve, and agreement of a common language will be both helpful and beneficial in the long term.

9.5 Strengths and limitations

9.5.1 Design

Once I had identified my research question it was important to consider which methodology was most appropriate. I chose to use a mixed methods approach with a qualitative dominant component (109). It is increasingly common to undertake qualitative research alongside RCTs and a systematic search of published literature and registered trials identified that qualitative research was undertaken with at least 12% of trials (179). The majority of these trials were of complex interventions with less than a third relating to drugs or devices (including surgery and acupuncture) (179). So why is qualitative research less common in randomised controlled drug trials compared to those of complex interventions? It may be that drug trials are perceived as being a simple intervention, which therefore does not need exploring in the same way as a complex intervention. However, there are aspects of feasibility relating to the intervention which are equally important in a drug trial compared to that of a complex intervention. These include willingness to be randomised, acceptability of the intervention including type of drug and concerns about side effects, the impact of the intervention, and process measures (Figure 2). Understanding the acceptability of a trial medication is important as concern about medication is a common reason for trial discontinuation (180, 181). It is also important to acknowledge that qualitative work within drug trials can address complexities independent to the intervention, often relating to the trial population or environment (107, 179). The qualitative interviews enabled me to explore what outcomes were important to participants, as well as what influenced them to take part and remain in the trial. The quantitative data (for example the proportion of missing data and screening to recruitment ratios) provided context for the qualitative data and were also used as a measure of feasibility. Integration of the qualitative and quantitative data enabled me to explore the extent to which quantitative outcome measure data collected in the trial captured important changes in the experience of breathlessness as reported by participants in the qualitative data (182).

As a physician working on the trial and recruiting participants at the London site, I was blinded to treatment allocation during the trial. This meant I was also blinded while conducting the

qualitative interviews. Blinding during mixed methods analysis, particularly of treatment allocation is desirable to reduce the potential risk of bias (183). However, when qualitative interviews are conducted as part of a blinded trial there can be potential for participant feedback to result in unblinding (184). This is particularly likely for trials where it is not possible to blind the participant, for example surgery. In comparison it is much simpler for the qualitative researcher to remain blinded in a drug trial. At the end of the trial I had the opportunity to be unblinded prior to analysis. I considered this carefully and decided to remain blinded. I believe this is a strength of the thesis and increases the confidence in the findings by reducing the risk of bias.

9.5.2 Setting and population

As discussed in chapter 6 recruiting people with advanced disease to participate in clinical trials is a challenge. People living with chronic or refractory breathlessness are often limited functionally and become fatigued quickly. We wanted to recruit those most severely affected by breathlessness identified to be mMRC scale 3 or 4. Other trials have struggled to recruit this population, and due to insufficient recruitment have resulted to changing their eligibility criteria to include people identified as mMRC scale 2 (153). A strength of this thesis was our person-centred approach to delivering the trial. By minimising the burden, we enabled this very sick cohort of people to be included. 58% of participants in our trial were identified as mMRC scale 4, which is considerably higher than other drug trials in chronic or refractory breathlessness (64, 153). Living with breathlessness can be unpredictable and it was common for participants to request for an appointment to be changed because they felt unwell or had been admitted to hospital. We were as flexible as possible often offering to change the time or date of appointment (the trial protocol allowed for assessments to be done +/- 1 day of the schedule) or visiting them in a different setting (for example hospital).

The availability of Pulmonary Rehabilitation across sites was raised as an issue early on in the trial. One of the inclusion criteria was that the underlying condition had been optimised prior to entering the trial, and for those with COPD this included Pulmonary Rehabilitation (20). However, in some geographical areas due to the clinical services available, patients were having to wait several months to receive this. It was agreed that we needed to be pragmatic and ideally patients with COPD should undertake Pulmonary Rehabilitation prior to entering the trial, but that if there was a long waiting list, we decided that they could enter the trial first.

In the planning and development stages of the qualitative interviews I developed a sampling frame. This was based on characteristics considered to be important, for example age and gender. However, due to the limited pool of participants I decided to take a pragmatic approach and used convenience sampling, offering each trial participant the opportunity to participate in a qualitative interview. This approach to recruitment has been used in other qualitative studies conducted alongside randomised controlled drug trials (185). However, despite the use of convenience sampling I was able to interview participants with all the characteristics considered to be important, except for trial decliners.

Quite quickly it became apparent that recruitment in some settings would be more challenging than others. For example, patients approached in the inpatient setting often had an acute illness and therefore either were not eligible to participate, and some were too sick in general. Recruitment from oncology proved particularly difficult and only 2 of those randomised had a cancer diagnosis. As described in section 9.4.1 there seemed to be several reasons for this including: ineligibility due to concurrent anticancer treat, gatekeeping from clinicians, and resistance from patients. Gatekeeping has previously been identified as a significant issue which can affect accrual rates (90, 154-156), and concurrent anticancer therapy was the commonest reason for ineligibility in a large observational multicentre palliative care study recently conducted (90). Due to limited resources I decided to focus on attending the lung disease clinics and not oncology. This is reflected in the higher numbers of participants recruited from these settings.

9.5.3 Data collection and analysis

I collected the data for all of the qualitative interviews which were conducted at the end of the trial. There are advantages to this in terms of rigour and I was able to ensure that the topic guide was delivered consistently. I had also collected the quantitative data at the London site which meant I understood the context for the interviews. During the quantitative data collection, I had the opportunity to build a relationship with trial participants. This may have facilitated them to feel more comfortable during the qualitative interview, resulting in rich data (186, 187). Conversely this also meant that some of the participants who were interviewed knew that I was a doctor, as I had consented them to come into the trial. This could have resulted in a bias, as participants may have answered questions in the way they thought I wanted them to, for example describing positive aspects of the trial and perceived benefits from the trial medication. The effects of social desirability bias have been shown in

other studies where participants underreported in order not to disappoint study staff (188). The risk of bias due to this was minimised by conducting interviews at the other two sites where I had not met participants. A comparison of results from the three sites did not identify any differences or discrepancies and therefore bias seems unlikely.

Sometimes a carer was present during data collection of both quantitative outcome measure data, and the qualitative data. This may have impacted on how questionnaires were completed and how questions were answered during the qualitative interviews. The time period between the trial ending and the qualitative interview being done varied therefore increasing the risk of recall bias (189). This was particularly important for the interviews done in Nottingham and Hull which required me to travel. To be efficient time wise I would wait until several participants had consented to an interview before travelling to these sites. In an ideal situation there would have been three people conducting the qualitative interviews, one at each site, and therefore the interviews could have been done at a specified time after completing the trial. However, this would have been more resource intensive and expensive. It may have also reduced the consistency of how the topic guide was delivered.

There were, however, some benefits to conducting the interviews at different time periods, and we were able to identify that some participants had requested to be prescribed mirtazapine by their General Practitioner once the trial had finished. I was able to do some interim analysis and explore aspects of feasibility for these participants (see section 8.4). These findings have influenced the design of the full-scale trial which will have a longer follow up period than the feasibility trial. It may have also been beneficial to conduct follow up interviews with participants. Serial interviews can give important insights into patients' changing experiences of illness and help to understand evolving experience and needs (190). There was some variability in how outcomes measures were administered between sites. At some sites the participants were well enough to complete the questionnaires without assistance, at other sites the participants required the questions and answers to be read out. The use of prompting may have resulted in bias unintentionally. Attempts to made to minimise this risk of bias through use of a training manual.

During analysis there was a risk of interpretation bias. I opted to remain blinded during the analysis phase, in an attempt to reduce the potential risk of bias (183). Additional attempts were made to enhance the credibility of the findings and reduce the risk of bias including; second coding of qualitative interview transcripts, field notes, use of a reflexive diary, and discussion of the main findings with other researchers and my supervisors (191).

9.5.4 Validity of NRS

Issues with validity emerged after the NRS had been chosen as an outcome measure for the feasibility trial. In many ways this has become a strength of the thesis, by contributing to the literature. This thesis has shown that the NRS Worst, a single-item measure, was able to capture important changes in the experience of breathlessness across multiple domains during the trial. Furthermore, we have identified some important research questions. Future work should aim to determine the construct validity of the NRS when accompanied by different questions. This remains outside of the remit of this thesis.

9.5.5 Personal reflections and learning

This PhD study sat within a multicentre feasibility trial, Better-B. Working within an existing study was beneficial for several reasons. There was funding available to support the trial set up and delivery including applying for ethical approval and quantitative data collection. Specific timelines had been agreed for the delivery of the trial and this helped to ensure that momentum was maintained, and the trial remained on track. There were also some challenges of working within an existing study and initially I found it quite difficult to identify a research question which was separate from the main trial aim. However, outcome measures were an area of particular interest to me, and so this became a first focus for the thesis. I also found that I often didn't know how much time it would take me to complete specific tasks and had to learn as I went along. Working within the Better-B trial made me appreciate how difficult it is to conduct a drug trial, particularly in advanced disease. I was surprised at how much time was required to screen and identify potential participants, only a number of which then entered the trial. I realised that the success of the trial to some degree is dependent on how engaged the clinicians are. I will try and remember this when I am working clinically and researchers' approach me as the identifying clinician.

I have a clinical background and previously worked at King's College Hospital as a doctor prior to undertaking this PhD study. This meant that I knew some of the clinicians who were working in the settings that we were recruiting from, and possibly supported good referral rates at the London site. I also have experience of visiting people in their homes and therefore felt confident in doing so during the trial. Building up a rapport with participants quickly may then have contributed to the high levels of retention within our trial. However, having spent the

past seven years working clinically I did find the transition to being 'a researcher' difficult. Participants often knew I was a doctor as I had consented them for the trial originally. Therefore, I was sometimes asked clinical questions about their medical condition and ongoing management. I reflected on this issue with my supervisors and became more comfortable with explaining what my role was and would signpost participants if they had specific clinical questions they wanted to ask.

The work in this thesis has changed the way I think about breathlessness. Previously when working clinically I would feel apprehensive if I was asked to review a patient experiencing chronic or refractory breathlessness. I now feel as though I have a better knowledge of the science, but also understand what may be important to those experiencing chronic or refractory breathlessness. I plan to incorporate this knowledge in my approach when assessing chronic or refractory breathlessness in the future. Conducting the qualitative interviews has also reminded me about the importance of listening to our patients. I think far too often as clinicians, we enter a consultation with our own agenda, and overlook the time it takes to really explore what is important to the person in front of us.

During this thesis I have been surprised to learn that patients describe chronic or refractory breathlessness as 'invisible' and 'neglected'. I therefore took the opportunity to do some public engagement work to increase awareness of the symptom. 'The sound of anxiety' was a live experiment held at the Science Gallery, King's College London. Members of the public listened to recordings of breathless people and attempted to guess the cause of the breathlessness from four options (exercise, anxiety, chronic lung disease, and approaching the end of life) (192). We also asked participants to rate their own breathing between recordings using the NRS Worst. The experiment was part of a larger exhibition called ON EDGE: Living in an Age of Anxiety season and aimed to raise awareness about how common breathlessness is, and some of the different causes. Over two hundred and fifty people took part and we are currently analysing the results. Preliminary analysis does however suggest that participants appeared to become more breathless the more recordings they listened to. This has important implications for the carers of breathless people who are exposed to the sound of breathlessness on a daily basis.

9.6 Conclusions

The research presented in this thesis used a mixed methods approach to explore the feasibility of, and ways to optimise recruitment, retention, and outcome measures in a double blind randomised controlled trial of mirtazapine for chronic or refractory breathlessness. Trial recruitment targets were met, and attrition levels were low, indicating that the trial design is feasible. However, I did identify new considerations which may influence recruitment and retention. The most important of these was the use of a person-centred approach. Prioritisation of the relationship between the patient and professional; person-centred processes including home visits, assistance with questionnaires, and involvement of the carer; and enabling people to participate by having processes in line with individual capabilities appeared to support recruitment and retention in this trial.

This research also contributes new findings for outcome measures in breathlessness research. When testing new interventions in breathlessness research it is important that the selected outcome measures capture changes perceived as important to those living with breathlessness but are also able to detect any effect of the intervention. My systematic review showed that people with advanced illness experiencing breathlessness describe concerns across six domains of 'total breathlessness': physical, emotional, spiritual, social, control, and context. It is therefore important that outcome measures can capture important changes across these domains. My mixed methods study found that the changing experience of breathlessness during the trial was usually captured by the NRS worst, NRS average, and CRQ. Agreement was however highest with the NRS worst, which despite being a single item measure captured changes across multiple domains, suggesting it is measuring more than one construct.

Findings from this research also raise questions about how outcome measures in breathlessness are validated. The NRS is increasingly adopted as a primary outcome measure in breathlessness trials, however, the original validation work was solely based on correlation of score to the Visual Analog Dyspnea Scale and included no test of content validity or reliability. While the results presented in this thesis suggest that the NRS worst may be a good candidate primary outcome measure in this type of trial. Future work should ensure the validity of this specific format of question.

There are important implications of this work. My model of total breathlessness provides clinicians with a practical framework they can use to assess breathlessness in clinical practice. Recognising the importance of control and context can help clinicians to tailor management strategies and enhance coping for patients. Additionally, the findings of my mixed methods

study suggest that the NRS worst may be able to capture important changes in experience of breathlessness across multiple domains. The NRS worst is short, simple to complete and could be easily integrated into routine clinical care. The findings from my qualitative study demonstrate the importance of a person-centred approach to clinical trials and have potential implications for the future funding of trials. While current research infrastructure funding models in the UK focus specifically on recruitment and not on retention, the results presented in this thesis highlight the importance of having a dedicated research team who are able to build good relationships with participants throughout the duration of a trial. Future work should aim to evaluate the application of a person-centred approach to clinical trials in different settings, and confirm the construct validity of the NRS worst using the rating question "How bad has your breathlessness felt at its worst over the past 24 hours?"

9.7 Key Implications for clinical practice, healthcare policy, and future research

9.7.1 Clinical Practice

The findings of this thesis have important implications for the assessment of breathlessness in clinical practice. While clinicians often recognise the significant impact of breathlessness for patients and carers, a lack of resources and training can leave them feeling ill-equipped when it comes to assessment and management (60). Primary care teams have a key role in the initiation and delivery of effective palliative care, and to support the management of these complex patients, training and educational resources are essential (193). My model of 'total breathlessness' was developed from a systematic synthesis of the literature (87), and provides clinicians with a simple yet practical framework they can use in clinical practice. The importance of all domains identified in the model was confirmed in the qualitative study embedded within the feasibility trial (138).

PROMs are increasingly used in clinical practice to assess change in a person's health status, quality of life, or symptoms over time (67). The use of PROMS in clinical practice, however, can be limited, due to time constraints and concerns about the burden of lengthy questionnaires for patients (70). This is particularly important when we consider those living with advanced disease. The findings of my mixed-methods study suggest that the NRS worst, a single-item measure may be able to capture important changes in experience of breathlessness across multiple domains (138). The NRS is short, simple to complete and could be easily integrated into routine clinical care.

9.7.2 Healthcare Policy

The findings of the research also have important implications for policy and funding. In our trial there appeared to be a clear benefit of having the same researchers work across all stages of a trial. Continuity helped to facilitate the development of a genuine relationship with the researcher and appeared to influence trial retention. Current funding models in the UK focus specifically on recruitment and not on retention and therefore the funding for follow-up often needs to be pooled from other budgets (166). To ensure that the same researchers are able to work across trials funding models need to be revised to rebalance of emphasis of recruitment and retention (167).

9.7.3 Future Research

Chronic or refractory breathlessness is common and distressing with few effective treatment options. While there is some randomised controlled trial evidence from a Cochrane Review to support the use of parental and oral opioids (55, 56), optimal dosing and potential issues arising from long-term use and safety remains to be determined (57-59). The 'Morphine and BrEathLessness trial' (MABEL) is a multicentre randomised controlled trial of low dose modified release morphine or placebo which has recently opened in the UK (194). It is running across 12 centres with a target sample size of 158 participants, and aims to determine the effectiveness of effectiveness and cost effectiveness of low dose oral modified release morphine versus placebo on patient-reported worst breathlessness.

While there is some evidence supporting use of opioids, new treatments are urgently needed. The findings from this feasibility trial have recently contributed to a successful funding application for a full-scale trial (195). 'BETTER-B: Better treatments for persistent breathlessness' plans to open to recruitment in March 2020 and aims to recruit 324 participants from five countries. Participants will be randomised to receive mirtazapine or placebo for 56 days. The trial aims to determine whether mirtazapine is an effective treatment for chronic or refractory breathlessness.

The research presented in this thesis shows that it is possible to recruit and retain people with advanced illness and breathlessness to a randomised controlled drug trial using a person-centred approach. As more people approach the end of their lives with chronic and complex conditions, the need for robust research and evidence has never been greater, and future work should aim to evaluate the application of this approach to clinical trials within and beyond palliative care settings (196-198). The research presented in this thesis also suggests that a single item outcome measure, the NRS worst, can capture important changes in the experience of breathlessness across multiple domains. It may therefore be a useful outcome measure in this type of trial, and for this type of intervention. However, future work should consider the validity of this format of question.

9.7.4 Recommendations for conducting a randomised controlled drug trial for chronic or refractory breathlessness in advanced disease

The findings of the research presented in this thesis identify important considerations for the future conduct of a randomised controlled drug trial for chronic or refractory breathlessness in

advanced disease. Recommendations include prioritising continuity of the research team where possible, the provision of clear trial related information, having processes in line with individual capabilities, minimising study burden where possible, and ensuring outcome measures are short and straight forward to complete, yet capture what is important (Table 7).

Table 7: Recommendations for conducting a randomised controlled drug trial for chronic or refractory breathlessness in advanced disease

Area	Recommendation
Study Team	Continuity of research team where possible
Ethics	Provision of clear trial related information
Procedures	Processes in line with individual capabilities Minimise study burden where possible (e.g. through home visits)
Outcome measures	Capture what is important to participants Short and straight forward to complete

With an aging population, an increasing number of people are living with chronic and complex conditions and multimorbidity (196-198). The findings of this research may therefore also be relevant and important for the conduct of other clinical trials in the future. The MORECare Statement is a checklist of components which require consideration when designing and conducting research evaluating palliative and end of life care, and includes 36 best practice solutions to improve study quality and set the standard for future research (88). The MORECare collaboration was established by the UK Medical Research Council (MRC) and National Institute of Health Research (NIHR) to identify, appraise and synthesise best practice methods for research evaluating palliative and end of life care (88). MORECare focused on 6 key areas for research: 1) participation and recruitment; 2) ethical considerations; 3) statistical analysis for attrition and response shift; 4) integration of mixed methods; 5) complex outcomes; and 6) economic evaluation (70, 120, 199, 200). It aimed to develop a statement of best research practice to complement existing tools that aid the conduct and reporting of research, for example the Consolidated Standards of Reporting Trials (CONSORT) (149). Results from systematic literature reviews, transparent expert consultations, and stakeholder workshops were synthesised to develop the MORECare guidance statement. I believe the

research presented in this thesis provide new items to be considered in any future revisions of the MORECare Statement.

Appendix 1 -Ethics approval letters

Favourable opinion ethics letter

NHS
Health Research Authority
London - Central Research Ethics Committee
3rd Floor, Barlow House
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7820

29 January 2016

Professor Irene Higginson, Professor of Palliative Care and Policy
King's College London
Bessemer Road
London
SE5 9PJ

Dear Professor Higginson

Study title:	**BETTER-B (Feasibility): BETter TreatmEnts for Refractory Breathlessness: a feasibility study of the use of mirtazapine for refractory breathlessness**
REC reference:	**16/LO/0091**
EudraCT number:	**2015-004064-11**
IRAS project ID:	**187894**

The Research Ethics Committee reviewed the above application at the meeting held on 27 January 2016. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Elaine Hutchings, NRESCommittee.London-Central@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Additional conditions

Main information sheet

- Please provide a clearer explanation of a placebo in the information sheet.
- Please include the requirements relating to pregnancy and contraception, as stated in the protocol, in the information sheet.
- An explanation of palliative care as an additional level of support should be given so that potential participants are aware of the situation and it does not come as a surprise.
- The suggestion on page 6 of the sheet that participants should discuss continuation of the study medication with their GP if they have found it beneficial should be revised. The sheet should ask participants to discuss the issue with the research team who can then raise it with the participant's GP.

Please notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites listed in the application taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

This was found to be a well-designed, potentially valuable study investigating an area with a current lack of effective treatment. You were commended on the patient involvement in the design of and throughout the trial, as well as on the clarity of the informed consent documentation and lay summary.

As anti-depressants generally take some time to take effect, you were asked whether 28 days of treatment will be sufficient to show a result, and upi assured the Committee that it will.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

It was asked whether exacerbations of COPD occurring during the study will be detected. You were confident that they will, since contact will be made with participants every 7 days during the study. You said that exacerbations will be expected in both arms of the study.

Informed consent process and the adequacy and completeness of participant information

It was queried whether participants will be aware that they are in a palliative setting. You said that some will and some will not. It was pointed out that the information sheet refers to palliative care and it should be ensured that this will not come as a shock to participants. You said that you will include an explanation of palliative care as an additional level of support so that potential participants will be aware of the situation.

With regard to the suggestion in the information sheet that participants could discuss continuation of the medication with their GPs if they have found it to be beneficial, the point was made to you that this would not be appropriate; participants should be asked to discuss the issue with the research team who can then raise it with the participant's GP.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Participant Poster]	1.0	25 November 2015
Copies of advertisement materials for research participants [Participant Summary Leaflet]	1.0	09 December 2015
Covering letter on headed paper		16 December 2015
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor Insurance]		15 July 2015
GP/consultant information sheets or letters [GP Letter]	1.0	09 December 2015
Investigator's brochure / IMP Dossier [IMPD]	1.0	09 December 2015
IRAS Checklist XML [Checklist_16122015]		16 December 2015
Letter from sponsor [KCL Sponsor Letter]		22 September 2015
Letters of invitation to participant [Database Participant Approach Letter]	1.0	09 December 2015
Non-validated questionnaire [BETTER-B mMRC]	1.0	09 December 2015
Non-validated questionnaire [BETTER-B GSES]	1.0	09 December 2015
Non-validated questionnaire [BETTER-B CSRI (Baseline)]	1.0	09 December 2015
Non-validated questionnaire [BETTER-B CSRI (Day28)]	1.0	09 December 2015
Non-validated questionnaire [BETTER-B Blinding Assessment]	1.0	09 December 2015
Non-validated questionnaire [Feedback Questionnaire]	1.0	09 December 2015
Other [KCH Sponsor Confirmation Email]		31 July 2015
Other [Participant Thank You Letter]	1.0	09 December 2015
Other [Baseline Participant Questionnaire Pack Template]	1.0	09 December 2015
Other [Day 14 Participant Questionnaire Pack Template]	1.0	09 December 2015
Other [Day 28 Participant Questionnaire Pack Template]	1.0	09 December 2015
Other [CRQ Prompt]	1.0	25 November 2015
Other [EQ-5D-5L Prompt]	1.0	25 November 2015
Other [GSES Prompt]	1.0	25 November 2015
Other [HADS Prompt]	1.0	25 November 2015
Other [IPOS Prompt]	1.0	25 November 2015
Other [NRS Prompt]	1.0	25 November 2015
Other [Interview Substudy Topic Guide (Participants)]	1.0	09 December 2015
Other [Interview Substudy Topic Guide (Decliners)]	1.0	09 December 2015
Other [mMRC Prompt]	1.0	25 November 2015
Other [Email with additional information]		19 December 2015
Other [Email with clarification re assessments]		21 December 2015
Participant consent form [Main Consent Form]	1.0	09 December 2015

Participant consent form [Interview Sub-study Consent Form (Participants)]	1.0	09 December 2015
Participant consent form [Interview Sub-study Consent Form (Decliners)]	1.0	09 December 2015
Participant information sheet (PIS) [Main Participant Information Sheet]	1.0	09 December 2015
Participant information sheet (PIS) [Interview Sub-study PIS (Participants)]	1.0	09 December 2015
Participant information sheet (PIS) [Interview Sub-study PIS (Decliners)]	1.0	09 December 2015
REC Application Form [REC_Form_16122015]		16 December 2015
Research protocol or project proposal [Protocol]	1.0	09 December 2015
Sample diary card/patient card [Patient ID card]	1.0	09 December 2015
Sample diary card/patient card [Participant Diary Booklet]	1.0	09 December 2015
Summary CV for Chief Investigator (CI) [Chief Investigator CV]		
Summary of product characteristics (SmPC) [Mirtazapine SPC]		09 July 2013
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Trial Summary]	1.0	09 December 2015
Validated questionnaire [EQ-5D-5L]	1.0	
Validated questionnaire [IPOS]	1.0	26 February 2014
Validated questionnaire [CRQ Initial]		
Validated questionnaire [CRQ Follow-up]		
Validated questionnaire [HADS questionnaire]		

Membership of the Committee

The members of the Ethics Committee present at the meeting are listed on the attached sheet.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/LO/0091	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Dr Andrew Hilson
Chair

E-mail: NRESCommittee.London-Central@nhs.net

Enclosures:	*List of names and professions of members present at the meeting*
	"After ethical review – guidance for researchers"
Copy to:	*Jackie Pullen, King's Health Partners Clinical Trials Office* *Jen McLean, King's College Hospital NHS Foundation Trust*

London - Central Research Ethics Committee

Attendance at Committee meeting on 27 January 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Louise Abrams	Consultant Physician and Clinical Pharmacologist	Yes	
Mr Clive Carsley	Retired Lawyer	Yes	
Dr Beverly Donaldson	Academic Research Midwife	Yes	
Dr Olivia Festy	Clinical Trials Administrator	Yes	
Mrs Sophie Forsyth	Lawyer	Yes	
Mr Stephen Gerry	Medical Statistician	Yes	
Dr Frances Goodhart	Consultant Clinical Psychologist	Yes	
Dr Andrew Hilson	Consultant in Nuclear Medicine	Yes	Chair
Dr Lorraine Ludman	Retired Psychologist	Yes	
Lady Karen Rix	Retired Lawyer	Yes	
Professor Lewis Spitz	Emeritus Nuffield Professor of Paediatric Surgery	Yes	
Mr Benjamin Stanfield-Davies	University Lecturer	Yes	
Dr Gareth Tudor-Williams	Consultant in Paediatric Infectious Diseases	No	

Also in attendance:

Name	*Position (or reason for attending)*
Glenys Davies	Observer
Elaine Hutchings	REC Manager

Letter of HRA approval

Health Research Authority

Professor Irene Higginson
Professor of Palliative Care and Policy
King's College London
Bessemer Road London
SE5 9PJ

Email: hra.approval@nhs.net

30 June 2016

Dear Professor Higginson,

Letter of HRA Approval for a study with an existing UK study wide review

Study title:	**BETTER-B (Feasibility): BETter TreatmEnts for Refractory Breathlessness: a feasibility study of the use of mirtazapine for refractory breathlessness**
IRAS project ID:	**187894**
Sponsor:	**King's College London**

Thank you for your request to bring the above referenced study under HRA Approval.

I am pleased to confirm that the study has been given **HRA Approval.** This has been issued on the basis that a study wide review has previously been undertaken, which has confirmed that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to add a new site between 23 March 2016 and the date of this letter, the addition of the new site is also approved.

Participation of NHS Organisations in England

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of

Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study.

For commercial studies the local document package should include a validated industry costing template and the template agreement to be used with participating NHS organisations in England.

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

After HRA Approval

In addition to the document, *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC Favourable Opinion, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

IRAS project ID	187894

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the HRA website.

Your IRAS project ID is **187894.** Please quote this on all correspondence.

Yours sincerely

David Williams
Application Administrator

Email: hra.approval@nhs.net

Copy to: *Jackie Pullen*
King's Health Partners Clinical Trials Office
Jen McLean
King's College Hospital NHS Foundation Trust

Letter of MHRA approval

MHRA
Regulating Medicines and Medical Devices

MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Ms J L Pullen
KING'S COLLEGE LONDON
16TH FLOOR, TOWER WING, GUY'S HOSPITAL
GREAT MAZE POND
LONDON
SE1 9RT
UNITED KINGDOM

16/02/2016

Dear Ms J L Pullen

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference:	14523/0265/001-0001
Eudract Number:	2015-004064-11
Product:	MEDREICH Mirtazapine tablets 15 mg
Protocol number:	BETTER-BFeasibility

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 15/02/2016.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

Medicines and Healthcare Products Regulatory Agency

Appendix 2 -Baseline Questionnaires

BETTER-B

ISRCTN32236160

BETTER-B (Feasibility) Baseline Participant Pack

To be completed by the trial staff

Participant Initials | Date of Birth (Day Month Year) | Participant ID (Centre No Trial No)

A large-print version of this questionnaire pack is available upon request

To be completed by the participant

Date completed (Day / Month / Year)

This pack consists of six questionnaires which we would be grateful if you could complete. The reason for doing this is to help us find out more about you and to understand how your condition affects you, from your point of view.

Most of the questionnaires contain a series of questions to which there is a choice of answers. **There are no right or wrong answers to any of the questions**; your answers should just reflect how you feel and your own experience.

These questionnaires have been used in several previous clinical research projects and can be completed in a relatively short time. However, there is no time limit; please complete as many of the questions as you can, **taking as much time as you need**.

If after answering any of the questions you realise you have made a mistake (for example, by ticking a box which doesn't reflect how you feel), please cross out your answer clearly and then select the answer that you meant to choose.

We appreciate that some of the questions included are of a sensitive and personal nature. We assure you that any information you provide will be dealt with in the strictest confidence, and will not be divulged or made available in any form that may subsequently reveal your identity.

After you have completed your questionnaires, hand it back to a member of the BETTER-B research team.

If the completion of the questionnaire raises any particular concerns we would encourage you to discuss these with either your GP or the research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 1: Integrated Palliative care Outcome Scale (IPOS)

Q1. What have been your main problems or concerns over the past week?

1.....

2.....

3.....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	Slightly	Moderately	Severely	Over-whelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.					
1.	0☐	1☐	2☐	3☐	4☐
2.	0☐	1☐	2☐	3☐	4☐
3.	0☐	1☐	2☐	3☐	4☐

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐
	Always	*Most of the time*	*Sometimes*	*Occasionally*	*Not at all*
Q6. Have you felt at peace?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you had as much information as you wanted?	0☐	1☐	2☐	3☐	4☐
	Problems addressed/ No problems	*Problems mostly addressed*	*Problems partly addressed*	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐
	On my own	*With help from a friend or relative*			*With help from a member of staff*
Q10. How did you complete this questionnaire?	☐	☐			☐

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 2: Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	D
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	A
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	A
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	D
Often	0
Sometimes	1
Not often	2
Very seldom	3

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 3: Chronic respiratory questionnaire (Self Reported)

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities which you still do, but which are limited by your shortness of breath.

Listed below are some activities which can make people with lung problems feel short of breath.

If you have felt **short of breath** doing any of the **activities** listed below **during the last two weeks** then please tick each relevant activity. If you have **not** done the activity during the last two weeks or it does **not** make you short of breath then leave it blank.

THE ACTIVITIES ARE:

☐	1. BEING ANGRY OR UPSET
☐	2. HAVING A BATH OR SHOWER
☐	3. BENDING
☐	4. CARRYING - SUCH AS GROCERIES
☐	5. DRESSING
☐	6. EATING
☐	7. GOING FOR A WALK
☐	8. DOING YOUR HOUSEWORK
☐	9. HURRYING
☐	10. MAKING YOUR BED
☐	11. MOPPING OR SCRUBBING A FLOOR
☐	12. MOVING FURNITURE
☐	13. PLAYING WITH CHILDREN/GRANDCHILDREN
☐	14. PLAYING SPORTS
☐	15. REACHING OVER YOUR HEAD
☐	16. RUNNING - SUCH AS FOR A BUS
☐	17. SHOPPING
☐	18. WHILE TRYING TO SLEEP
☐	19. TALKING
☐	20. VACUUMING
☐	21. WALKING AROUND YOUR OWN HOME
☐	22. WALKING UPHILL
☐	23. WALKING UPSTAIRS
☐	24. WALKING WITH OTHERS ON LEVEL GROUND
☐	25. PREPARING MEALS

Please list **any other activities** that you have done during the last two weeks which have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life.

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

We would now like you to identify the **most <u>important</u> activities** in which you have been limited by your **shortness of breath** in the last **two weeks**.

Using the list you have made on the previous page, write down the **<u>five most important activities</u>** that have made you short of breath on the lines below. We would then like you to tell us **how short of breath** you have been while performing each activity by ticking the box which best describes how you feel.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1. _____	☐	☐	☐	☐	☐	☐	☐
2. _____	☐	☐	☐	☐	☐	☐	☐
3. _____	☐	☐	☐	☐	☐	☐	☐
4. _____	☐	☐	☐	☐	☐	☐	☐
5. _____	☐	☐	☐	☐	☐	☐	☐

PLEASE MAKE SURE YOU HAVE COMPLETED THE ABOVE TABLE BEFORE TURNING THE PAGE

Thank you

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

8. What about fatigue? How tired have you felt over the last 2 weeks?

Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMLY TIRED ❑
2. VERY TIRED ❑
3. QUITE A BIT OF TIREDNESS ❑
4. MODERATELY TIRED ❑
5. SOMEWHAT TIRED ❑
6. A LITTLE TIRED ❑
7. NOT AT ALL TIRED ❑

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

11. How much energy have you had in the last 2 weeks?

Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ❑
2. A LITTLE ENERGY ❑
3. SOME ENERGY ❑
4. MODERATELY ENERGETIC ❑
5. QUITE A BIT OF ENERGY ❑
6. VERY ENERGETIC ❑
7. FULL OF ENERGY ❑

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?

Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?

Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?

Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

15. How often during the last 2 weeks have you felt low in energy?

Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

17. How often during the last 2 weeks have you felt worn out or sluggish?

Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?

Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ❑
2. GENERALLY DISSATISFIED, UNHAPPY ❑
3. SOMEWHAT DISSATISFIED, UNHAPPY ❑
4. GENERALLY SATISFIED, PLEASED ❑
5. HAPPY MOST OF THE TIME ❑
6. VERY HAPPY MOST OF THE TIME ❑
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ❑

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

20. In general how often during the last 2 weeks have you felt restless, tense or uptight?

Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Thank you very much for taking the time to complete this questionnaire.

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 4: EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

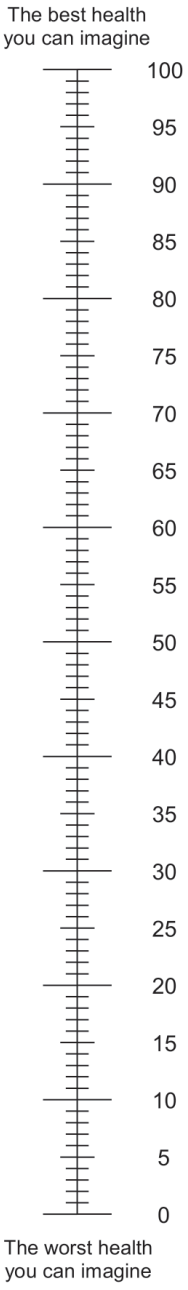
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 5: Generalised Self-Efficacy Scale (GSES)

Instructions: Please indicate the extent to which each statement applies to you by ticking the appropriate box

		Not at all true	Barely true	Moderately true	Exactly true
1	I can always manage to solve difficult problems if I try harder				
2	If someone opposes me, I can find means and ways to get what I want				
3	It is easy for me to stick to my aims and accomplish my goals				
4	I am confident that I could deal efficiently with unexpected events				
		Not at all true	**Barely true**	**Moderately true**	**Exactly true**
5	Thanks to my resourcefulness, I know how to handle unforeseen situations				
6	I can solve most problems if I invest the necessary effort				
7	I can remain calm when facing difficulties because I can rely on my coping abilities				
8	When I am confronted with a problem, I can usually find several solutions				
9	If I am in a bind, I can usually think of something to do				
10	No matter what comes my way, I'm usually able to handle it				

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 6: Client Services Receipt Inventory (CSRI)

Instructions: This questionnaire is about your use of health and social care, accommodation, living situation and informal care (i.e. given by family member) **over the last 12 weeks** Information provided here is used to calculate the costs of care.

Health and Social services you have received - these are some of the services that you may be receiving, most people will have received only a few of them.

Section 1: In-patient or other residential services

In the past 12 weeks, have you stayed in a hospital/ other residential care setting?

1. **Yes ☐0 No ☐1** **If you answered 'No', please go to section 2.**

If you answered 'Yes', please state the total number of days you stayed in any of the following wards or settings during the last 12 weeks.

A.	Intensive care unit	..... days
B.	Neurology ward	..... days
C.	Medical ward	..... days
D.	Specialist rehabilitation ward or unit	..... days
E.	Other ward (please state).....	..... days
F.	Hospice	..... days
G.	Nursing or Residential home	..... days
H.	Respite care setting	..... days
I.	Other residential setting (please state)	..... days
J.	A&E department	..... days
K.	Number of hospital admissions	..... attendances
L.	Emergency ambulance service	..... attendances

Section 2: Day care or community services

In the last 12 weeks, have you spent time in a day care or community setting?

2. **Yes ☐0 No ☐1 If you answered 'No', please go to section 3.**

If you answered 'Yes', please state the average number of times in the last 12 weeks you attended any of the following:

A.	Day hospital	.....attendances / month
B.	NHS day care	.....attendances / month
C.	Palliative day care	.....attendances / month
D.	Rehabilitation day unit	.....attendances / month
E.	Neurology day care	.....attendances / month
F.	Social services day centre	.....attendances / month
G.	Voluntary organisation day/ resource centre	.....attendances / month
H.	Support groups or societies	.....attendances / month
I.	Other day setting (please state)	.....attendances / month

Section 3: Out-patient clinic or surgery based appointments

In the last 12 weeks, have you had any appointments or consultations with professionals in a hospital out-patient department or other type of clinic/surgery? **This can include face-to-face, telephone or email consultations.**

3. **Yes ☐0 No ☐1 If you answered 'No', please go to section 4.**

If you answered 'Yes', please state the number of visits made to any of these professionals over the last 12 weeks and the average time for a visit in minutes.

A.	General Practitioner (GP)	.....visits	.....minutes/visit
B.	Neurologist	.....visits	.....minutes/visit

C.	Palliative care doctor/ palliative care consultant	……visits	……..minutes/visit
D.	Psychiatrist	……visits	……..minutes/visit
E.	Other doctor (please state)……	……visits	……..minutes/visit
F.	Other doctor (please state)……	……visits	……..minutes/visit
G.	General practice nurse	……visits	……..minutes/visit
H.	Community mental health nurse	……visits	……..minutes/visit
I.	Palliative care nurse	……visits	……..minutes/visit
J.	Specialist Parkinson's nurse	……visits	……..minutes/visit
K.	Specialist MS nurse	……visits	……..minutes/visit
L.	Specialist MND nurse	……visits	……..minutes/visit
M.	Other nurse (please state)……	……visits	……..minutes/visit
N.	Physiotherapist	……visits	……..minutes/visit
O.	Occupational therapist	……visits	……..minutes/visit
P.	Speech therapist	……visits	……..minutes/visit
Q.	Social worker	……visits	……..minutes/visit
R.	Palliative care social worker	……visits	……..minutes/visit
S.	Other therapist (please state)……	……visits	……..minutes/visit
T.	Psychologist	……visits	……..minutes/visit
U.	Counsellor	……visits	……..minutes/visit
V.	Priest/Clergy/Chaplain/Imam/Rabbi (please state)……	……visits	……..minutes/visit
W.	Mental health worker	……visits	……..minutes/visit
X.	Dentist	……visits	……..minutes/visit

Y. Dietician .....visits .....minutes/visit

Z. Other* ....visits .....minutes/visit

*For example, osteopath, homeopath, acupuncturist etc.

Section 4: Home based services

In the last 12 weeks, have you had any home based services?

4. **Yes ☐0 No ☐1 If you answered 'No', please go to section 5.**

If you answered 'Yes', please fill in the average number of visits in the last 12 weeks, and the average time a visit took.
Please note: Some services are timed in minutes / visit and others in hours / visit.

A.	Home palliative care/hospice service	.....visits/month	.....minutes/visit
B.	General Practitioner (GP)	.....visits	.....minutes/visit
C.	Palliative care doctor	.....visits	.....minutes/visit
D.	Qualified general nurse	.....visits	.....minutes/visit
E.	Community nurse	.....visits/month	.....minutes/visit
F.	District nurse	.....visits	.....minutes/visit
G.	General Practice nurse	.....visits	.....minutes/visit
H.	Community mental nurse	.....visits/month	.....minutes/visit
I.	Specialist palliative care nurse	.....visits	.....minutes/visit
J.	Specialist Parkinson's nurse	.....visits	.....minutes/visit
K.	Specialist MS nurse	.....visits	.....minutes/visit
L.	Specialist MND nurse	.....visits	.....minutes/visit
M.	Physiotherapy	.....visits/month	.....minutes/visit
N.	Occupational therapy	.....visits/month	.....minutes/visit
O.	Speech therapy	.....visits/month	.....minutes/visit
P.	Dietician	.....visits	.....minutes/visit

Q.	Home care manager	.....visits	……..minutes/visit
R.	Chiropodist	.....visits	……..minutes/visit
S.	Priest/Clergy/Chaplain/Imam/ Rabbi (please state)……	.....visits	……..minutes/visit
T.	Social worker	.....visits	……..minutes/visit
U.	Counsellor	.....visits	……..minutes/visit
V.	Psychologist	.....visits	……..minutes/visit
W.	Palliative care social worker	.....visits	……..minutes/visit
X.	Domestic help	.....visits	……..hours/visit
Y.	Paid formal caregiver (e.g. assist with personal hygiene, preparing meals)	.....visits	……..minutes/visit
Z	Day time sitting service	.....visits	……..hours/visit
AA.	Overnight sitting service	.....visits	……..hours /visit
AB.	Other service (please state)……..	.....visits	…..hours…….minutes/visit
AC.	Meals on Wheels		…… times/month
AD.	Telephone call to 111 service		…… times/month

Section 5: investigations / diagnostic tests

In the last 12 weeks, have you had any investigations / diagnostic tests?

5. **Yes ☐0 No ☐1 If you answered 'No', please go to section 6.**

If you answered 'Yes', please fill in the investigations / diagnostic test you have received in the last 12 weeks.

A.	Respiratory function test	……..number/last 4 weeks
B.	Chest x-ray	……..number/last 4 weeks
C.	Echocardiogram	……..number/last 4 weeks
D.	ECG	……..number/last 4 weeks
E.	Blood gas test	……..number/last 4 weeks
F.	Magnetic Resonance Image (MRI)	……..number/last 4 weeks
G.	CT / CAT scan	……..number/last 4 weeks
H.	Blood test	……..number/last 4 weeks
I.	Ultrasound scan bladder	……..number/last 4 weeks
J.	DEXA scan	……..number/last 4 weeks
K.	Other investigations / tests	……..number/last 4 weeks
L.	Any other information	

Section 6: help from friends or family

Please give details of any help you have received from your **friends or family** members in the12 weeks **as a result of your illness.**

A.	Personal care (e.g. bathing, dressing)	……..hours/ week
B.	Help with medical procedures	……..hours/ week
C.	Help inside the home (e.g. cooking, cleaning)	……..hours/ week
D.	Help outside the home (e.g. shopping)	……..hours/ week
E.	Time spent 'on-call' i.e. needing someone to be with them even if they don't have specific needs for help	……..hours/ week
F.	Other (please state) ……	……..hours/ week
G.	Any other information	

Section 7: additional equipment

Please list below any **additional equipment** you have been using over the last 12 weeks.

A. Ambulatory oxygen (oxygen cylinders) .....hours/ day

B. Long term oxygen therapy (oxygen concentrator) .....hours/ day

C. Non-invasive ventilation (or CAPC) .....hours/ day
☐ overnight ☐ during the day ☐ both overnight & during the day

D. Walking stick, rollator .....hours/ day

E. Wheelchair – manual or electric .....hours/ day

F. Buggy/ electric vehicle .....hours/ day

G. Adapted car .....hours/ day

H. For transfers standing frame .....hours/ day

I. For transfers hoist .....hours/ day

J. Feeding pump .....hours/ day

K. Specialised cutlery / equipment to dress .....hours/ day

L. Commode .....hours/ day

M. Special bed .....hours/ day

N. Bathroom or toilet adapted .....hours/ day

O. Catheter .....hours/ day

P. Manual evacuation of bowels / Peristeen system .....hours/ day

Q. Botulinum toxin .....hours/ day

R. Splinting .....hours/ day

S. Other equipment (please state) ....hours/ day

T. Any other information?

Please give this completed booklet to a member of the BETTER-B research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study.

Appendix 3 -Day 14 Questionnaires

BETTER-B

ISRCTN32236160

BETTER-B (Feasibility) Day 14 Participant Pack

To be completed by the trial staff

Participant Initials | Date of Birth (Day Month Year) | Participant ID (Centre No Trial No)

A large-print version of this questionnaire pack is available upon request

To be completed by the participant

Date completed (Day / Month / Year)

This pack consists of four questionnaires which we would be grateful if you could complete. The reason for doing this is to help us find out more about you and to understand how your condition affects you, from your point of view.

Most of the questionnaires contain a series of questions to which there is a choice of answers. **There are no right or wrong answers to any of the questions**; your answers should just reflect how you feel and your own experience.

These questionnaires have been used in several previous clinical research projects and can be completed in a relatively short time. However, there is no time limit; please complete as many of the questions as you can, **taking as much time as you need**.

If after answering any of the questions you realise you have made a mistake (for example, by ticking a box which doesn't reflect how you feel), please cross out your answer clearly and then select the answer that you meant to choose.

We appreciate that some of the questions included are of a sensitive and personal nature. We assure you that any information you provide will be dealt with in the strictest confidence, and will not be divulged or made available in any form that may subsequently reveal your identity.

After you have completed your questionnaires, hand it back to a member of the BETTER-B research team.

If the completion of the questionnaire raises any particular concerns we would encourage you to discuss these with either your GP or the research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 1: Modified Medical Research Council (mMRC) Dyspnoea Scale

Instructions: Please tell us which of the following statements best describes how breathless you are feeling by ticking the appropriate box (please only tick 1 box).

Grade	Statements	Please only tick 1
0	"I only get breathless with strenuous exercise"	
1	"I get short of breath when hurrying on the level or walking up a slight hill"	
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"	
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"	
4	"I am too breathless to leave the house" or "I am breathless when dressing"	

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 2: Integrated Palliative care Outcome Scale (IPOS)

Q1. What have been your main problems or concerns over the past week?

1.....

2.....

3.....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	Slightly	Moderately	Severely	Over-whelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.					
1.	0☐	1☐	2☐	3☐	4☐
2.	0☐	1☐	2☐	3☐	4☐
3.	0☐	1☐	2☐	3☐	4☐

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐
	Always	*Most of the time*	*Sometimes*	*Occasionally*	*Not at all*
Q6. Have you felt at peace?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you had as much information as you wanted?	0☐	1☐	2☐	3☐	4☐
	Problems addressed/ No problems	*Problems mostly addressed*	*Problems partly addressed*	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐
	On my own	*With help from a friend or relative*			*With help from a member of staff*
Q10. How did you complete this questionnaire?	☐	☐			☐

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 3: Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 4: Chronic respiratory questionnaire (Self Reported)

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities which you still do, but which are limited by your shortness of breath.

Listed below are some activities which can make people with lung problems feel short of breath.

If you have felt **short of breath** doing any of the **activities** listed below **during the last two weeks** then please tick each relevant activity. If you have **not** done the activity during the last two weeks or it does **not** make you short of breath then leave it blank.

THE ACTIVITIES ARE:

☐ 1. BEING ANGRY OR UPSET	☐ 14. PLAYING SPORTS
☐ 2. HAVING A BATH OR SHOWER	☐ 15. REACHING OVER YOUR HEAD
☐ 3. BENDING	☐ 16. RUNNING - SUCH AS FOR A BUS
☐ 4. CARRYING - SUCH AS GROCERIES	☐ 17. SHOPPING
☐ 5. DRESSING	☐ 18. WHILE TRYING TO SLEEP
☐ 6. EATING	☐ 19. TALKING
☐ 7. GOING FOR A WALK	☐ 20. VACUUMING
☐ 8. DOING YOUR HOUSEWORK	☐ 21. WALKING AROUND YOUR OWN HOME
☐ 9. HURRYING	☐ 22. WALKING UPHILL
☐ 10. MAKING YOUR BED	☐ 23. WALKING UPSTAIRS
☐ 11. MOPPING OR SCRUBBING A FLOOR	☐ 24. WALKING WITH OTHERS ON LEVEL GROUND
☐ 12. MOVING FURNITURE	☐ 25. PREPARING MEALS
☐ 13. PLAYING WITH CHILDREN/GRANDCHILDREN	

Please list **any other activities** that you have done during the last two weeks which have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life.

_____

_____

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

We would now like you to identify the **most <u>important</u> activities** in which you have been limited by your **shortness of breath** in the last **two weeks**.

Using the list you have made on the previous page, write down the **<u>five most important activities</u>** that have made you short of breath on the lines below. We would then like you to tell us **how short of breath** you have been while performing each activity by ticking the box which best describes how you feel.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1. _____	☐	☐	☐	☐	☐	☐	☐
2. _____	☐	☐	☐	☐	☐	☐	☐
3. _____	☐	☐	☐	☐	☐	☐	☐
4. _____	☐	☐	☐	☐	☐	☐	☐
5. _____	☐	☐	☐	☐	☐	☐	☐

PLEASE MAKE SURE YOU HAVE COMPLETED THE ABOVE TABLE BEFORE TURNING THE PAGE

Thank you

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

8. What about fatigue? How tired have you felt over the last 2 weeks?

Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMLY TIRED ❑
2. VERY TIRED ❑
3. QUITE A BIT OF TIREDNESS ❑
4. MODERATELY TIRED ❑
5. SOMEWHAT TIRED ❑
6. A LITTLE TIRED ❑
7. NOT AT ALL TIRED ❑

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

11. How much energy have you had in the last 2 weeks?

Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ❑
2. A LITTLE ENERGY ❑
3. SOME ENERGY ❑
4. MODERATELY ENERGETIC ❑
5. QUITE A BIT OF ENERGY ❑
6. VERY ENERGETIC ❑
7. FULL OF ENERGY ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?

Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?

Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?

Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

15. How often during the last 2 weeks have you felt low in energy?

Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

17. How often during the last 2 weeks have you felt worn out or sluggish?

Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?

Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ❑
2. GENERALLY DISSATISFIED, UNHAPPY ❑
3. SOMEWHAT DISSATISFIED, UNHAPPY ❑
4. GENERALLY SATISFIED, PLEASED ❑
5. HAPPY MOST OF THE TIME ❑
6. VERY HAPPY MOST OF THE TIME ❑
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ❑

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

20. In general how often during the last 2 weeks have you felt restless, tense or uptight?

Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Thank you very much for taking the time to complete this questionnaire.

Please give this completed booklet to a member of the BETTER-B research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study.

Appendix 4 -Day 28 Questionnaires

BETTER-B

ISRCTN32236160

BETTER-B (Feasibility) Day 28 Participant Pack

To be completed by the trial staff

Participant Initials | Date of Birth (Day Month Year) | Participant ID (Centre No Trial No)

A large-print version of this questionnaire pack is available upon request

To be completed by the participant

Date completed (Day / Month / Year)

This pack consists of four questionnaires which we would be grateful if you could complete. The reason for doing this is to help us find out more about you and to understand how your condition affects you, from your point of view.

Most of the questionnaires contain a series of questions to which there is a choice of answers. **There are no right or wrong answers to any of the questions**; your answers should just reflect how you feel and your own experience.

These questionnaires have been used in several previous clinical research projects and can be completed in a relatively short time. However, there is no time limit; please complete as many of the questions as you can, **taking as much time as you need**.

If after answering any of the questions you realise you have made a mistake (for example, by ticking a box which doesn't reflect how you feel), please cross out your answer clearly and then select the answer that you meant to choose.

We appreciate that some of the questions included are of a sensitive and personal nature. We assure you that any information you provide will be dealt with in the strictest confidence, and will not be divulged or made available in any form that may subsequently reveal your identity.

After you have completed your questionnaires, hand it back to a member of the BETTER-B research team.

If the completion of the questionnaire raises any particular concerns we would encourage you to discuss these with either your GP or the research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 1: Modified Medical Research Council (mMRC) Dyspnoea Scale

Instructions: Please tell us which of the following statements best describes how breathless you are feeling by ticking the appropriate box (please only tick 1 box).

Grade	Statements	Please only tick 1
0	"I only get breathless with strenuous exercise"	
1	"I get short of breath when hurrying on the level or walking up a slight hill"	
2	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"	
3	"I stop for breath after walking about 100 yards or after a few minutes on the level"	
4	"I am too breathless to leave the house" or "I am breathless when dressing"	

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 2: Integrated Palliative care Outcome Scale (IPOS)

Q1. What have been your main problems or concerns over the past week?

1.....

2.....

3.....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick one box that best describes how it has affected you over the past week.

	Not at all	Slightly	Moderately	Severely	Over-whelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick one box to show how they have affected you over the past week.					
1.	0☐	1☐	2☐	3☐	4☐
2.	0☐	1☐	2☐	3☐	4☐
3.	0☐	1☐	2☐	3☐	4☐

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Over the past week:

	Not at all	*Occasionally*	*Sometimes*	*Most of the time*	*Always*
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐
	Always	*Most of the time*	*Sometimes*	*Occasionally*	*Not at all*
Q6. Have you felt at peace?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you had as much information as you wanted?	0☐	1☐	2☐	3☐	4☐
	Problems addressed/ No problems	*Problems mostly addressed*	*Problems partly addressed*	*Problems hardly addressed*	*Problems not addressed*
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐
	On my own	*With help from a friend or relative*			*With help from a member of staff*
Q10. How did you complete this questionnaire?	☐	☐			☐

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 3: Hospital Anxiety and Depression Scale (HADS)

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

I feel cheerful:	D
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	A
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	A
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	D
Often	0
Sometimes	1
Not often	2
Very seldom	3

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 4: Chronic respiratory questionnaire (Self Reported)

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities which you still do, but which are limited by your shortness of breath.

Listed below are some activities which can make people with lung problems feel short of breath.

If you have felt **short of breath** doing any of the **activities** listed below **during the last two weeks** then please tick each relevant activity. If you have **not** done the activity during the last two weeks or it does **not** make you short of breath then leave it blank.

THE ACTIVITIES ARE:

☐	1. BEING ANGRY OR UPSET
☐	2. HAVING A BATH OR SHOWER
☐	3. BENDING
☐	4. CARRYING - SUCH AS GROCERIES
☐	5. DRESSING
☐	6. EATING
☐	7. GOING FOR A WALK
☐	8. DOING YOUR HOUSEWORK
☐	9. HURRYING
☐	10. MAKING YOUR BED
☐	11. MOPPING OR SCRUBBING A FLOOR
☐	12. MOVING FURNITURE
☐	13. PLAYING WITH CHILDREN/GRANDCHILDREN
☐	14. PLAYING SPORTS
☐	15. REACHING OVER YOUR HEAD
☐	16. RUNNING - SUCH AS FOR A BUS
☐	17. SHOPPING
☐	18. WHILE TRYING TO SLEEP
☐	19. TALKING
☐	20. VACUUMING
☐	21. WALKING AROUND YOUR OWN HOME
☐	22. WALKING UPHILL
☐	23. WALKING UPSTAIRS
☐	24. WALKING WITH OTHERS ON LEVEL GROUND
☐	25. PREPARING MEALS

Please list **any other activities** that you have done during the last two weeks which have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life.

_____

_____

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

We would now like you to identify the **most <u>important</u> activities** in which you have been limited by your **shortness of breath** in the last **two weeks**.

Using the list you have made on the previous page, write down the **<u>five most important activities</u>** that have made you short of breath on the lines below. We would then like you to tell us **how short of breath** you have been while performing each activity by ticking the box which best describes how you feel.

HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST TWO WEEKS WHILE PERFORMING THESE ACTIVITIES?

	Extremely short of breath	Very short of breath	Quite short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath
1. _____	☐	☐	☐	☐	☐	☐	☐
2. _____	☐	☐	☐	☐	☐	☐	☐
3. _____	☐	☐	☐	☐	☐	☐	☐
4. _____	☐	☐	☐	☐	☐	☐	☐
5. _____	☐	☐	☐	☐	☐	☐	☐

PLEASE MAKE SURE YOU HAVE COMPLETED THE ABOVE TABLE BEFORE TURNING THE PAGE

Thank you

6. In general, how much of the time during the last 2 weeks have you felt frustrated or impatient?

Please indicate how often during the last 2 weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

7. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

8. What about fatigue? How tired have you felt over the last 2 weeks?

Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMLY TIRED ❑
2. VERY TIRED ❑
3. QUITE A BIT OF TIREDNESS ❑
4. MODERATELY TIRED ❑
5. SOMEWHAT TIRED ❑
6. A LITTLE TIRED ❑
7. NOT AT ALL TIRED ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

9. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

10. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

11. How much energy have you had in the last 2 weeks?

Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL ❑
2. A LITTLE ENERGY ❑
3. SOME ENERGY ❑
4. MODERATELY ENERGETIC ❑
5. QUITE A BIT OF ENERGY ❑
6. VERY ENERGETIC ❑
7. FULL OF ENERGY ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

12. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks?

Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

13. How often during the last 2 weeks did you feel you had complete control of your breathing problems?

Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

14. How much of the time during the last 2 weeks did you feel relaxed and free of tension?

Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME ❑
2. A LITTLE OF THE TIME ❑
3. SOME OF THE TIME ❑
4. A GOOD BIT OF THE TIME ❑
5. MOST OF THE TIME ❑
6. ALMOST ALL OF THE TIME ❑
7. ALL OF THE TIME ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

15. How often during the last 2 weeks have you felt low in energy?

Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

16. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

17. How often during the last 2 weeks have you felt worn out or sluggish?

Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

18. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks?

Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME ❑
2. GENERALLY DISSATISFIED, UNHAPPY ❑
3. SOMEWHAT DISSATISFIED, UNHAPPY ❑
4. GENERALLY SATISFIED, PLEASED ❑
5. HAPPY MOST OF THE TIME ❑
6. VERY HAPPY MOST OF THE TIME ❑
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED ❑

19. How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

20. In general how often during the last 2 weeks have you felt restless, tense or uptight?

Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME ❑
2. MOST OF THE TIME ❑
3. A GOOD BIT OF THE TIME ❑
4. SOME OF THE TIME ❑
5. A LITTLE OF THE TIME ❑
6. HARDLY ANY OF THE TIME ❑
7. NONE OF THE TIME ❑

Thank you very much for taking the time to complete this questionnaire.

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 5: EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

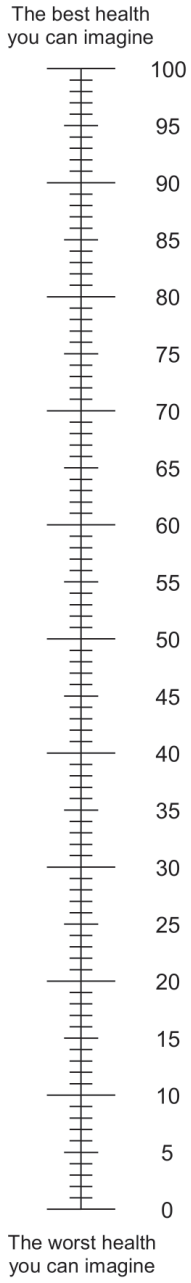
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 6: Generalised Self-Efficacy Scale (GSES)

Instructions: Please indicate the extent to which each statement applies to you by ticking the appropriate box

		Not at all true	Barely true	Moderately true	Exactly true
1	I can always manage to solve difficult problems if I try harder				
2	If someone opposes me, I can find means and ways to get what I want				
3	It is easy for me to stick to my aims and accomplish my goals				
4	I am confident that I could deal efficiently with unexpected events				
		Not at all true	**Barely true**	**Moderately true**	**Exactly true**
5	Thanks to my resourcefulness, I know how to handle unforeseen situations				
6	I can solve most problems if I invest the necessary effort				
7	I can remain calm when facing difficulties because I can rely on my coping abilities				
8	When I am confronted with a problem, I can usually find several solutions				
9	If I am in a bind, I can usually think of something to do				
10	No matter what comes my way, I'm usually able to handle it				

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 7: Client Services Receipt Inventory (CSRI)

Instructions: This questionnaire is about your use of health and social care, accommodation, living situation and informal care (i.e. given by family member) **over the last 12 weeks** Information provided here is used to calculate the costs of care.

Health and Social services you have received - these are some of the services that you may be receiving, most people will have received only a few of them.

Section 1: In-patient or other residential services

In the past 12 weeks, have you stayed in a hospital/ other residential care setting?

1. **Yes ☐0 No ☐1** **If you answered 'No', please go to section 2.**

If you answered 'Yes', please state the total number of days you stayed in any of the following wards or settings during the last 12 weeks.

A.	Intensive care unit	..... days
B.	Neurology ward	..... days
C.	Medical ward	..... days
D.	Specialist rehabilitation ward or unit	..... days
E.	Other ward (please state).....	..... days
F.	Hospice	..... days
G.	Nursing or Residential home	..... days
H.	Respite care setting	..... days
I.	Other residential setting (please state)	..... days
J.	A&E department	..... days
K.	Number of hospital admissions	..... attendances
L.	Emergency ambulance service	..... attendances

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section 2: Day care or community services

In the last 12 weeks, have you spent time in a day care or community setting?

2. **Yes ☐0 No ☐1 If you answered 'No', please go to section 3.**

If you answered 'Yes', please state the average number of times in the last 12 weeks you attended any of the following:

A.	Day hospital	.....attendances / month
B.	NHS day care	.....attendances / month
C.	Palliative day care	.....attendances / month
D.	Rehabilitation day unit	.....attendances / month
E.	Neurology day care	.....attendances / month
F.	Social services day centre	.....attendances / month
G.	Voluntary organisation day/ resource centre	.....attendances / month
H.	Support groups or societies	.....attendances / month
I.	Other day setting (please state)	.....attendances / month

Section 3: Out-patient clinic or surgery based appointments

In the last 12 weeks, have you had any appointments or consultations with professionals in a hospital out-patient department or other type of clinic/surgery? **This can include face-to-face, telephone or email consultations.**

3. **Yes ☐0 No ☐1 If you answered 'No', please go to section 4.**

If you answered 'Yes', please state the number of visits made to any of these professionals over the last 12 weeks and the average time for a visit in minutes.

A.	General Practitioner (GP)	.....visits	.....minutes/visit
B.	Neurologist	.....visits	.....minutes/visit

C.	Palliative care doctor/ palliative care consultant	……visits	……..minutes/visit
D.	Psychiatrist	……visits	……..minutes/visit
E.	Other doctor (please state)……	……visits	……..minutes/visit
F.	Other doctor (please state)……	……visits	……..minutes/visit
G.	General practice nurse	……visits	……..minutes/visit
H.	Community mental health nurse	……visits	……..minutes/visit
I.	Palliative care nurse	……visits	……..minutes/visit
J.	Specialist Parkinson's nurse	……visits	……..minutes/visit
K.	Specialist MS nurse	……visits	……..minutes/visit
L.	Specialist MND nurse	……visits	……..minutes/visit
M.	Other nurse (please state)……	……visits	……..minutes/visit
N.	Physiotherapist	……visits	……..minutes/visit
O.	Occupational therapist	……visits	……..minutes/visit
P.	Speech therapist	……visits	……..minutes/visit
Q.	Social worker	……visits	……..minutes/visit
R.	Palliative care social worker	……visits	……..minutes/visit
S.	Other therapist (please state)……	……visits	……..minutes/visit
T.	Psychologist	……visits	……..minutes/visit
U.	Counsellor	……visits	……..minutes/visit
V.	Priest/Clergy/Chaplain/Imam/Rabbi (please state)……	……visits	……..minutes/visit
W.	Mental health worker	……visits	……..minutes/visit
X.	Dentist	……visits	……..minutes/visit

Y. Dietician .....visits .....minutes/visit

Z. Other* ....visits .....minutes/visit

*For example, osteopath, homeopath, acupuncturist etc.

Section 4: Home based services

In the last 12 weeks, have you had any home based services?

4. **Yes ☐0 No ☐1 If you answered 'No', please go to section 5.**

If you answered 'Yes', please fill in the average number of visits in the last 12 weeks, and the average time a visit took.
Please note: Some services are timed in minutes / visit and others in hours / visit.

A.	Home palliative care/hospice service	.....visits/month	.....minutes/visit
B.	General Practitioner (GP)	.....visits	.....minutes/visit
C.	Palliative care doctor	.....visits	.....minutes/visit
D.	Qualified general nurse	.....visits	.....minutes/visit
E.	Community nurse	.....visits/month	.....minutes/visit
F.	District nurse	.....visits	.....minutes/visit
G.	General Practice nurse	.....visits	.....minutes/visit
H.	Community mental nurse	.....visits/month	.....minutes/visit
I.	Specialist palliative care nurse	.....visits	.....minutes/visit
J.	Specialist Parkinson's nurse	.....visits	.....minutes/visit
K.	Specialist MS nurse	.....visits	.....minutes/visit
L.	Specialist MND nurse	.....visits	.....minutes/visit
M.	Physiotherapy	.....visits/month	.....minutes/visit
N.	Occupational therapy	.....visits/month	.....minutes/visit
O.	Speech therapy	.....visits/month	.....minutes/visit
P.	Dietician	.....visits	.....minutes/visit

Q.	Home care manager	.....visits	.....minutes/visit
R.	Chiropodist	.....visits	.....minutes/visit
S.	Priest/Clergy/Chaplain/Imam/ Rabbi (please state).....	.....visits	.....minutes/visit
T.	Social worker	.....visits	.....minutes/visit
U.	Counsellor	.....visits	.....minutes/visit
V.	Psychologist	.....visits	.....minutes/visit
W.	Palliative care social worker	.....visits	.....minutes/visit
X.	Domestic help	.....visits	.....hours/visit
Y.	Paid formal caregiver (e.g. assist with personal hygiene, preparing meals)	.....visits	.....minutes/visit
Z	Day time sitting service	.....visits	.....hours/visit
AA.	Overnight sitting service	.....visits	.....hours /visit
AB.	Other service (please state).....	.....visits	.....hours.....minutes/visit
AC.	Meals on Wheels		..... times/month
AD.	Telephone call to 111 service		..... times/month

Section 5: investigations / diagnostic tests

In the last 12 weeks, have you had any investigations / diagnostic tests?

5. **Yes ☐0 No ☐1 If you answered 'No', please go to section 6.**

If you answered 'Yes', please fill in the investigations / diagnostic test you have received in the last 12 weeks.

A.	Respiratory function test	……..number/last 4 weeks
B.	Chest x-ray	……..number/last 4 weeks
C.	Echocardiogram	……..number/last 4 weeks
D.	ECG	……..number/last 4 weeks
E.	Blood gas test	……..number/last 4 weeks
F.	Magnetic Resonance Image (MRI)	……..number/last 4 weeks
G.	CT / CAT scan	……..number/last 4 weeks
H.	Blood test	……..number/last 4 weeks
I.	Ultrasound scan bladder	……..number/last 4 weeks
J.	DEXA scan	……..number/last 4 weeks
K.	Other investigations / tests	……..number/last 4 weeks
L.	Any other information	

Section 6: help from friends or family

Please give details of any help you have received from your **friends or family** members in the12 weeks **as a result of your illness.**

A.	Personal care (e.g. bathing, dressing)	……..hours/ week
B.	Help with medical procedures	……..hours/ week
C.	Help inside the home (e.g. cooking, cleaning)	……..hours/ week
D.	Help outside the home (e.g. shopping)	……..hours/ week
E.	Time spent 'on-call' i.e. needing someone to be with them even if they don't have specific needs for help	……..hours/ week
F.	Other (please state) ……	……..hours/ week
G.	Any other information	

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section 7: additional equipment

Please list below any **additional equipment** you have been using over the last 12 weeks.

A. Ambulatory oxygen (oxygen cylinders) .....hours/ day

B. Long term oxygen therapy (oxygen concentrator) .....hours/ day

C. Non-invasive ventilation (or CAPC) .....hours/ day
☐ overnight ☐ during the day ☐ both overnight & during the day

D. Walking stick, rollator .....hours/ day

E. Wheelchair – manual or electric .....hours/ day

F. Buggy/ electric vehicle .....hours/ day

G. Adapted car .....hours/ day

H. For transfers standing frame .....hours/ day

I. For transfers hoist .....hours/ day

J. Feeding pump .....hours/ day

K. Specialised cutlery / equipment to dress .....hours/ day

L. Commode .....hours/ day

M. Special bed .....hours/ day

N. Bathroom or toilet adapted .....hours/ day

O. Catheter .....hours/ day

P. Manual evacuation of bowels / Peristeen system .....hours/ day

Q. Botulinum toxin .....hours/ day

R. Splinting .....hours/ day

S. Other equipment (please state) ....hours/ day

T. Any other information?

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Part 8: Blinding Assessment

Which treatment do you ***think*** you received?

- ☐ Mirtazapine
- ☐ Placebo
- ☐ Don't know

Why do you feel you received this treatment?

- ☐ Treatment seemed not to work
- ☐ Treatment seemed to work
- ☐ I had side-effects (please list below)
- ☐ Appearance of capsules
- ☐ I was told by staff
- ☐ Other reason (please write below)

If you ticked 'side-effects', what were they?

If you ticked 'other reason', what is your reason?

On a scale of 1 to 10 how certain are you of your choice? ☐

s

Please give this completed booklet to a member of the BETTER-B research team.

Thank you for your time and valuable contribution to the BETTER-B (Feasibility) study.

Appendix 5 -Topic guide

Topic guide

You have recently taken part in a study called Better B. I would like to talk to you to understand your experience of taking part, what you expected, and what it was like.

If you want to stop the interview at any point let me know. You don't need to give a reason, and your clinical care won't be affected. Everything you say will be kept confidential.

Do you have any questions before we begin?

Introduction/ Better-B

What did you understand about the study?

What was your experience of taking part?

Prompt: Can you tell me a bit about that?

Recruitment/ joining the study

How were you asked to take part in the study?

What was that like?

Prompt: Who spoke to you? What were you told? Where were you at the time?

What were your expectations?

Why did you decide to take part?

Prompt: What specifically did you want to see improved? What change were you hoping for?

Trial processes/ taking part

What did you understand about the treatment you received?

Prompt: What did you think about taking an antidepressant medication? What do you understand about a placebo drug/ randomisation?

How did you find taking the medication?

Probe: Did you have any difficulties? How did you manage with your other medications? (Dosette Box/ Blister Pack/ Diary as reminder).

How did you being visited at home?

Would you have preferred to have been seen somewhere else?

How did you find it completing the questionnaires?

Probe: What did you think about the questions we asked? Do you think they were the right questions? Did they capture what is important to you?

Would anything have made it easier to take part?

Probe: What were the downsides to taking part?

Benefit

Tell me in what ways the drug changed how you felt?

Prompt: Did you notice any change in your breathing, sleep, appetite, drowsiness?

What did you hope would change?

For you what would be the most important change?

Were there any changes you had not expected?

Closing section

Is there anything else that you think is important for me to know?

Is there anything that has worried you during the course of this conversation?

Is there anything else you would like to talk about?

Appendix 6 -Better-B Protocol

BETTER-B Feasibility:
BETter TreatmEnts for Refractory Breathlessness

A feasibility study of the use of mirtazapine for refractory breathlessness

EudraCT Number:	**2015-004064-11**
ISRCTN Number:	**XXXXX**
REC Number:	**XXXXX**

Sponsors: King's College London and King's College Hospital NHS Foundation Trust

Funded by: Marie Curie Cancer Care, Cancer Research UK (Grant Ref: A18859)
Supported by: Yorkshire Cancer Research
National Institute for Health and Care Excellence (NIHR)
Cicely Saunders International

Chief Investigator: Prof Irene J. Higginson, Professor of Palliative Care,
King's College London, Cicely Saunders Institute,
Department of Palliative Care, Policy & Rehabilitation,
Bessemer Road, Denmark Hill, London, SE5 9PJ

Key Contacts

General Enquiries:	Email: better-b@leeds.ac.uk
Randomisation:	Tel: 0113 343 1486
Pharmacovigilance:	Fax: 0113 343 6774

Chief Investigator

Professor Irene Higginson
Professor of Palliative Care
Cicely Saunders Institute
King's College London

Tel: 0207 848 5516
Fax: 0207 848 5517
Email: irene.higginson@kcl.ac.uk

Sponsor Representative

Jackie Pullen
King's Health Partners Clinical Trials Office
Great Maze Pond
London SE1 9RT

Tel: 0207 188 5732
Fax: 0207 188 8330
Email: jackie.pullen@kcl.ac.uk

Trial Management *(for queries regarding site set up and regulatory and governance queries)*

Ms Katie Neville
Senior Trial Coordinator
Clinical Trials Research Unit
University of Leeds

Tel: 0113 343 4108
Fax: 0113 343 0686
Email: k.neville@leeds.ac.uk

Mrs Victoria Hiley
Head of Trial Management - Solid Tumours
Clinical Trials Research Unit
University of Leeds

Tel: 0113 343 2657
Fax: 0113 343 0686
Email: v.hiley@leeds.ac.uk

Data Management *(for queries regarding eligibility, treatment, CRF and data query completion, SAE and SUSAR reporting and randomisation process)*

Ms Vicky Liversedge
Trial Coordinator
Clinical Trials Research Unit
University of Leeds

Tel: 0113 343 1486
Fax: 0113 343 6774
Email: v.liversedge@leeds.ac.uk

Statistics

Dr Sarah Brown
Principal Statistician
Clinical Trials Research Unit
University of Leeds

Tel: 0113 343 1472
Fax: 0113 343 1471
Email: s.brown@leeds.ac.uk

Mrs Avie-Lee Tillotson
Medical Statistician
Clinical Trials Research Unit
University of Leeds

Tel: 0113 343 0217
Fax: 0113 343 1471
Email: a.coney@leeds.ac.uk

Trial Physician and Qualitative Interview Sub-study Researcher

Dr Natasha Lovell
Academic Clinical Fellow
Cicely Saunders Institute
King's College London

Tel: 0207 848 5825
Email: natasha.lovell@kcl.ac.uk

Clinical Advisors

Prof Miriam Johnson
Professor of Palliative Medicine, York Medical School, University of Hull and Honorary Consultant to St Catherine's Hospice, Scarborough

Dr Andrew Wilcock
Macmillan Clinical Reader in Palliative Medicine and Medical Oncology, Hayward House Macmillan Specialist Care Cancer Unit, Nottingham City Hospital

Prof David Currow
Professor of Palliative and Supportive Services, Flinders University, Adelaide, Australia

Health Economics Advisor

Dr DeokHee Yi
Health Economist, Cicely Saunders Institute, King's College London

Patient Advisor

Mandy Paine
National Council for Palliative Care

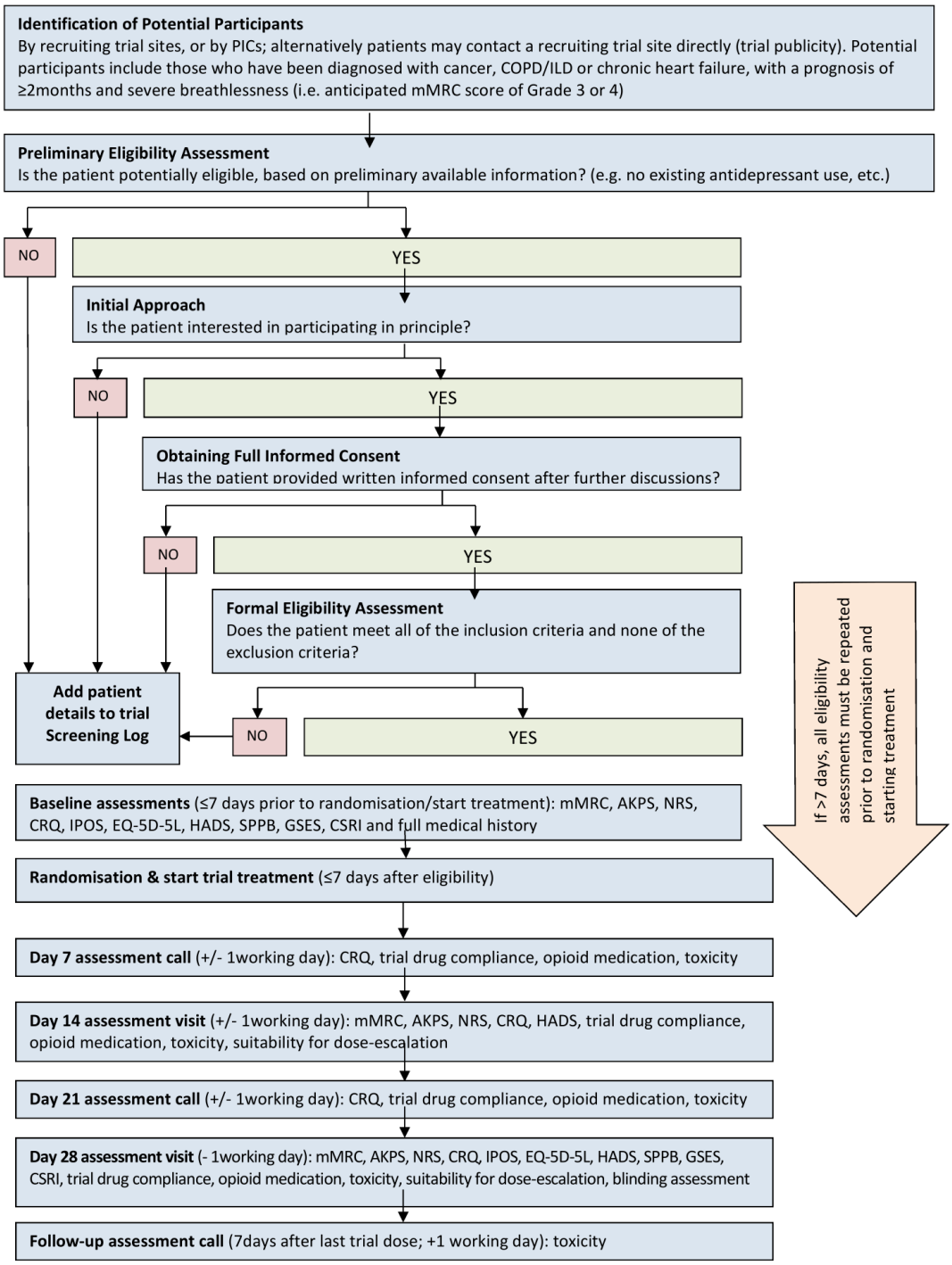
1. Contents

2. Trial Summary

Trial Title (Full)	BETTER-B (Feasibility): **BET**ter Treatm**E**nts for **R**efractory **B**reathlessness: A feasibility study of the use of mirtazapine for refractory breathlessness
Trial Title (Short)	BETTER-B (Feasibility): **BET**ter Treatm**E**nts for **R**efractory **B**reathlessness
Trial Acronym	BETTER-B (Feasibility)
Trial Background	Breathlessness (also called dyspnea or dyspnoea) is a common, distressing symptom in advanced disease, particularly those affecting the heart and lungs, causing considerable disability for patients, and anxiety and social isolation for them and their family and carers. Breathlessness which continues despite optimal management of the underlying causes and current symptom relief measures, is termed 'intractable' or 'refractory'. It generally worsens as the disease progresses and is one of the most frightening aspects facing a person with advanced disease. Over 2 million people experience breathlessness each year in the UK. This includes more than 90% of the over 1 million people in the UK diagnosed with moderate to severe chronic lung disease, over 50% of the 200,000+ with incurable cancer and 50% of the 2 million with chronic heart failure (many of whom will suffer refractory breathlessness). Breathlessness is associated with shortened life expectancy and often results in emergency visits and hospitalisation. There are few effective treatments for refractory breathlessness, thus, refractory breathlessness represents a huge unmet need and new approaches are desperately required. Morphine has a role, but there are no other proven pharmacological treatments. Preliminary data suggest that serotonergic modulation is beneficial but rigorous evaluation has not been conducted. There is therefore a need to explore the potential role of antidepressants in this setting. Mirtazapine is a widely used noradrenergic and specific serotonergic antidepressant (NaSSA). There is clinical experience to support its use in anxiety and panic disorder and clinical evidence for its use in major depressive disorders associated with anxiety. BETTER-B (Feasibility) will help address this unmet need by exploring if mirtazapine has a role in the management of refractory breathlessness in patients with cancer, chronic obstructive pulmonary disease, interstitial lung disease, or chronic heart failure. If successful, a larger trial will be conducted.
Trial Design	A randomised (1:1) placebo-controlled, double-blind, mixed-methods, multicentre (3 trial sites) feasibility trial.
Trial Aim	The aim of the study is to determine the feasibility of performing a large-

	scale double-blind, placebo-controlled randomised trial of mirtazapine for refractory breathlessness.
Trial Endpoints	Primary endpoint: • Number of patients recruited across 3 trial sites over a 12-month period Secondary endpoints: • Feasibility • Activity • Safety and toxicity • Symptoms and Quality of Life: *Ancillary study*: • Qualitative Interviews
Trial Population	60 participants suffering from severe refractory breathlessness, diagnosed with cancer, lung disease (COPD/ILD) or chronic heart failure.
Randomisation	Randomisation (1:1) to the placebo arm or the active arm (mirtazapine) will be carried out by the Clinical Trials Research Unit (CTRU), Leeds at baseline prior to starting treatment.
Trial Treatment	All participants are planned to receive 28 days of trial treatment, taking 1 capsule of trial drug (placebo or 15mg mirtazapine) daily. After an initial 14 days of treatment, participants will be assessed for suitability to escalate their dose. If deemed suitable, participants will increase their dose to 2 capsules daily (placebo or 30mg mirtazapine).
Duration	Trial recruitment will continue for 12 months and be followed by a short follow-up period (until the last randomised participant's follow-up assessment).
Evaluation of outcome measures	Participants will be assessed (either by phone or in person) every 7 days during trial treatment (day 7, 21 and 28) and then have a follow-up assessment (by phone) 7 days after their last trial drug dose.

3. Trial Schema



4. Abbreviations

AE	Adverse Event
AKPS	Australia-modified Karnofsky Performance Scale
AR	Adverse Reaction
ATS	American Thoracic Society
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ	Chronic Respiratory Questionnaire
CSRI	Client Services Receipt Inventory
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Connective Tissue Disease
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring & Ethics Committee
DSUR	Development Safety Update Report
ETS	European Respiratory Society
GCP	Good Clinical Practice
GSES	Generalized Self-Efficacy Scale
GSTFT	Guy's and St Thomas' NHS Foundation Trust
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ILD	Interstitial Lung Disease
IME	Important Medical Event
IMP	Investigational Medicinal Product
IPF	Idiopathic Pulmonary Fibrosis
IPOS	Integrated Palliative care Outcome Scale
ITT	Intention To Treat
MAO-I	Monoamine Oxidase Inhibitor
MDT	Multi-Disciplinary Teams
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Authority
mMRC	modified Medical Research Council
NaSSA	Noradrenergic and Specific Serotonergic Antidepressant
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NYHA	New York Heart Association
PI	Principal Investigator
PIC	Participants Identification Centre
PIS	Participant Information Sheet
PSL	Participant Summary Leaflet
QALY	Quality Adjusted Life Year
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SPPB	Short Physical Performance Battery
SSOP	Study Site Operating Procedure
SSRI	Selective Serotonin Re-uptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction

TCA	Tricyclic Antidepressant
TMG	Trial Management Group
TSC	Trial Steering Committee

5. Background

5.1 Breathlessness

Breathlessness is a common, distressing symptom in life-limiting conditions, particularly those affecting the heart and lungs, causing considerable disability for patients [1-3], and anxiety and social isolation for them and their family and carers [4-6]. Breathlessness (also called dyspnea or dyspnoea) is usually described as: "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioural responses" [1]. Breathlessness which continues despite optimal management of the underlying causes and current symptom relief measures, is termed 'intractable' or 'refractory'. It generally worsens as the disease progresses and is one of the most frightening aspects facing a person with advanced disease. Caregivers often report a feeling of helplessness while watching their loved ones suffer; clinicians too experience similar feelings due to the lack of effective interventions [4-6].

Over 2 million people experience breathlessness each year in the UK. This includes more than 90% of the over 1 million people in the UK diagnosed with moderate to severe chronic lung disease, over 50% of the 200,000+ with incurable cancer and 50% of the 2 million with chronic heart failure (many of whom will suffer refractory breathlessness) [7-10]. In addition, breathlessness is found in people severely affected by renal and liver failure, neurological conditions, HIV/AIDS and many autoimmune diseases [8, 11-13]. Breathlessness increases as the disease progresses [14, 15], is associated with shortened life expectancy [16-18], is very frightening for patients and families [5, 6, 9, 10, 19] and often results in emergency visits and hospitalisation [3, 20-22].

5.2 Treatments

There are few effective treatments for refractory breathlessness. Morphine has a role [23-29], but there are no other proven pharmacological treatments. Animal studies, case reports, observational series and a phase II trial of 10 patients suggest that serotonergic modulation is beneficial [30-34], but rigorous evaluation has not been conducted.

Opioids, oxygen and benzodiazepines

The most relevant reviews are available for opioids, oxygen and benzodiazepines [29, 35-38]. Although opioids by mouth and injection can reduce breathlessness, optimal dosing, titration and potential issues arising from longer term use (e.g. safety, tolerance, dependence, misuse) remain to be determined. Further, not all patients may be suitable for, or want them [27, 29, 39], especially those with non-malignant disease. In one Dutch study, only 2% of people with advanced Chronic Obstructive Pulmonary Disease (COPD) were prescribed

strong opioids [9]. Evidence does not support the use of nebulized opioids or transmucosal fentanyl [29, 38]. Benefit from oxygen is similar to medical air in mildly or non-hypoxaemic breathless patients with various diseases, and there are limitations to its use (e.g. safety, cost) [40]. The evidence currently does not support a role for benzodiazepines [37]. Thus, the need remains to develop new palliative approaches with fewer limitations.

Antidepressants

Antidepressants are an attractive option to explore, particularly given their low risk of respiratory depression and dependence [30]. There are no systematic reviews relating to such use. Data is limited, but animal work [32] and case series of patients with chronic breathlessness reporting improvement in breathlessness ± exercise tolerance with older tricyclic antidepressants (TCA) or selective serotonin re-uptake inhibitor (SSRI) antidepressants [30, 31, 33], suggest that serotonin plays a role in the control of respiration and generation/perception of breathlessness. The exact mechanism is unclear; a reduction in sensitivity to CO2 has been reported [41]; ultimately it probably involves modulation of brain stem centres responsible for respiratory rhythm and/or of centres involved in the perception of breathlessness [31].

Benefit does not appear to relate to antidepressant or anxiolytic effects *per se*, as improvements in breathlessness are also reported by patients without concurrent anxiety and/or depression [31, 33, 42]. However, manipulation of serotonin in patients with panic disorder reduces experimentally induced panic (using CO2 challenges) and given that 'respiratory anxiety and panic' are common in patients with chronic breathlessness, this could be relevant [41].

Mirtazapine

Mirtazapine is a widely used noradrenergic and specific serotonergic antidepressant (NaSSA). It antagonises receptors (α2, 5HT2A and 5HT2C) which inhibit the release of serotonin, noradrenaline and dopamine [43, 44]. In addition, it antagonizes H1- and 5HT3-receptors.

Mirtazapine is a commonly used antidepressant with good data supporting its efficacy, acceptability and safety in the treatment of depressive illness [31, 42, 45]. There is clinical experience to support its use in anxiety and panic disorder and clinical evidence for its use in major depressive disorders associated with anxiety [46].

It is an antidepressant which appears to have a quicker onset of action and fewer drug interactions than other antidepressants, has a good safety record and may be better tolerated than other antidepressants in this population [45-50]. It also has the added advantage of reducing anxiety [47-49, 51], which is a common consequence of severe episodes of breathlessness [52-54].

Mirtazapine is increasingly preferred over SSRIs (and other antidepressants) in advanced disease because it appears to have a quicker onset of action [45] and it has fewer undesirable effects leading to early discontinuation, fewer drug interactions and is not associated with cardiovascular toxicity or sexual dysfunction [55].

Further, it also has appetite stimulation, anti-emetic and analgesic properties, which could be of particular benefit to patients with advanced disease, and the side effect of weight gain may also be an advantage for some patients who have weight loss in advanced disease [50, 51, 56-59]. Thus, mirtazapine is a promising alternative to SSRIs to test in this setting.

5.3 Current Research and Rationale for BETTER-B Feasibility Trial

Despite an increase in the understanding of the mechanisms associated with the generation and perception of breathlessness, this has not yet translated into effective new treatment options [1]. Thus, refractory breathlessness represents a huge unmet need and new approaches are desperately required. Authoritative guidelines have highlighted the need for interdisciplinary research to test new treatments in sufficiently powered clinical trials. They have also stressed the importance of not limiting potentially universally beneficial approaches to one particular patient group [1, 35, 36, 60-62].

There is a need to explore the potential role of antidepressants in this setting. Existing data is limited, but reflects that SSRIs (e.g. sertraline) are now generally preferred over TCAs from a tolerability point of view [50, 55-58]. A search of current trial databases on the management of breathlessness (and dyspnoea), including clinicaltrials.gov and controlled-trials.com, and contact with leaders in the field identified one study of morphine (Johnson), one relevant phase II [34] and one phase III study of sertraline [63] (Currow, personal communication) and no studies of mirtazapine. Currow's randomised trial in Australia is testing sertraline in the management of breathlessness across several conditions following promising phase II data [34, 63]. This trial, recruiting in 12 hospitals, has (as of October 2015) 160 patients randomised (total needed 220), and 107 completed (total needed 150). However, as a partner in this application, the Australian group has raised concerns that because of the many contra-indications for sertraline use, the number of potential drug interactions and undesirable effects, many otherwise eligible patients are excluded from the trial, leading not only to slow recruitment (first patient enrolled January 2011), but more importantly, to concerns that the results may have limited generalisability. Thus, BETTER-B will test a different category of antidepressant in this setting, one which may have advantages over sertraline and other SSRIs.

Preliminary data suggest that serotonergic modulation is beneficial but rigorous evaluation has not been conducted. BETTER-B will help address this need by exploring if mirtazapine

has a role in the management of refractory breathlessness in patients with cancer, chronic obstructive pulmonary disease, interstitial lung disease, or chronic heart failure.

5.4 Justification for Double-Blind Feasibility Trial

Breathlessness is a complex, multifactorial experience and is reported as a subjective measure, and refractory breathlessness is a feature of advanced disease where participants may suffer from adverse events due to their underlying condition(s). Therefore, in order to gain a measure of the benefits and harms of an intervention in a trial, a placebo control is needed.

A large-scale trial was considered, however in light of the uncertainty around recruitment, blinding and attrition in this trial, and in order to obtain an estimate of likely activity of this drug to inform the design of the large-scale trial, a feasibility trial was deemed necessary first. This feasibility trial will determine whether a large-scale trial in this advanced illness setting can be performed. The trial is placebo-controlled and double-blind, to reflect exactly the proposed design of a subsequent large-scale trial. A 7-day follow-up period has been chosen in order to provide sufficient data on recruitment and retention for a large-scale trial.

The results of this trial will be used to determine the feasibility of proceeding with a large randomised, placebo-controlled, double-blind trial of approximately 250 patients in this setting and this population and the best methods/design for that study. They will inform future studies in patients with advanced diseases, especially recruitment and trial design, and advance our understanding of breathlessness and ways to research it.

A formal feasibility trial design was not deemed necessary as there is evidence of the activity and safety of other similar drugs in the same class as mirtazapine, providing preliminary evidence that a large-scale trial of mirtazapine is warranted (see section 5.2 and personal confidential communication, Currow et al., Trial Management Group member).

6. Aims and Objectives

This is a randomised placebo-controlled, double-blind, mixed-methods feasibility trial of mirtazapine for refractory breathlessness in 60 patients with a diagnosis of cancer, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) or chronic heart failure.

6.1 Aims

The aim of the trial is to determine the feasibility of performing a large-scale double-blind, placebo-controlled randomised trial of mirtazapine for refractory breathlessness.

6.2 Primary Objective

The primary objective is to determine whether a randomised, double-blind, placebo-controlled large-scale trial of mirtazapine for refractory breathlessness is feasible in terms of recruitment, as assessed by the number of patients recruited across 3 hospitals over a 12-month period.

6.3 Secondary Objectives

6.3.1 Feasibility

To quantitatively assess a number of other aspects of feasibility, which will be used to determine whether the current design is suitable to be taken forward to a large-scale trial. To be assessed in terms of:

- Recruitment in different settings: outpatient, community services and inpatient settings
- Acceptability of randomisation to patients
- Ability to deliver placebo-control and maintain the double-blind
- Ability to assess outcome measures and minimise missing data for the future large-scale trial
- Compliance with treatment

6.3.2 Activity, Quality of Life and Toxicity

To obtain average and worst breathlessness severity estimates (measured using Numerical Rating Scale (NRS)) on day 28 to inform the sample size calculations for the future large-scale trial.

To determine patient eligibility to increase the dose of mirtazapine further at 28 days.

To assess the potential activity and impact on the activity of mirtazapine and quality of life (QoL) for patients with refractory breathlessness using the following tools:

- Breathlessness mastery: Chronic Respiratory Questionnaire (CRQ) and modified Medical Research Council (mMRC) dyspnoea scale [64] on days 14 and 28;
- Lower extremity functioning: Short Physical Performance Battery (SPPB) [65] on day 28 [66];
- Coping self-belief assessment: Generalized Self-Efficacy Scale (GSES) [67] on day 28;
- Palliative symptoms: Integrated Palliative care Outcome Scale (IPOS) on days 14 and 28;
- Anxiety and depression: Hospital Anxiety and Depression Scale (HADS) on days 14 and 28;

- QoL: EQ-5D-5L on day 28 and Australia-modified Karnofsky Performance Scale (AKPS) [68] on days 14 and 28;
- Health Economics: Client Services Receipt Inventory (CSRI) on day 28;
- Opioid medication: on days 7, 14, 21 and 28;

To monitor adverse reactions, using the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v4) [69], on days 7, 14, 21 and 28, in order to evaluate the toxicity profile of mirtazapine in patients with refractory breathlessness.

If we are able to demonstrate feasibility within this trial, i.e. the ability to recruit an average of 5 patients per month within a 12-month period (approximately 60 patients) then we plan to seek funding to run a larger double-blind, placebo-controlled randomised trial. Secondary outcome measures of feasibility will be assessed to determine whether the design of the future large-scale trial may need to be adapted to improve recruitment or reduce attrition. Physical activity and toxicity outcomes will be used to inform the design of the future trial however they will not be used to inform the decision as to whether or not to proceed to a larger scale trial. The primary aim of the future trial would be to determine whether mirtazapine improves breathlessness in patients with refractory breathlessness compared to placebo, based on breathlessness severity at day 28 as the primary outcome measure.

6.3.3 Qualitative Interview Sub-study

We will conduct interviews with a sub-set of patients to explore acceptability of trial procedures, materials and intervention for patients and clinicians, and the main impact, if any, of the intervention to enhance recruitment procedures, and ensure that the outcome measures are appropriate for a large-scale trial.

7. Design

The trial is designed as a multi-centre, randomised, placebo-controlled, double-blind, mixed-methods feasibility trial. It is planned to recruit approximately 60 participants with refractory breathlessness over a 12-month period from approximately three UK trial sites.

Participants will be randomised via minimisation on a 1:1 ratio to receive either oral mirtazapine (15mg/day) or placebo medication for 28 days.

At day 14 of treatment breathlessness intensity (“at worst” over the previous 24 hours) will be assessed using the numerical rating scale (NRS). This will be assessed by a member of the research team. If there is no improvement in NRS (i.e. NRS does not increase by 1 point or more compared to baseline NRS) and the drug has been well tolerated, the daily dose of treatment will be doubled.

Participants will be followed up for 7 days after completing trial treatment to assess safety and toxicity of treatment.

All participants, trial site research teams and pharmacies will be blinded to participants' treatment allocation to minimise possible bias. Further information regarding blinding can be found in section 10.

8. Eligibility

Eligibility waivers to inclusion and exclusion criteria are not permitted.

8.1 Inclusion Criteria

1. Male or female aged ≥ 18 years old
2. Diagnosed with:
   - Cancer, or
   - Chronic obstructive pulmonary disease (COPD), or
   - Interstitial lung disease (ILD), or
   - Chronic heart failure (New York Heart Association (NYHA) class III or IV)
3. Breathlessness severity: Modified MRC dyspnoea scale grade 3 or 4 (i.e. stops for breath after walking about 100 yards or after a few minutes on level ground, or is too breathless to leave the house or is breathless when dressing) .
4. On optimal treatment of the underlying condition in the opinion of the identifying clinician (see section 9.3.3 of protocol for guidance)
5. Management of the underlying condition unchanged for the previous 1 week
6. Reversible causes of breathlessness optimally treated in the opinion of the identifying clinician[i]
7. Expected prognosis of ≥2 months
8. If female and of child-bearing potential, must agree to use adequate contraception
9. Able to complete questionnaires and trial assessments
10. Able to provide written informed consent

[i] According to the current appropriate society national guidance.

8.2 Exclusion Criteria

1. Existing antidepressant use[ii]
2. Known contraindication to mirtazapine[iii]
3. Hypersensitivity to the active substance or to any of the components of the mirtazapine or placebo (e.g. lactose intolerance)
4. Australia modified Karnofsky Performance Scale ≤40[iv]
5. Pregnant or breast-feeding women
6. Patients with acute cardiac events within 3 months of randomisation (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)
7. Patients with known hepatic impairment
8. Patients with known renal impairment
9. Patients with uncontrolled blood pressure
10. Patients with uncontrolled diabetes mellitus
11. Patients with uncontrolled seizures, epilepsy or organic brain syndrome
12. Patients with severe depression or suicidal thoughts
13. Patients with a history of psychotic illness (schizophrenia, bipolar disorder, mania or hypomania, or other psychotic disturbances)

9. Recruitment Process

9.1 Recruitment Setting

Participants will be recruited from approximately three trial sites with trial coordination and data collection performed by the Clinical Trials Research Unit (CTRU) in Leeds. Participants may be identified from within the trial sites, or referred to the trial sites by community services, hospices and various other settings (e.g. patient support groups, etc.) Trial sites will

[ii] Previous antidepressant use is permitted provided there is a wash-out period of 14 days prior to randomisation.
[iii] One class of contraindicated concomitant medications listed in the mirtazapine Summary of Product Characteristics (SPC) are monoamine oxidase inhibitors (MAO-Is). Where a patient has previously taken a MAO-I, they must not be treated with mirtazapine for 14 days from the last dose.
[iv] i.e. in bed more than 50% of the time, due to association with short survival.

be required to have obtained management approval and undertake a site initiation meeting with the Sponsor, and CTRU prior to the start of recruitment into the trial. Screening and recruitment processes must not be initiated at site until approval to open to recruitment has been formally issued by the CTRU.

The trial aims to recruit 60 participants over a 12-month period.

9.2 Screening

Patients diagnosed with cancer, heart failure or lung disease (COPD or ILD) and who have significant breathlessness[v] will be screened for trial entry. All participating trial sites will be required to complete monthly Screening Logs of all patients screened for entry into the trial who do not go on to be randomised. This information will be collected from trial sites on a regular basis. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU.

9.3 Informed Consent and Eligibility

The Principal Investigator (PI) will retain overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice and Declaration of Helsinki 1996. Informed consent must be obtained by the PI, or another medically qualified member of the team authorised to consent by the PI on the BETTER-B delegation log, prior to the participant undergoing procedures that are specifically for the purposes of the trial and are not standard routine care at the participating site.

Assenting participants will be broadly assessed for eligibility during the screening process based on their medical history according to the inclusion and exclusion criteria.

The right of a patient to refuse participation without giving reasons will be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment, and will be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

[v] For the purposes of this protocol, “significant breathlessness” is defined as an **anticipated** score of grade 3 or grade 4 on the modified Medical Research Council (mMRC) dyspnoea scale.

As this is a feasibility trial, we will investigate reasons why patients decline to participate using a Feedback questionnaire: completion of this questionnaire is entirely optional. Patients who decline entry into the trial are provided with the questionnaire and an envelope in which they can seal their completed questionnaire before returning to the research team. The questionnaire is provided at the time the patient refuses participation; this may be when they are first approached or after they have had time to consider the participant information sheet. There is also a planned qualitative sub-study which will involve patients being interviewed (see Appendix D). Patients who decline to participate in the trial will still be eligible for this sub-study. For those decliners who choose to complete the Feedback questionnaire, there is a section therein for them to indicate if they would be happy to be approached for this sub-study at a future time. For those who do decide to participate in the main trial, the trial consent form includes a section for them to indicate if they would be happy to be approached for this sub-study.

9.3.1 Initial Information and Initial Approach

Potential participants may be identified through a variety of methods: by staff at the recruiting site itself (e.g. through hospital clinic lists, searching of existing hospital databases, cancer Multi-Disciplinary Teams (MDT) meetings, etc.), by staff at Participants Identification Centres (PICs), and through the use of trial publicity in various settings (e.g. hospices, patient support groups, etc.).

The use of existing hospital databases of patients who have previously consented to be contacted about research may be used and initial contact with these patients will be in-line with what they had previously agreed with that site (e.g. initial contact by phone, or by letter, etc.). Potential participants identified through such databases may be contacted directly by the trial site's research team (if such contact has previously been agreed by the patient), or alternatively may be approached via an 'Invitation' Letter which will provide contact details of the recruiting site's research team. Brief trial information in the form of a Participant Summary Leaflet (PSL) will also be provided.

Potential participants identified at a PIC, who agree to receive further information about the trial, will be provided with the PSL and will be asked if their details may be passed on to the research team at the nearest recruiting site so they can be contacted. If the potential participant is interested in participating in the trial, they will also be provided with the contact details of the research team so they can themselves contact the recruiting site's research team directly if they so choose.

Trial publicity (posters and PSLs) will also be available in various NHS and non-NHS settings (non-NHS hospices, patient support groups, etc.) and these will include contact details of the nearest recruiting site's research team. Potential participants may directly contact a recruiting site's research team via the use of such publicity.

Once the potential participant has been contacted by, or have themselves contacted, the recruiting site's research team, an appointment will be made to meet with a member of the research team to discuss the trial further. At this visit, they will be provided with further verbal explanation of the trial, the Participant Information Sheet (PIS) and Informed Consent Form (ICF), which include detailed information about the rationale, design and personal implications of the trial.

9.3.2 Consent Process

Following initial information provision, participants will have as long as they need to consider participation in the trial (usually at least 24 hours) and will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to take part in the trial.

Assenting potential participants will be invited to provide written informed consent. The PI or any other delegated medic who has received Good Clinical Practice (GCP) training and is authorised on the trial Delegation Log is permitted to take informed consent for trial participation.

Where the patient is able to provide fully informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team.

A record of the consent process detailing the date of consent and all those present will be kept in the participant's medical notes. The original signed consent form(s) will be filed in the Investigator Site File, a copy will be given to the participant, a copy will be returned to the CTRU and another copy will be filed in the hospital notes (as per local practice).

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Participants who lose capacity after informed consent has been obtained will continue with protocol treatment, assessments and follow-up in consultation with the PI and participant's carer / family with the participant's best interests foremost in the decision-making process. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes. The PI will take responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

9.3.3 Eligibility Process

The following assessments must be carried out **prior to randomisation** in order to establish eligibility (see section 8 above for full eligibility criteria):

- Medical review (including medical history, assessment of management of the underlying disease and concomitant medication use)
- mMRC dyspnoea scale assessment
- AKPS assessment

The assessment of whether the participant is receiving optimal treatment for their underlying disease is to be made by the identifying clinician and should be based on the following guidance:

- For COPD or ILD:[vi]
    - On optimal immunosuppression for Connective Tissue Disease (CTD) ILD
    - On pirfenidone for IPF if suitable [70, 71].
    - On oxygen if hypoxic at rest or on activity
    - On appropriate treatment for pulmonary hypertension, if applicable
    - Had pulmonary rehabilitation if appropriate.

- For heart failure:
    - Reached target dose (or be on maximally tolerated dose, or be intolerant) of an inhibitor of the renin-angiotensin system shown to improve prognosis;

    AND
    - Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis;

    AND
    - Reached target dose (or be on maximally tolerated dose, or be intolerant) of an aldosterone antagonist.

- For cancer: chemotherapy, radiotherapy or other anti-cancer treatment not currently appropriate or planned, as assessed at MDT meeting including oncologists, surgeons and relevant specialists, with review of radiological and histological data.

Informed consent must be obtained prior to undertaking any trial-specific procedures, including non-routine eligibility assessments. All eligibility assessments must be performed

[vi] Based on NICE Idiopathic Pulmonary Fibrosis (IPF) / pirfenidone guidelines, British Thoracic Society ILD guidelines (includes CTD assoc ILD), American Thoracic Society (ATS) / European Respiratory Society (ERS) guideline ILD.

no more than 7 days prior to the participant being randomised and beginning trial treatment. Where more than 7 days have elapsed since the initial eligibility assessments, these must be repeated prior to randomisation and the participant beginning trial treatment; if these repeated assessments show ineligibility, the patient must not be randomised into the trial.

9.4 Randomisation

9.4.1 Timing of Randomisation

Informed written consent for entry into the trial must be obtained, and baseline assessments[vii] performed prior to randomisation. Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by an authorised member of staff at the trial site. Randomisation will be performed centrally using the CTRU 9:00 – 17:0-00 (office hours)[viii] randomisation system and should take place as soon as possible after consent is obtained and eligibility confirmed, and no more than 7 days prior to the start date of trial treatment.[ix]

9.4.2 Treatment Allocation

Participants will be randomised on a 1:1 basis to receive either mirtazapine or placebo and will be allocated a trial number and a unique kit-code to identify which container of trial drug (mirtazapine or placebo) will be dispensed. The participant's randomisation allocation will not be disclosed in order to maintain the blinding of the trial.

A computer-generated minimisation programme that incorporates a random element will be used to ensure that treatment groups are well balanced by:

- Disease (cancer vs non-cancer)
- HADS score (≥15 vs <15)
- Currently receiving opioids (yes vs no)

9.4.3 Randomisation Process

Randomisation should take place as soon as possible after consent is obtained and eligibility confirmed, and must be performed by an authorised member of the team at the site using the CTRU office hours telephone randomisation service (open 9:00 to 17:00 Monday to Friday,

[vii] It is important that baseline assessments are performed prior to randomisation, as the HADS score is used as a minimisation factor.
[viii] Exceptions: public / bank holidays, the period between Christmas Eve and New Year, Thursday afternoon before Good Friday and all Tuesdays following a bank holiday except for Mayday and New Year's Day.
[ix] Where this is not possible, the eligibility assessments must be repeated so that they are no more than 7 days old at the time of starting treatment; if the repeated assessments show ineligibility, the patient must not be entered into the trial.

excluding public / bank holidays, the period between Christmas Eve and New Year, Thursday afternoon before Good Friday and all Tuesdays following a bank holiday except for Mayday and New Year's Day).

The following information is required in order for the participant to be randomised. The person making the randomisation telephone call should have all details to hand:

- Name and code (assigned by the CTRU) of trial site
- Patient initials and date of birth
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (see section 9.4.2 above)

Direct line for office hours randomisation
0113 343 1486
Please ensure that you have completed the Initial Eligibility Checklist and Randomisation Case Report Forms (CRFs) before telephoning

At the end of this phone call a unique BETTER-B trial participant identifier will be assigned but the participant's randomisation allocation will not be disclosed in order to maintain the blinding of the trial. Instead, a unique kit-code will be provided which identifies a container of capsules that need to be dispensed by pharmacy.

9.4.4 Post-Randomisation Actions

At the end of the randomising phone call, the trial participant identifier and kit-code number must be added to the Randomisation Case Report Form (CRF) and all participant details must be added to the main Participant ID Log.

Two Confirmation of Randomisation notifications, detailing the participant details and the kit-code number they have been allocated will be sent to site: one to the nominated contact in the local research team and another to pharmacy. These should be filed in the Investigator Site File and Pharmacy Site File, respectively. The kit-code provided will inform pharmacy which container of capsules needs to be dispensed to the participant. These notifications are generated and sent from the CTRU. In the event of a system failure, the kit-code number may need to be provided to the pharmacy directly by the member of site staff randomising the participant (this information will be provided as part of the randomising phone-call).

10. Trial Medicinal Product Management

Please refer to the BETTER-B Pharmacy and Investigational Medicinal Product (IMP) Study Site Operating Procedure (SSOP) for full details of the trial IMP management requirements. Within the trial the following are classed as IMPs:

Mirtazapine

- Composition: one capsule contains 15mg of mirtazapine.
- Supplied by Medreich Plc.

Placebo

- Composition: gelatin capsule shell containing lactose.
- Manufactured by Guy's and St Thomas' NHS Foundation Trust's (GSTFT) Pharmacy Production Unit.

For handling guidance of both mirtazapine and placebo, please refer to the latest Summary of Product Characteristics (SPC) for mirtazapine (as supplied by Medreich Plc; PL number 21880/0053).

10.1 GSTFT Manufacture, packaging and Labelling

The Pharmacy Production Unit at GSTFT will act as the trial's Central Pharmacy and holds a Manufacturer's Authorisation for IMPs.

The trial IMP placebo will be manufactured by the trial Central Pharmacy. The trial IMP mirtazapine will be sourced by the Central Pharmacy where the capsules will be over-encapsulated in such a way that they are identical to the placebo capsules in order to maintain the blind of the trial.

The Central Pharmacy will also package up the trial IMPs (each container will hold 42 capsules or either placebo or over-encapsulated mirtazapine) and label the containers. In order to maintain the blinding of the trial the capsules and containers will be identical and labelled with the same study-specific label in accordance with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended).

Containers will be identified only by a unique kit-code assigned at random. Management of kit-codes on the kit logistics application will be conducted by the CTRU Trial Statistician in addition to maintaining the back-up kit-code lists for each site. The CTRU Trial Statistician will be responsible for maintaining this list, which will be securely password-protected when treatment information is contained within the list.

10.2 Supply, Distribution and Storage

Trial IMPs (mirtazapine and placebo) will be provided to sites free of charge for use in this clinical trial. Blinded supplies will be sent to trial sites from Central Pharmacy (see above) in pre-labelled containers which will be identifiable by a kit-code printed on the label. In addition to the trial IMP containers, sites will receive sealed Code-Break Envelopes to allow emergency unblindings where necessary. Each envelope will be linked to a specific container of trial IMP capsules using the unique kit-code system. See section 11.2 below for further details on emergency unblinding.

Once received from the trial Central Pharmacy, all trial IMP stock and Code-Break Envelopes must be documented as received in accordance with the BETTER-B Pharmacy and IMP SSOP provided within the BETTER-B Pharmacy Site File.

All trial IMP containers must be stored in a secure ring-fenced location within the site pharmacy. There are no special storage requirements in terms of temperature management.

The supply of trial IMPs (mirtazapine and placebo) must not be used for any purpose other than that outlined in this protocol and should be clearly ring-fenced from standard hospital stock.

10.3 Dispensing

In order to maintain the blinding of the trial the site pharmacist will not be told the participant's treatment allocation. Blinded containers of capsules, identifiable only by a unique kit-code are received at site pharmacies from the Central Pharmacy and will be stored in a ring-fenced section of the site pharmacy until dispensing. To ensure that the correct treatment is dispensed to the participant the relevant site pharmacist will be told which container to dispense to each participant using this kit-code numbering system.

The relevant site pharmacist will be notified by the CTRU of all participants randomised at that site; each Confirmation of Randomisation notification will detail the participant trial ID number, date of birth and initials and also the kit-code assigned to that participant which will identify which container of capsules should be given to the participant. The member of the local research team randomising the participant will also have been told which kit-code should be dispensed to the participant whilst making the randomisation telephone call, and will also receive a Confirmation of Randomisation Fax detailing the kit-code.

The participant's trial identifier must be added to the label of each trial IMP container by the pharmacist (or authorised delegate) at the time of dispensing, and the Code-Break Envelope assigned to that kit-code annotated with the participant details and then securely stored in pharmacy.

Dispensing must only be performed by an authorised member of site staff as delegated on the trial Pharmacy Authorised Personnel Log. Once randomised, at baseline the participant will receive one trial IMP container, containing 42 capsules, of either mirtazapine or placebo, identifiable only by the unique kit-code on the outer container label. All dispensed trial IMP must be recorded on the trial Accountability and Dispensing Log in accordance with the BETTER-B Pharmacy and IMP SSOP.

Each container of trial IMP capsules, identifiable only by the unique kit-code, will have a corresponding Code-Break Envelope. Each time a container of capsules is dispensed, the participant identifiers must be added to the trial IMP container label and also to the corresponding Code-Break Envelope. This Code-Break Envelope will then be held securely within the site pharmacy (see section 11.2 for access required in the event of unblinding).

10.4 Reconciliation

All trial IMP stock received by site pharmacies from Central Pharmacy, dispensed to trial participants (and any returned unused doses from participants) must be recorded on the BETTER-B Accountability and Dispensing Logs. These completed logs will be reviewed by Sponsor at monitoring visits. Trial IMP stock (dispensed and returned, or un-dispensed) may only be destroyed by trial site pharmacies once full reconciliation has been performed by Sponsor and formal permission for destruction issued.

Code-Break Envelopes for all trial IMP containers (whether or not dispensed) will be returned to CTRU at the end of trial for destruction.

11. BETTER-B Treatment

11.1 Treatment Details

The local Investigator, the site pharmacist, other members of the site staff involved with the trial, and the participants themselves, will remain blinded to the treatment allocation (except where emergency unblinding is necessitated).

11.1.1 Treatment Regimen

Participants will be randomised to receive either mirtazapine or placebo for 28 days. Participants will be dispensed 42 capsules (15mg per tablet for mirtazapine) at baseline. Participants should take their capsules in the evening.

For participants randomised to receive mirtazapine, the daily dose will be 15mg (one capsule) for the first 14 days; participants will be assessed for possible dose escalation at the trial assessment visit for day 14 and if appropriate, their daily dose will be escalated to 30mg (two capsules) on days 15 through to 28; see section 12.5.2.1 below for further details.[x] Where dose escalation is not appropriate, the participant will continue to take a daily dose of 15mg (one capsule) on days 15 through to 28.

For participants randomised to receive placebo the daily dose will be 1 capsule for the first 14 days; participants will be assessed for possible dose escalation on day 14 and if appropriate, their daily dose will be escalated to 2 capsules on days 15 through to 28; see section 12.5.2.1 below for further details.[xi] Where dose escalation is not appropriate, the participant will continue to take a daily dose of 1 capsule on days 15 through to 28.

11.1.2 Treatment Compliance

In order to assess participant compliance with the trial treatment, at the assessment phone-calls (day 7 and day 21) and visits (day 14 and day 28) the research team will ask the participant if they have had any delayed, missed or modified doses. This information will be recorded on the appropriate Assessment CRF. Any unused capsules should be collected from the participants by the research team at the last assessment visit (day 28)[xii] and returned to pharmacy for drug reconciliation then destruction (see section 10.4 above for further details).

Participants will be given a medication diary to complete in order to aid in the monitoring of treatment compliance. This diary will be given to participants at baseline and they will be asked to complete this every day and to bring it along to all trial visits (days 14 and 28) and have it available during trial calls (days 7, 21 and follow-up call at 7 days after ending trial treatment).

11.1.3 Concomitant Medications / Interactions

For management of concomitant therapies, please refer to the latest mirtazapine Summary of Product Characteristics (produced by Medreich Plc; PL 21880/0053).

---

[x] Where dose escalation is deemed appropriate for a participant, and the Day 14 trial visit occurs before the 14th day of treatment, the participant must be instructed to begin taking two capsules per day only from day 15 onwards. Where dose escalation is deemed appropriate for a participant, and the Day 14 trial visit occurs after the 14th day of treatment, the participant must be instructed to begin taking two capsules per day from that point forward until the end of their trial treatment (i.e. day 28).

[xi] See footnote x above.

[xii] If the Day 28 visit occurs before the 28th day of trial treatment, all capsules should be left with the participant at that visit, and another visit arranged for collection of unused capsules after the participant has completed 28 days of treatment.

11.1.4 Most frequent anticipated toxicities

The most frequent anticipated toxicities of mirtazapine are as follows:

- Increased appetite
- Weight gain
- Somnolence
- Sedation
- Headache
- Dry mouth
- Lethargy
- Dizziness
- Tremor
- Nausea
- Diarrhoea
- Vomiting
- Exanthema
- Arthralgia
- Myalgia
- Back pain
- Orthostatic hypotension
- Oedema peripheral
- Fatigue
- Abnormal dreams
- Confusion
- Anxiety
- Insomnia

11.2 Emergency Unblinding

Whilst the safety of participants in the trial must always take priority, maintenance of blinding is crucial to the integrity of the trial. Investigators should only break the blind when information about the participant‘s trial treatment is clearly necessary for the appropriate medical management of the participant and where stopping the blinded medication is not sufficient.

Unblinding may be requested on the grounds of safety by the Chief Investigator (CI), local PI or treating physician. It is anticipated that requests for unblinding will most likely originate from a participant, carer (or friend / family member) or personal physician (e.g. GP) at the time of an adverse event or planned change in non-trial related drug therapy. Requests for unblinding will first be handled by the local PI or delegate who will explore the reason for the request and evaluate the importance of knowledge of treatment assignment for participant safety. In the event of a Serious Adverse Event (SAE), all participants should be treated as though they are receiving the active medication.

Should an alternative to unblinding not be identified, and if unblinding is required to optimise medical management of the participant, investigators should follow the emergency unblinding process.

Emergency unblinding is provided by the CTRU during Office Hours and the participating site pharmacy at all other times, thereby covering each 24-hour period. It is encouraged that requests for Emergency Unblinding should be made directly with CTRU wherever possible.

The following information will be needed to perform an emergency unblinding:

- Participant details, including trial ID number, initials and date of birth
- Name of trial research site and site code
- Name of person making the request for a code-break
- Reason for requesting a code-break
- Confirmation of whether the PI authorised the request

11.2.1 Emergency Unblinding during Office Hours

The emergency unblinding process will be undertaken by telephoning the CTRU during Office Hours, 9.00 to 17.00 Monday to Friday. Exceptions: public / bank holidays, the period between Christmas Eve and New Year, Thursday afternoon before Good Friday and all Tuesdays following a bank holiday except for Mayday and New Year's Day.

Direct line for CTRU emergency unblinding: 0113 343 1486

Following the emergency unblinding of a participant, CTRU will send a notification to the requester, the local PI and the Sponsor. The details of the emergency unblinding should be recorded on the BETTER-B Unblinding Log provided by CTRU.

11.2.2 Emergency Unblinding outside of Office Hours

Outside of Office Hours, or where the Investigator or treating physician is unable to contact CTRU, emergency unblinding must be performed by the local pharmacy department. The responsible pharmacist on duty will complete the Unblind Request CRF, retrieve the code-break information (Code-Break Envelopes for unblindings will be provided to pharmacy at the time of IMP delivery and each envelope will be linked to a specific container of capsules using a unique kit-code) and reveal the treatment allocation to the person requesting the unblind. The pharmacist must send the completed Unblind Request CRF to the CTRU within 24 hours of the unblinding request (please see section 21 for details of acceptable methods of transfer).

All Code-Break Envelopes will be returned to CTRU by the site pharmacy department at the end of trial. Code-Break Envelopes must not be opened for participants when they have completed trial therapy.

11.2.3 Treatment of Participants following Emergency Unblinding

Following an emergency unblinding the participant should be treated according to the treating clinician's assessment.

11.3 Withdrawal of Treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants withdrawn from treatment or prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and CRFs will continue to be completed.

The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

It should be made clear to any participant specifically withdrawing consent for further data collection that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

12. Assessments and Data Collection

12.1 Schedule of Events

The timings of interventions and assessments required for the BETTER-B Feasibility trial are summarised in Table 1.

Table 1: Schedule of Events

Abbreviations: mMRC (modified Medical Research Council), AKPS (Australia-modified Karnofsky Performance Status), Tx (treatment), NRS (Numerical Rating Scale), CRQ (Chronic Respiratory Questionnaire), SPPB (Short Physical Performance Battery), GSES (Generalized Self-Efficiency Scale), IPOS (Integrated Palliative care Outcome Scale), CSRI (Client Services Receipt Inventory).

TIMEPOINT	Eligibility (≤ 7 calendar days prior to starting treatment)	Baseline (≤ 7 calendar days prior to starting treatment)	Day 7 (+/- 1 working day)	Day 14 (+/- 1 working day)	Day 21 (+/- 1 working day)	Day 28 (-1 working day)	7 days post treatment end (+1 working day)
METHOD	Face-to-face	Face-to-face	Phone-call	Face-to-face	Phone-call	Face-to-face	Phone-call
ASSESSMENTS							
Demographic data and full medical review [disease, prognosis, optimal Tx, concomitant medications, contraindications, cardiac history, symptoms]	X[1]	X[2]					
Randomisation and dispensing		X					
mMRC dyspnoea scale (participant-reported)	X[1]	X[2]		X		X	
CRQ (participant-reported)		X		X		X	
GSES (participant-reported)		X				X	
IPOS (participant-reported)		X		X		X	
HADS (participant-reported)		X		X		X	
CSRI (participant-reported)		X				X	
EQ-5D-5L (participant-reported)		X				X	
NRS (participant-reported)		X	X	X	X	X	
AKPS	X[1]	X[2]		X		X	
SPPB		X				X	
Vital signs (blood pressure and blood oxygen level)				X		X	
Toxicity assessment		X	X	X	X	X	X
Opioid medication assessment		X	X	X	X	X	
Mirtazapine compliance assessment (and modifications)			X	X	X	X[3]	X[3]
Suitability for dose escalation				X		X	
Blinding assessment						X	
Collection of unused medication						X[3]	

1. Eligibility assessments must be no more than 7 days before starting treatment. Where more than 7 days elapse from the initial eligibility assessments, they must be repeated before randomisation and starting treatment.
2. Eligibility assessments may be used for baseline so long as they are no more than 7 days old at the time starting treatment.
3. If the participant has not completed 28 days of trial treatment at the time of the Day 28 trial visit, trial IMP compliance will be assessed at the follow-up call (7days after completing trial treatment) and an unused trial IMP collected in.
4. If the participant has not completed 28 days of trial treatment at the time of the Day 28 trial visit, another visit must be arranged in order to collect any unused trial IMP.

12.2 Screening Data

All patients who have significant breathlessness[xiii] but do not go on to be randomised must be included on the monthly Screening Log[xiv]. Anonymised information for these patients will be collected including:

- Disease area diagnosis (e.g. cancer, heart or liver disease)
- Identification setting (community services, outpatient clinic, inpatient clinic)
- Method of initial approach
- Date screened
- Approached / Not approached for the trial
- Reason for non-randomisation:
    - not eligible for trial participation, or
    - eligible but declined and reason for this (where appropriate), or
    - other reason for non-randomisation

This information will be collected from trial sites on a monthly basis. Documented reasons for ineligibility or declining participation will be closely monitored by the CTRU. Screening data forms a crucial endpoint of this feasibility study therefore it is essential that this information is completed and returned to CTRU as outlined.

12.3 Eligibility Assessments

The following assessments need to be performed in order to assess eligibility (see section 8 above for full eligibility criteria):

- Medical review (including medical history, assessment of management of the underlying disease and concomitant medication use)
- Modified Medical Research Council (mMRC) dyspnoea scale assessment
- Australia-modified Karnofsky Performance Scale (AKPS) ≤40

Eligibility assessments must be no more than 7 days old at the time of starting treatment; if more than 7 calendar days elapse from the date of the eligibility assessments and the participant has not commenced trial treatment, all eligibility assessments must be repeated.

[xiii] For the purposes of this protocol, “significant breathlessness” is defined as an **anticipated** score of grade 3 or grade 4 on the modified Medical Research Council (mMRC) dyspnoea scale.
[xiv] If a participant’s screening process spans more than one month, their details should only be included on the Screening Log for the month that the screening outcome is final.

For patients who do not go on to be randomised, details should be added to the Screening Log (see section 9.2).

12.4 Baseline Assessments and Data Collection

Following written informed consent and prior to randomisation[xv], the participant will be assessed by a member of the research team and the following baseline assessments will be carried out. This visit may be conducted either at the trial site, or, if the participant prefers, at the participant's home / agreed convenient location (e.g. care home, etc.)[xvi].

Assessments to be performed by the research team:

- Medical review
- Australia-modified Karnofsky Performance Scale (AKPS)[xvii]
- Short Physical Performance Battery (SPPB)
- Numerical Rating Scale (NRS) – on average and "at worst" in the last 24 hours

A number of participant-reported questionnaires will also be completed. These may be completed by the participants themselves, or, if preferred, by a member of the research team on behalf of the participant. Where this is the case, separate booklets are provided for staff to complete, along with a number of laminated "prompt sheets" to be given to the participant to facilitate this process:

- Modified Medical Research Council (mMRC) dyspnoea scale[xviii]
- Chronic Respiratory Questionnaire (CRQ)
- Integrated Palliative care Outcome Scale (IPOS)
- Hospital Anxiety and Depression Scale (HADS)
- EQ-5D-5L

[xv] The baseline HADS score will be used at randomisation as a minimisation factor. Ideally, randomisation and day 1 of trial treatment should occur on the same day.
[xvi] Where research team members visit a participant's home, they should follow their local "lone worker" policy to minimise any risks to their personal safety.
[xvii] The AKPS assessment performed for eligibility may be used (this must not be more than 7 days prior to starting treatment).
[xviii] The mMRC dyspnoea scale assessment performed for eligibility may be used (this must not be more than 7 days prior to starting treatment).

- Generalized Self-Efficacy Scale (GSES)
- Client Services Receipt Inventory (CSRI) [72]

12.5 Trial Treatment Assessments and Data Collection

12.5.1 Day 7 Assessment Phone Call

On day 7[xix] of trial treatment, the research team will contact the participant by phone to perform the following assessments:

- Numerical Rating Scale (NRS) – on average and "at worst" over the last 24 hours
- Toxicity assessment: collection of any adverse events or reactions which may have occurred since the baseline assessment[xx]
- Opioid medication assessment: collection of information of any opioids taken by the participant since the baseline assessment
- Treatment compliance (and any modifications) assessment since the baseline assessment (mirtazapine or placebo)

12.5.2 Day 14 Assessment Visit and potential dose escalation

On day 14[xxi] of trial treatment, the participant will be seen in person by a member of the research team and the following assessments will be carried out. This visit may be conducted either at the recruiting trial site, or, if the participant prefers, at another location of their choice (e.g. the participant's home, care home, etc.)[xxii].

Assessments to be performed by the research team:

- Australia-modified Karnofsky Performance Scale (AKPS)
- Numerical Rating Scale (NRS) – on average and "at worst" over the last 24 hours

[xix] Where this phone-call cannot take place on day 7 of treatment, it should be no more than 1 working day either side.
[xx] Where this toxicity assessment raises any safety concerns, the assessing research team member may request that the participant is assessed by a medically qualified member of the team.
[xxi] Where this visit cannot take place on day 14 of treatment, it should be no more than 1 working day either side.
[xxii] Where research team members visit a participant's home, they should follow their local "lone worker" policy to minimise any risks to their personal safety.

- Toxicity assessment: collection of any adverse events or reactions which may have occurred since the Day 7 assessment call[xxiii]
- Opioid medication assessment: collection of information of any opioids taken by the participant since the Day 7 assessment call
- Treatment compliance assessment (and any modifications) since the Day 7 assessment call (mirtazapine or placebo)
- Assessment of appropriateness to dose escalate (see section 12.5.2.1 below)
- Medical review including vital signs (blood pressure and blood oxygen level)

A number of participant-reported questionnaires will also be completed. These may be completed by the participants themselves, or, if preferred, by a member of the research team on behalf of the participant. Where this is the case, separate booklets are provided for staff to complete, along with a number of laminated "prompt sheets" to be given to the participant to facilitate this process.

- Modified Medical Research Council (mMRC) dyspnoea scale
- Chronic Respiratory Questionnaire (CRQ)
- Integrated Palliative care Outcome Scale (IPOS)
- Hospital Anxiety and Depression Scale (HADS)

12.5.2.1 Dose Escalation

All BETTER-B participants will be assessed for dose escalation (to two capsules of mirtazapine (30mg total dose) or placebo daily) at their day 14 assessment visit. The assessment of suitability for dose escalation will be based on the participant's NRS score ("at worst" over last 24 hours), and clinical review. Participants will be eligible for dose escalation where their NRS score has not improved by at least 1 point since baseline. If participants have experienced toxicity since baseline, they will have a clinical review prior to being assessed as eligible for dose escalation.

For participants for whom it is determined that dose escalation is appropriate at the day 14 assessment visit, they should be instructed by the research team member to begin taking an additional capsule every day from day 15 onwards[xxiv] (so 2 capsules daily to be taken from day 15 through to day 28).

[xxiii] Where this toxicity assessment raises any safety concerns, the assessing research team member may request that the participant is assessed by a medically qualified member of the team.
[xxiv] Or from the day of the trial assessment visit, where this occurs after day 14 of trial treatment.

For participants for whom it is determined dose escalation is not appropriate at the day 14 assessment visit, they should be instructed to continue to take one capsule daily.

12.5.3 Day 21 Assessment Phone Call

On day 21[xxv] of trial treatment, the research team will contact the participant by phone to perform the following assessments:

- Numerical Rating Scale (NRS) – on average and "at worst" over the last 24 hours
- Toxicity assessment: collection of any adverse events or reactions which may have occurred since the Day 14 assessment visit[xxvi]
- Opioid medication assessment since the Day 14 assessment visit
- Treatment compliance assessment (and any modifications) since the Day 14 assessment visit (mirtazapine or placebo)

12.5.4 Day 28 Assessment Visit

On day 28[xxvii] of trial treatment, the participant will be seen in person by a member of the research team and the following assessments will be carried out. This visit may be conducted either at the recruiting trial site, or, if the participant prefers, at another location of their choice (e.g. the participant's home, care home, etc.)[xxviii].

Assessments to be performed by the research team:

- Australia-modified Karnofsky Performance Scale (AKPS)
- Numerical Rating Scale (NRS) – on average and "at worst" over the last 24 hours
- Short Physical Performance Battery (SPPB)
- Toxicity assessment: collection of any adverse events or reactions which may have occurred since the Day 21 assessment call[xxix]

[xxv] Where this phone-call cannot take place on day 21 of treatment, it should be no more than 1 working day either side.
[xxvi] Where this toxicity assessment raises any safety concerns, the assessing research team member may request that the participant is assessed by a medically qualified member of the team.
[xxvii] Where this visit cannot take place on day 28 of treatment, it **must not** be earlier than day 28 of treatment, and should not be more than 1 working day later.
[xxviii] Where research team members visit a participant's home, they should follow their local "lone worker" policy to minimise any risks to their personal safety.
[xxix] Where this toxicity assessment raises any safety concerns, the assessing research team member may request that the participant is assessed by a medically qualified member of the team.

- Opioid medication assessment: collection of information (drug name and dose) of any opioids taken by the participant since the Day 21 assessment call
- Treatment compliance assessment (and any modifications) since the Day 21 assessment call (mirtazapine or placebo)
- Assessment of potential to dose escalate
- Medical review including vital signs (blood pressure and blood oxygen level)

A number of participant-reported questionnaires will also be completed. These may be completed by the participants themselves, or, if preferred, by a member of the research team on behalf of the participant. Where this is the case, separate booklets are provided for staff to complete, along with a number of laminated "prompt sheets" to be given to the participant to facilitate this process.

- Modified Medical Research Council (mMRC) dyspnoea scale
- Chronic Respiratory Questionnaire (CRQ)
- Integrated Palliative care Outcome Scale (IPOS)
- Hospital Anxiety and Depression Scale (HADS)
- EQ-5D-5L
- Generalized Self-Efficacy Scale (GSES)
- Client Services Receipt Inventory (CSRI)
- Blinding Assessment

12.6 Follow-up Assessment and Data Collection

Participants will be followed-up 7 days[xxx] after the end of trial treatment. The research team will contact the participant by phone to perform the following assessments:

- Toxicity assessment: collection of any adverse events or reactions which may have occurred since the participant stopped trial treatment

[xxx] Where this phone-call cannot take place exactly 7 days after the end of trial treatment, it **must not** be earlier than 7days after completing treatment, and should be no more than 1 working day later.

12.7 End of Trial Treatment

Participants should continue on trial treatment for 28 days, however if a participant discontinues trial treatment for any reason before that time, an End of Trial Treatment CRF must be completed and sent to the CTRU **within 7 days** of the research team becoming aware of this (please see section 21for details of acceptable methods of transfer).

12.8 Adverse Events and Serious Adverse Events

All Adverse Events (AEs) or Adverse Reactions (ARs) occurring in the trial will be collected on the weekly Trial Treatment Assessment CRFs and on the Follow-up Assessment CRF. These should be reported via the standard data management routes to the CTRU and not expedited.

For all Serious Adverse Events (SAEs) or Serious Adverse Reactions (SARs) occurring in the trial, a SAE/SAR Report CRF must be completed and sent to the CTRU **within 24 hours** of the site becoming aware of the event (see pharmacovigilance section 13 and section 21 for details of acceptable methods of transfer).

For all Suspected Unexpected Serious Adverse Reactions (SUSARs), a SUSAR Report CRF must be completed and sent to the CTRU **within 24 hours** of the site becoming aware of the event (see pharmacovigilance section 13 and section 21 for details of acceptable methods of transfer).

12.9 Pregnancies

All pregnancies and suspected pregnancies (in a trial participant or their partner) occurring from the date of randomisation to 7 days following permanent cessation of trial treatment must be reported to the CTRU by completing the Notification of Pregnancy CRF which must be sent to the CTRU **within 7 days** of the site becoming aware of the pregnancy (please see section 21 for details of acceptable methods of transfer).

The CTRU will report all pregnancies occurring during trial treatment to the Sponsor along with any follow-up information.

12.10 Deaths

All deaths occurring from the date of randomisation to 7 days after the participant has completed trial treatment must be recorded on the Notification of Death CRF and sent to the CTRU **within 7 days** of the site becoming aware of the death (please see section 21 for details of acceptable methods of transfer).

At the end of the trial, sites will be contacted to provide data on any subsequent deaths and survival data.

12.11 Important Medical Events (IMEs)

Events that may not be immediately life-threatening or result in death or hospitalisation, but which may jeopardise the patient or require intervention to prevent one of the outcomes listed in the definition of a Serious Adverse Event (see section 13.1 below), should also be considered serious and should be expedited to the CTRU **within 24 hours** of the site becoming aware.

12.12 Protocol Deviations and Violations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the CTRU. All such deviations or violations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations or violations will be detailed in the published report. We will analyse the reasons for deviations or violations and report on whether and how these might be avoided in a future large-scale trial.

12.13 End of Trial Definition

The end of trial is defined as the date of the collection of the last participant's last data item, i.e. the last participant's Follow-Up trial phone-call assessment, which will be no earlier than 7 days after the last participant has completed trial treatment.

12.14 Trial Data and Documentation held at sites

Participating sites must maintain essential trial documentation in an Investigator Site File and a Pharmacy Site File, which will be provided by the CTRU. It is the responsibility of the site staff to ensure these files are properly maintained during the trial and archived according to Sponsor requirements at the end of the trial (see section 22 on archiving).

12.15 Case Report Forms (CRFs)

Data will be recorded by site research staff on trial-specific paper CRFs which will be provided by CTRU in the form of an electronic booklet. The originals will be submitted by

post to the BETTER-B trial team at CTRU within two weeks of the data being collected, and photocopies of the completed CRFs will be held at site. A number of CRFs require expedited reporting to the CTRU:

- Within 24 hours of the site research team becoming aware: SAE and SUSAR CRFs, and notification of any IMEs
- Within 7 days of the research team becoming aware: Death, Notification of Pregnancy and End of Trial CRFs

Only the participant's trial number, date of birth and initials will be added to the CRFs – **site staff are responsible for ensuring the CRFs returned to CTRU do not contain any other personal identifiable data** (with the exception of the participant's NHS number which will be recorded at baseline). Following receipt of the completed CRFs, the CTRU will contact sites on a regular basis to resolve any missing or discrepant data.

It is the responsibility of the site to ensure all photocopies of the completed CRFs are appropriately maintained at site during the trial (including any amendments) and archived according to Sponsor requirements at the end of the trial (see section 22 on archiving).

13. Pharmacovigilance

13.1 General Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

An AE can therefore be any unfavourable and unintended sign (Including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the use of a medicinal product, whether or not considered to be related to the medicinal product.

Adverse Reaction (AR): any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject.

This definition implies a reasonable possibility of a causal relationship between the event and the IMP which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol

(i.e. if an AR occurs as a result of a medication error), including misuse and abuse of the product.

Serious Adverse Event (SAE): any adverse event that:

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical and scientific judgement must be exercised in deciding whether an event is 'serious' in accordance with these criteria. **Serious Adverse Reaction (SAR)**: reference is made to the criterion of 'Seriousness' above in relation to SAE. Where an SAE is deemed to have been related to an IMP used within the trial, the event is termed as a SAR. (Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.)

Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction, the nature and severity of which is not consistent with the pharmacovigilance reference copy of the mirtazapine SPC (or another version as instructed by the CTRU):

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported to the CTRU in an expedited manner (i.e. within 7 days of the site becoming aware).

Death as a result of disease progression are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

13.2 BETTER-B Operational Definitions

Adverse events will be collected for all participants and will be evaluated for intensity and causal relationship with the trial medication or other factors according to the National Cancer Institute (NCI) CTCAE V4.0 (NCI-CTCAE). A copy is provided in the BETTER-B Investigator Site File and may also be obtained at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Published date: May 28, 2009

13.2.1 Adverse Events (AEs) / Adverse Reactions (ARs) and Serious Adverse Events (SAEs) / Serious Adverse Reactions (SARs)

For general definitions of AEs, ARs, SAEs and SARs, please see section 13.1 above.

As this is a blinded trial, all AEs and SAEs should be assessed for causal relationship assuming that the participant has been receiving mirtazapine.

Routinely breaking the blind could compromise the integrity of the trial. For this reason blind-breaking will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator would be expected to evaluate the causality of AEs or SAEs as though the participant was receiving the active medication.

When determining whether a SAE or SAR is expected or not, please refer to the pharmacovigilance reference copy of the mirtazapine Summary of Product Characteristics (SPC) supplied in the BETTER-B Investigator Site File (or another version as instructed by the CTRU).

Events <u>not</u> to be classed as SAEs on this BETTER-B Feasibility trial

The following events will **<u>not</u>** be classed as SAEs within this trial and will therefore not be subject to **<u>expedited</u>** reporting (they will still need to be reported to CTRU along with other AEs):

Hospitalisation or admission into a hospice, nursing home or palliative care unit due to:

- Care-giver burden;
- Expected deterioration related to underlying cancer diagnosis;
- Expected deterioration related to underlying lung disease diagnosis (COPD / ILD);

- Expected deterioration related to underlying chronic heart failure diagnosis (e.g. acute decompensation of heart failure, angina with or without raised troponins, cardiac arrhythmia Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications;
- Any admission to hospital or other institution for general care where there was no deterioration in condition;
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

Events classed as <u>expected</u> SAEs / SARs

Examples of events which will be classed as **expected** SAEs / SARs within this trial are given below. These will **<u>not</u>** be reportable as SUSARs on the trial, unless the severity of the event is considered to be unexpected.

<u>This is not intended to be an exhaustive list</u>, therefore when determining whether a SAE / SAR is expected or not, the pharmacovigilance reference copy of the mirtazapine SPC provided in the BETTER-B Investigator Site File (or another version as instructed by the CTRU) must always be referred to.

Examples of expected SARs (related to mirtazapine):

- Increase in appetite
- Weight gain
- Somnolence
- Sedation
- Headache
- Dry mouth

All events should be reviewed and classified by the site PI, or another clinically qualified member of the medical team authorised in the BETTER-B Delegation Log.

13.2.2 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For general a definition of SUSARs, please see section 13.1 above.

Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore expedited reporting. However, where SUSARs are thought to be associated with placebo (e.g. reaction due to excipient or impurity) the CTRU will report such cases to the Sponsor for onward reporting to the MHRA.

Routinely breaking the blind could compromise the integrity of the trial. For this reason blind-breaking will only take place where information about the participant's trial treatment is clearly necessary for the appropriate medical management of the participant. In all cases the Investigator would be expected to evaluate the causality and expectedness of SAEs/SARs as though the participant was receiving the active medication.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Authority (MHRA) and Research Ethics Committee (REC).

13.3 BETTER-B Reporting Requirements

Information about all events (AEs, ARs, SAEs, SARs and SUSARs), whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation, must be collected and reported to the CTRU.

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring expedited reporting) must be reported immediately (and certainly **no later than 24 hours**) by the trial site team to the CTRU.

For each SAE/SAR or SUSAR the following information will be collected:

- event duration (start and end dates, if applicable)
- action taken
- outcome
- "key information":
    - full details in medical terms and case description (or signs / symptoms / diagnosis – i.e. adequate information describing the event)
    - seriousness criteria
    - causality (i.e. relatedness to mirtazapine / investigation), in the opinion of the investigator
    - whether the event would be considered expected or unexpected
    - PI signature (or another clinically qualified member of the medical team authorised in the BETTER-B Authorised Personnel Log)

All events must be reviewed and assessed (for seriousness, causality and expectedness) by the PI, or another clinically qualified member of the medical team authorised in the BETTER-B Delegation Log. If an authorised medic is not available on the day the site team become aware of the event, initial reports without causality and expectedness must still be sent to the CTRU **within 24 hours** of the site becoming aware, and must be followed-up by medical assessment as soon as possible thereafter. Any outstanding "key information" (see above) must be reported within a further 24 hours. Subsequently, follow-up reports (detailing changes in condition) must be reported to the CTRU within 24 hours of the site becoming aware of a change relating to "key information", or at the time of the event resolving or, for all other data, when requested by the CTRU.

13.3.1 Reporting of Adverse Events (AEs) and Adverse Reactions (ARs)

All AEs occurring **from randomisation up to 7 days after the last dose of trial treatment** and all ARs occurring **from the first trial treatment dose up to 7 days after the last dose of trial treatment** must be recorded on the appropriate Trial Treatment Assessment CRF or Follow-up Assessment CRF, which will be posted to CTRU within 2 weeks of the assessment. These are not subject to expedited reporting to CTRU.

13.3.2 Expedited Reporting of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs, SARs and SUSARs (see section 13.2 above for definitions) must be recorded on the appropriate CRF (SAE or SUSAR) and reported to the CTRU **within 24 hours** of the local research team site staff becoming aware of the event (this includes participants who have withdrawn consent for data collection, see section 11.3). Once all resulting queries have been resolved, the original wet-ink CRF will be posted to the CTRU and a copy retained at site.

Please ensure that only one event is reported on each SAE and SUSAR CRF (details of multiple symptoms should be listed if they relate to the same event).

SAEs, SARs and SUSARs must be reported in an expedited manner (within 24 hours of the research team becoming aware) during the active monitoring period, which is defined as occurring **from randomisation (for SAEs) or from the first trial treatment dose (for SARs and SUSARs) up to 7 days after the last dose of trial treatment**.

If sites become aware of any SARs or SUSARs occurring after this active monitoring period, these must still be reported in an expedited manner **up until 90 days after the End of Trial**.

13.4 Responsibilities

Principal Investigator:

1. Checking for AEs and ARs when participants attend for treatment / follow-up (this may be delegated to an appropriate member of the trial team) and ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.
2. Checking for SAEs when participants attend for treatment / follow-up (this may be delegated to an appropriate member of the trial team).
3. Using medical judgement in assigning seriousness, causality and expectedness using the version of the pharmacovigilance reference copy of the mirtazapine SPC provided in the BETTER-B Investigator Site File (or another version as instructed by the CTRU).
4. Ensuring that all SAEs (occurring up to 7 days after a participant's last trial treatment dose) and SARs, including SUSARs (occurring up to 90 days after the End of Trial) are recorded and reported to the CTRU **within 24 hours** of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
5. Ensuring that SAEs are reported to local committees in line with local arrangements.

Chief Investigator (or nominated individual):

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Review of all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and the Chief Investigator (CI), local assessment will not be downgraded but the CI may add comments prior to reporting to MHRA and REC.
5. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System Coding to all SAEs and SARs.

6. The Chief Investigator, with input from CTRU and Sponsor, will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

CTRU:

1. Central data collection and verification of AEs and ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the independent oversight committee identified for the trial (Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
3. Expedited reporting of SUSARs to the MHRA, REC and Sponsor within required timelines.
4. Notifying Investigators of SUSARs that occur within the trial.
5. Checking for (annually) and notifying Principal Investigators of updates to the Reference Safety Information for the trial.
6. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI.
7. Ensuring timely submission of the DSUR to Sponsor and the REC.

Sponsor:

1. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Sponsor's Risk Assessment.
2. Ensuring timely submission of the DSUR to the MHRA.

Trial Steering Committee (TSC):

1. In accordance with the Trial Terms of Reference for the TSC, periodically reviewing unblinded overall safety data to determine patterns and trends of events or identify safety issues which would not be apparent on an individual case basis.
2. Unblinded safety data would only be discussed in a closed session without blinded members of the trial team present.

14. Participant-reported measures

The various participant-reported measures (all of which will be administered by the researcher) of symptoms, activity, Quality of Life (QoL) and outcomes used in the BETTER-B Feasibility trial have been selected based on a national consensus statement of a National Cancer Research Institute (NCRI) Group on breathlessness [2], two systematic reviews of measures of breathlessness [73, 74], and a study estimating the size of a clinically important difference [25].

Most of these measures are brief scales, with a total of 70 participant-reported questions (at baseline), which overall (time for the questions and observation) take around 30-45 minutes to complete. This has been found acceptable in other studies [75, 76]. As part of this BETTER-B Feasibility trial we will assess which scales are suitable for a future large-scale trial based on missing data, patient acceptability and time to complete, so that the questions can be kept to a minimum in the future trial.

The participant-reported measures used in the BETTER-B Feasibility trial are:

- Numerical Rating Scale (NRS) for breathlessness: this assesses the severity of breathlessness in the previous 24 hours on a 0-10 numerical rating scale, for average, and worst [76]. It will be administered to participants at baseline and at the assessment calls/visits for days 7, 14, 21 and 28.
- Modified Medical Research Council (mMRC) dyspnoea scale:[64] this assesses the overall level of breathlessness and will be administered to participants at assessment visits for days 14 and 28.
- Chronic Respiratory Disease Questionnaire (CRQ):[xxxi] this is a 20 item widely validated health-related quality of life questionnaire. Experiences are rated on 7-point scale ranging 1 (maximum impairment) to 7 (no impairment) [77, 78] This will be administered to participants at baseline and at the assessment visits for days 14 and 28 [74].
- EQ-5D-5L: this assesses mobility, self-care, usual activities, pain/discomfort, anxiety/depression according to three levels of severity (1=no problems; 2=some or moderate problems; 3=extreme problems), plus a Visual Analogue Scale (VAS) of current health-related quality of life, scored 0-100.[76] This will be administered to participants at baseline and at the assessment visit for days 28.
- Integrated Palliative care Outcome Scale (IPOS):[xxxii] this is a brief measure for advanced disease widely validated in cancer and non-cancer. Each item is rated 0

[xxxi] Copyright University Hospitals of Leicester NHS Trust.
[xxxii] Permission to use obtained from the Cicely Saunders Institute.

(no problem) to 4 (overwhelming problem). This will be administered to participants at baseline and at the assessment visits for days 14 and 28 [79, 80].

- Generalized Self-Efficacy Scale (GSES):[67] this assesses optimistic self-beliefs to cope with a variety of difficult demands in life. This will be administered to participants at baseline and at the assessment visit for days 28.
- Hospital Anxiety and Depression Scale (HADS):[xxxiii] this is a widely used and validated scale used to assess anxiety and depression and has validity in older people to assess change, which will be administered to participants at baseline and at the assessment visits for days 14 and 28 [81].
- Client Services Receipt Inventory (CSRI):[72] is an assessment tool where patients reported the health, voluntary and social care services received over the last four weeks at baseline and at the assessment visit for day 28 .[76]

15. Economic Evaluation

The economic evaluation component of this trial aims to test the feasibility of collecting cost data, with modified CSRI, and quality of life data, with EQ-5D-5L. We will develop the tailored CSRI questionnaire, considering patient understanding and care settings. It will be ideal to collect cost data by formal health care, social care and informer care separately. We will identify difficulties answering CSRI questions, if any, by checking item response rate and reading free text answers to open-ended questions.

We will calculate the summary statistics of formal and informal care costs (and social care costs, if possible) for the last four weeks at baseline and at the assessment visit for day 28.

Finally we will examine the possibility of assessing the cost-effectiveness using outcome measurements (average breathlessness severity measured by NRS for breathlessness, breathlessness mastery measured by CRQ and IPOS and Quality Adjusted Life Years (QALYs) derived from using EQ-5D-5L) at 4 weeks. We will explore if it is possible to produce a cost-effectiveness plane with the results from the cost-effectiveness analysis.

[xxxiii] HADS copyright © R.P. Snaith and A.S. Zigmond, 1983, 1992, 1994.Record form items originally published in Acta Psychiatrica Scandinavica 67, 361–70, copyright © Munksgaard International Publishers Ltd, Copenhagen, 1983.This edition first published in 1994 by nferNelson Publishing Company Ltd (now GLAssessment Ltd),389 Chiswick High Road, London W4 4AL GL Assessment Ltd is part of the Granada Learning Group.

16. Endpoints

16.1 Primary Endpoint

The primary endpoint is the number of patients recruited across 3 hospitals over a 12-month period. This has been chosen to determine whether a larger scale trial of the same design is feasible, when expanded to additional centres [82]. The decision to proceed to a future without further amendments will be based on the ability to recruit an average of 5 patients per month within a 12-month period (e.g. approximately 60 patients).

16.2 Secondary Endpoints

16.2.1 Feasibility

Other outcome measures of feasibility will be assessed to determine whether the design of the future large-scale trial may need to be adapted to improve recruitment or reduce attrition. Physical activity and toxicity outcomes will be used to inform the design of the future trial, however they will not be used to inform the decision as to whether or not to proceed to a future large-scale trial. These are:

- Number of patients screened for eligibility and reasons for non-eligibility
- Proportion of eligible patients randomised and reasons for non-randomisation
- Proportion of participants for which blinding is maintained
- Proportion of research assessors for which blinding is maintained
- Proportion of participants remaining on study for 28 days
- Proportion of, and reasons for, participants with missing data for trial outcomes
- Proportion of participants who would be eligible for dose escalation at 28 days
- Treatment compliance over the period

Feasibility outcome measures relating to recruitment will be assessed by the use of screening logs completed at each site.

Blinding will be assessed using the Bang Blinding index [83].

Missing data and study compliance will be assessed based on completed and received CRFs, summarised for each trial outcome measure [84].

Eligibility for dose escalation will be assessed based on breathlessness intensity at day 28 and tolerability of treatment.

16.2.2 Activity

- **Key Activity endpoint:** severity of breathlessness at the assessment visit for day 28 as assessed by the NRS ("at worst" severity of breathlessness over the last 24 hours).
- Severity of breathlessness at the assessment visits/calls for days 7, 14 and 21, as assessed by NRS (average and "at worst" severity of breathlessness as assessed over the last 24 hours).
- Lower extremity functioning as assessed by the Short Physical Performance Battery (SPPB) [66] at the assessment visit for day 28.
- Opioid medication: at the assessment visits/calls for days 7, 14, 21 and 28.

16.2.3 Safety and Toxicity

- Adverse events, using the Common Terminology Criteria for Adverse Events (CTCAE) categorisation (v4) [69] as reported at the assessment visits/calls for days 7, 14, 21 and 28.
- Safety will be reported based on the occurrence of SAEs, SARs and SUSARs.
- Australia-modified Karnofsky Performance Status (AKPS) and modified Medical Research Council (mMRC) dyspnoea scale at the assessment visits for days 14 and 28.

16.2.4 Symptoms and Quality of Life

- Coping self-belief assessment as assessed by the General Self-Efficacy Scale (GSES) at the assessment visit for day 28.
- Mobility, self-care, usual activities, pain/discomfort and anxiety/depression as assessed by EQ-5D-5L at the assessment visit for day 28.
- Palliative symptoms as assessed by the Integrated Palliative care Outcome Scale (IPOS) at the assessment visits for days 14 and 28.
- Anxiety and depression as assessed by the Hospital Anxiety and Depression Scale (HADS) at the assessment visits for days 14 and 28.
- QoL as assessed by Chronic Respiratory Questionnaire (CRQ) at the assessment visits for days 14 and 28.

17. Statistical Considerations

Sample size and planned recruitment rates

As the trial is designed to assess the feasibility of conducting a future definitive large-scale trial, a formal power calculation is not considered appropriate as effectiveness is not being formally evaluated.

The future large-scale trial would be designed to detect a minimum clinically important effect size of 0.5 in NRS (or a 1 point change) [2, 25]. With 90% power testing at the 5% two-sided significance level, approximately 90 participants per arm would be required. This sample size calculation will be revisited based on the observed variability of the primary outcome in this feasibility trial. It is expected that attrition rates will be approximately 20%, however this will be assessed within this feasibility trial. Assuming a 20% attrition rate, the future trial would require approximately 230 participants in total.

Feasibility of recruitment to a future large-scale trial of the same design will be concluded if the trial is able to recruit an average of 5 patients per month over a 12-month period, equivalent to approximately 60 patients, based on 3 recruiting sites. This equates to 1-2 patients per month, per site. The sites taking part in the feasibility trial are representative of those sites which would be involved in the future larger trial. Assuming 11 sites open to recruitment in the future trial, recruiting 1-2 patients per month each, this would mean a 230-participant trial would be expected to recruit in approximately 18 months to allow for the setup and initiation of all sites.

For this feasibility trial we plan to recruit approximately 60 patients in total (i.e. 30 patients to each treatment arm) from 3 sites in the UK over a 12-month period. Guidance on pilot study design by Browne et al [85, 86] state that at least 30 patients should be included to estimate a parameter for future sample size calculation [86]. In order to estimate the expected variability of the future large-scale trial's primary outcome measure of breathlessness ("at worst") at day 28 in the mirtazapine arm, 30 participants are required. As the future trial will be randomised, this equates to a total of 60 participants required, with 1:1 randomisation.

18. Statistical Analysis

18.1 General Considerations

Statistical analysis of the main feasibility trial is the responsibility of the CTRU Statisticians. The analysis plan outlined in this section gives a brief description of the statistical analyses which will be carried out at the end of recruitment and trial follow-up. A final, more detailed, statistical analysis plan will be written before any analysis is undertaken. Given that this is a feasibility trial, the analysis will require descriptive statistics rather than any formal hypothesis testing.

Baseline characteristics of patients will be summarised.

Qualitative and Health Economics analyses will be the responsibility of the qualitative researcher and health economist respectively.

18.2 Analysis populations

The primary endpoint analysis will be based on the population of participants randomised within the 12-month recruitment period.

Endpoints which relate to data collected prior to randomisation will be analysed using all patients approached for entry to the study.

Analyses of safety data will be carried out on the safety population, defined as those participants receiving at least one dose of trial treatment, and will summarise participants according to the treatment actually received.

The remaining analysis will be carried out on the intention-to-treat (ITT) population defined as all participants randomised to the trial, regardless of adherence to the protocol, withdrawal of consent or losses to follow-up. Participants will be included within the treatment arm to which they were randomised.

18.3 Frequency of analysis

There are no formal analyses planned until after the trial is closed to recruitment. The analysis of the primary endpoint and all secondary endpoints will take place when all participants have been followed up for safety, i.e. 7 days after last trial treatment dose.

A Trial Steering Committee (TSC) will be set up to independently review data on safety, protocol adherence and recruitment. The TSC will review safety data for all participants entered into the trial approximately 6 months into recruitment (or as deemed appropriate by the TSC). Interim reports containing safety data, protocol adherence and recruitment will be presented to the TSC in strict confidence.

18.4 Primary Endpoint Analysis

The average number of patients recruited per month across 3 trial sites over a 12-month period will be summarised, overall and by trial site. The total number of patients recruited will be summarised by month, overall and by trial site.

Summaries will be presented overall by treatment arm, and by recruitment setting and diagnosis.

18.5 Secondary Endpoint Analysis

18.5.1 Feasibility

The number of approaches to patients and randomisations in total throughout the randomisation period and per month will be summarised overall and by recruitment setting and diagnosis. The proportion of screened patients who are eligible for randomisation will be presented with corresponding 95% confidence intervals. Reasons for non-eligibility will be summarised. The proportion of eligible patients who are randomised will be presented with corresponding 95% confidence intervals. Reasons for non-randomisation will be summarised.

The proportion of participants for whom blinding is maintained will be summarised overall and by treatment arm, and also by recruitment setting and diagnosis, with corresponding 95% confidence intervals. The proportion of participants who became unblinded and the reasons for unblinding will also be presented. The blinding index for each arm will be calculated using the bang blinding method along with 95% confidence interval. The blinding index calculates the difference between the proportion of correct and incorrect “guesses”. The blinding index takes values between -1 and 1.

The proportion of participants who remain on study for 28 days, will be summarised overall and by treatment arm, and also by recruitment setting and diagnosis, with corresponding 95% confidence intervals. The proportion of participants who stop treatment early and the reasons for stopping treatment will be presented.

The proportion of participants who would be eligible for dose escalation at 28 days, will be summarised overall and by treatment arm, and also by recruitment setting and diagnosis, with corresponding 95% confidence intervals. Those participants who would have not been eligible for dose escalation will be summarised along with the reason why they were not eligible for dose escalation.

The proportion of participants with missing data for each trial outcome separately will be summarised overall and by arm, at each time point of assessment. Where available, reasons for missing data will be provided.

Treatment compliance will be summarised by the proportion of participants with dose reductions or omissions and total number of missed doses, by treatment arm. Reasons for dose reductions or omissions will also be presented.

Qualitative data will be analysed by the qualitative researcher. A separate analysis plan will be written outlining the proposed analysis.

Health Economic data will be analysed by the Health Economics researcher. A separate analysis plan will be written outlining the proposed analysis.

18.5.2 Activity

Descriptive summaries of average severity of breathlessness over the last 24 hours and at worst, as assessed by NRS score, will be presented overall and by arm at each time point (baseline, days 7, 14, 21 and 28). Change in average and worst 24 hour breathlessness NRS score from baseline will also be presented with corresponding 95% confidence intervals. Average and worst breathlessness/24 hours will also be presented graphically using line graphs.

Differences in average and worst breathlessness/24 hours at day 28 between arms will be estimated using multi-level repeated measures modelling adjusting for NRS score at baseline, days 7, 14 and 21, and for minimisation factors, and incorporating time, treatment, and treatment by time interaction terms. Covariate estimates will be presented with corresponding standard errors. Treatment effect size (change in average and worst breathlessness) will be presented with corresponding 95% confidence intervals.

Mean Chronic Respiratory Questionnaire (CRQ) total score will be summarised with corresponding 95% confidence intervals and presented by treatment arm for baseline, days 14 and 28 by treatment arm. Mean change from baseline will also be summarised.

Mean lower extremity functioning, measured by the Short Physical Performance Battery (SPPB) at baseline and on day 28 will be summarised with corresponding 95% confidence intervals and presented by treatment arm. Mean change from baseline will also be summarised.

Opioid medication

The proportion of participants receiving opioid medication at each visit (days 7, 14, 21 and 28) will be summarised along with the type of medication by treatment arm.

18.5.3 Safety and Toxicity

The number of SAEs, SARs and SUSARs will be summarised descriptively by arm, by causality, seriousness, and body system.

The proportion of participants experiencing each toxicity will be summarised by maximum NCI CTCAE grade experienced over 28 days, by treatment arm.

The change in AKPS and mMRC from baseline to day 14 and 28 will be summarised.

18.5.4 Quality of Life and Patient-reported outcomes

The percentage of non-responders and missing data will be summarised for each measurement and time-point, overall, by treatment arm and will include the proportion of expected patient-completed questionnaire packs that are missing, the proportion with missing questionnaires from each pack, the proportion of questionnaires with missing item level data, the number of missing items on each questionnaire and the number of missing scores due to missing individual question responses (items).

Outcome measures relating to Quality of Life and patient-reported outcomes (GSES, EQ-5D-5L, IPOS, HADS) will be summarised by point estimates and 95% confidence intervals and presented by treatment arm, at each time point collected.

The mean score of the GSES will be presented by treatment arm along with standard deviations and 95% confidence intervals. The change in mean score from baseline to day 28 will also be presented.

The proprtion of particiapants reporting each level of percieved problems will be presented for the EQ-5D-5L by domain and treatment arm for day 28.

The mean IPOS score will be presented overall and for each domain by treatment arm along with 95% confidence intervals for each visit.

HADS scores will be calculated for each patient and the proportion of participants in each level of Anxiety and Depression will be presented by treatment arm for day 28.

19. Trial Monitoring

19.1 Trial Steering Committee

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and Trial Steering Committee (TSC) based on the trial risk assessment; this will include on site monitoring by Sponsor.

The independent TSC will review the safety and ethics of the study. Detailed un-blinded reports will be prepared by the CTRU for the TSC approximately 6 months into recruitment, and then at the end of recruitment. The TSC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan.

Any unblinded interim reports provided to the TSC will be provided by the CTRU Trial Statistician for consideration in a closed session and the reports will be securely password-protected.

19.2 Data Monitoring

Due to the feasibility nature of this trial, which has no planned interim analyses or review of activity data, a separate Data Monitoring & Ethics Committee (DMEC) has not been established. Independent data and ethical monitoring activities will be conducted by the TSC as described above. For any subsequent future large-scale trial however, both a DMEC and a TSC would be established.

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. However, missing data items will not be chased from participants. The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing Sponsor, Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.).

19.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

20. Quality Assurance, Ethical and Regulatory Considerations

20.1 Quality Assurance

Monitoring of this trial will be to ensure compliance with GCP and scientific integrity will be managed and oversight retained, by the Sponsor Quality Team.

20.2 Serious Breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

20.3 Ethical and Regulatory Considerations

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the NHS Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. Informed written consent will be obtained from the patients prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a REC, the MHRA for Clinical Trial Authorisation and the appropriate Site Specific Assessor for each participating trial site prior to entering patients into the trial. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

The Chief Investigator will submit a final report at conclusion of the trial to the Sponsor and the REC, and the Sponsor will upload this report to the EudraCT website and notify the MHRA, within the timelines defined in the Regulations.

21. Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU and at Sponsor offices. The CTRU and Sponsor will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants to record personal details including name, date of birth and NHS number;
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details;
- consent from participants for access to their medical records by responsible individuals from the research staff, Sponsor or from regulatory authorities, where it is relevant to trial participation;
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research;

- participant name will be collected when a participant is randomised into the trial but all other data collection forms that are transferred to or from the CTRU or Sponsor will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth;
- where central monitoring of source documents by CTRU or Sponsor (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending;
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU or Sponsor.

If a participant withdraws consent from further trial treatment and / or further collection of data their data collected to date will remain on file and will be included in the final study analysis.

Most CRFs will be sent to the CTRU via normal Royal Mail post, however for CRFs which need expediting to the CTRU (SAE, SUSAR, Death, Notification of Pregnancy, End of Trial Treatment CRFs), these must be sent either by fax or by secure encrypted electronic transfer.

For patients who take part in the Qualitative sub-study (see Appendix D), their data related to this sub-study will include audio-recordings of their interviews. This data will be collected from trial sites by the Qualitative sub-study Researcher and held at the Cicely Saunders Institute (King's College London). All data (paper and electronic) will be held securely and in accordance with the 1998 Data Protection Act.

22. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsor Archiving Standard Operating Procedure (SOP). Data held by the CTRU will be archived in the Leeds archive facility and site data and documents will be archived at the participating sites. Data held by Sponsor (on behalf of the Sponsors) on the main trial, and all Qualitative Interview data associated with the sub-study will be archived in a dedicated archive facility as designated by Sponsor. Following authorisation from Sponsor, arrangements for confidential destruction will then be made.

23. Statement of Indemnity

The trial is sponsored by King's College London and King's College London NHS Foundation Trust. The Sponsors will at all times maintain adequate insurance in relation to the study independently. King's College London, through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

24. Study Organisational Structure

24.1 Individuals and Individual Organisations

Chief Investigator (CI) – The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Trial Sponsor –is responsible for site monitoring, submissions to the MHRA and trial initiation management and financing of the trial as defined by Directive 2001/20/EC.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the trial as delegated by Sponsor in accordance with relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, safety management and reporting, protocol development, CRF design, trial design and statistical analysis (excluding qualitative interview and health economic analyses) for the trial. In addition the CTRU will support REC, Site Specific Assessment and NHS Permissions submissions and clinical set-up, ongoing management including training and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management and the main statistical analysis.

Central Research Nurse – The Central Research Nurse will provide support to site research nurses.

Central pharmacy – The Central pharmacy will have responsibility for trial IMP manufacture, labelling and distribution to trial sites.

Qualitative Sub-study Researcher – The Qualitative Sub-study Researcher will have responsibility for the conduct of the qualitative interview sub-study. Duties will include the training and supervision of site research teams involved in the interviews, and collection and analysis of the sub-study data.

Health Economist – The Health Economist will have responsibility for the analysis of the health economy data (EQ-5D-5L and CSRI).

24.2 Oversight and Trial Monitoring Groups

Trial Management Group (TMG) – The TMG, comprising the CI, Sponsor representative(s), CTRU team, other key external members of staff involved in the trial and a nursing representative will be assigned responsibility for the clinical set-up, ongoing management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and supporting applications for Site Specific Assessments, (iv) submitting a Clinical Trial Authorisation (CTA) and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC) – The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. It is planned that this committee will meet before the trial opens to recruitment, 6 months into the recruitment period, and then again after the end of trial recruitment.

25. Publication Policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,

- and that all these conditions must be met (www.icmje.org).

In light of this, the CI, key clinical advisors and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

26. References

1. Parshall, M.B., et al., *An official American Thoracic Society statement: update on the mechanisms, assessments, and management of dyspnea.* Am J Respir Crit Care Med, 2012. **185**(4): p. 435-52.
2. Dorman, S., et al., *Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup.* Palliat Med, 2009. **23**(3): p. 213-27.
3. Dudgeon, D.J., *Managing dyspnea and cough.* Hematol Oncol Clin North Am, 2002. **16**(3): p. 557-77, viii.
4. Bausewein, C., et al., *Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer.* J Palliat Med, 2010. **13**(9): p. 1109-18.
5. Gysels, M.H. and I.J. Higginson, *The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND.* BMC Palliat Care, 2011. **10**(15).
6. Malik, F.A., M. Gysels, and I.J. Higginson, *Living with breathlessness: a survey of caregivers of breathless patients with lung cancer or heart failure.* Palliat Med, 2013. **27**(7): p. 647-56.
7. Kavalieratos, D., et al., *Comparing unmet needs between community-based palliative care patients with heart failure and patients with cancer.* J Palliat Med, 2014. **17**(4): p. 475-81.
8. Solano, J.P., B. Gomes, and I.J. Higginson, *A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease.* J Pain Symptom Manage, 2006. **31**(1): p. 58-69.
9. Janssen, D.J., et al., *Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure.* J Palliat Med, 2011. **14**(6): p. 735-43.
10. Janssen, D.J., et al., *Self-perceived symptoms and care needs of patients with severe to very severe chronic obstructive pulmonary disease, congestive heart failure or chronic renal failure and its consequences for their closest relatives: the research protocol.* BMC Palliat Care, 2008. **7**(5).
11. Beynon, T., et al., *How common are palliative care needs among older people who die in the emergency department?* BMJ Support Palliat Care, 2011. **1**(2): p. 184-88.
12. Kane, P.M., K. Vinen, and F.E. Murtagh, *Palliative care for advanced renal disease: a summary of the evidence and future direction.* Palliat Med, 2013. **27**(9): p. 817-21.
13. Murtagh, F.E., J.M. Addington-Hall, and I.J. Higginson, *End-stage renal disease: a new trajectory of functional decline in the last year of life.* Journal of the American Geriatrics Society, 2011. **59**(2): p. 304-08.
14. Bausewein, C., et al., *Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study.* Palliat Med, 2010. **24**(8): p. 777-86.
15. Seow, H., et al., *Trajectory performance status and symptom scores for patients with cancer during the last six months of life.* J Clin Oncol, 2011. **29**(9): p. 1151-58.
16. Frostad, A., et al., *Impact of respiratory symptoms on lung cancer: 30-year follow-up of an urban population.* Lung cancer, 2008. **60**(1): p. 22-30.
17. Frostad, A., et al., *Respiratory symptoms and long-term cardiovascular mortality.* Respir Med, 2007. **101**(11): p. 2289-96.
18. Frostad, A., et al., *Respiratory symptoms as predictors of all-cause mortality in an urban community: a 30-year follow-up.* Journal of internal medicine, 2006. **259**(5): p. 520-29.

19. Janssen, D.J., et al., *A call for high-quality advance care planning in outpatients with severe COPD or chronic heart failure.* Chest, 2011. **139**(5): p. 1081-88.
20. Barbera, L., et al., *Do patient-reported symptoms predict emergency department visits in cancer patients? A population-based analysis.* Ann Emerg Med, 2013. **61**(4): p. 427-37 e5.
21. Barbera, L., C. Taylor, and D. Dudgeon, *Why do patients with cancer visit the emergency department near the end of life?* Cmaj, 2010. **182**(6): p. 563-68.
22. Currow, D.C. and A.P. Abernethy, *Breathlessness in an age of noncommunicable diseases.* Curr Opin Support Palliat Care, 2012. **6**(2): p. 127-28.
23. Yoong, J., et al., *A Pilot study to investigate adherence to long-acting opiods among patients with advanced lung cancer.* J Palliat Med, 2013. **16**(4): p. 391-96.
24. Oxberry, S.G., et al., *Repeat dose opiods may be effective for breathlessness in chronic heart failure if given for long enough.* J Palliat Med, 2013. **16**(3): p. 250-55.
25. Johnson, M.J., et al., *Opioids for chronic refractory breathlessness: patient predictors of benficial response.* Eur Respir J, 2013. **42**(3): p. 758-66.
26. Currow, D.C., M. Ekstrom, and A.P. Abernethy, *Opioids for chronic refractory breathlessness: right patient, right route?* Drugs, 2014. **74**(1): p. 1-6.
27. Currow, D.C., et al., *Once-daily opiods for chronic dyspnea: a dose increment and pharmacovigilance study.* J Pain Symptom Manage, 2011. **42**(3): p. 388-99.
28. Currow, D.C., et al., *Can we predict which patients with refractory dyspnea will respond to opioids?* J Palliat Med, 2007. **10**(5): p. 1031-36.
29. Jennings, A.L., et al., *A systematic review of the use of opioids in the management of dyspnoea.* Thorax, 2002. **57**(11): p. 939-44.
30. Smoller, J.W., et al., *Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations.* American Journal of Respiratory and Critical Care Medicine, 1996. **154**(1): p. 6-17.
31. Smoller, J.W., et al., *Sertraline effects on dyspnea in patients with obstructive airways disease.* Psychosomatics, 1998. **39**(1): p. 24-29.
32. Rampin, O., O. Pierrefiche, and M. Denavit-Saubie, *Effects of serotonin and substance P on bulbar respiratory neurons in vivo.* Brain Research, 1993. **622**(1-2): p. 185-93.
33. Papp, L.A., et al., *Sertraline for chronic obstructive pulmonary disease and comorbid anxiety and mood disorders.* The American Journal of Psychiatry, 1995. **152**(10): p. 1531.
34. Currow, D., *A phase II, double-blind, multi-site randomised controlled pilot study of sertraline compared with placebo in relieving refractory breathlessness*. 2008, Australian New Zealand Clinical Trials Registry.
35. Ben-Aharon, I., et al., *Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis.* Acta Oncologica (Stockholm, Sweden), 2012. **51**(8): p. 996-1008.
36. Booth, S., S.H. Moosavi, and I.J. Higginson, *The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy.* Nature Clinical Practice Oncology, 2008. **5**(2): p. 90-100.
37. Simon, S.T., et al., *Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults.* Cochrane database systematic reviews (Online), 2010. **1**: p. CD007354.
38. Simon, S.T., et al., *Fentanyl for the relief of refractory breathlessness: a systematic review.* J Pain Symptom Manage, 2013. **46**(6): p. 874-86.
39. Jennings, A.L., et al., *Opioids for the palliation of breathlessness in terminal illness.* Cochrane database systematic reviews 2001. **4**: p. CD002066.
40. Abernethy, A.P., 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**(9743): p. 784-93.

41. Schruers, K., et al., *Acute L-5-hydroxytryptophan administration inhibits carbon dioxide-induced panic in panic disorder patients.* Psychiatry Research, 2002. **113**(3): p. 237-43.
42. Perna, G., R. Cogo, and L. Bellodi, *Selective serotonin re-uptake inhibitors beyond psychiatry: are they useful in the treatment of severe, chronic, obstructive pulmonary disease?* Depression and Anxiety, 2004. **20**(4): p. 203-04.
43. Devoto, P., et al., *Mirtazapine-induced corelease of dopamine and noradrenaline from noradrenergic neurons in the medal prefrontal and occipital cortex.* Eur J Pharmacol, 2004. **487**(1-3): p. 105-11.
44. Stahl, S.M., *Psychopharmacology: neuroscientific basis and practical applications*. 3rd ed. ed. 2008, Cambridge: Cambridge University Press.
45. Watanabe, N., et al., *MIrtazapine versus other antidepressive agents for depression.* Cochrane database systematic reviews, 2011. **12**: p. CD006528.
46. Kim, J.E., et al., *Efficacy and tolerability of mirtazapine in treating major depressive disorder with anxiety symptoms: an 8-week open-lable randomised paroxetine-controlled trial.* International Journal of Clinical Practice, 2011. **65**(3): p. 323-29.
47. Rayner, L., et al., *Antidepressants for the treatment of depression in palliative care: systematic review and meta-analysis.* Palliat Med, 2011. **25**(1): p. 36-51.
48. Rayner, L., et al., *Expert opinion on detecting and treating depression in palliative care: a Delphi study.* BMC Palliat Care, 2011. **10**(10).
49. Rayner, L., et al., *The development of evidence-based European guidelines on the management of depression in palliative cancer care.* Eur J Cancer, 2011. **47**(5): p. 702-12.
50. Kim, S.W., et al., *Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression.* Psychiatry and Clinical Neurosciences, 2008. **62**(1): p. 75-83.
51. Bet, P.M., et al., *Side effects of antidepressants during long-term use in a naturalistic setting.* European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology, 2013. **23**(11): p. 1443-51.
52. Disler, R.T., et al., *Experience of advanced chronic obstructive pulmonary disease: metasynthesis of qualitative research.* J Pain Symptom Manage, 2014. **48**(6): p. 1182-99.
53. Ramsenthaler, C., et al., *Cognitive behavioural therapy in COPD: a systematic review and meta-analysis of its effect on anxiety, panic, breathlessness and quality of life*.
54. Dudgeon, D.J., M. Lertzman, and G.R. Askew, *Physiological changes and clinical correlations of dyspnea in cancer outpatients.* J Pain Symptom Manage, 2001. **21**(5): p. 373-39.
55. Croom, K.F., C.M. Perry, and G.L. Plosker, *Mirtazapine: a review of its use in major depression and other pyschiatric disorders.* CNS Drugs, 2009. **23**(5): p. 427-52.
56. Chen, C.C., et al., *Premedication wtih mirtazapine reduces preoperative anxiety and postoperative nausea and vomiting.* Anesthesia and analgesia, 2008. **106**(1): p. 109-13.
57. Brannon, G.E. and K.D. Stone, *The use of mirtazapine in a patient with chronic pain.* J Pain Symptom Manage, 1998. **18**(5): p. 382-85.
58. Ritzenthaler, B.M.E. and D.J. Pearson, *Efficacy and tolerability of mirtazapine in neuropathic pain.* Palliat Med, 2000. **14**(4): p. 325-51.
59. Alam, A., Z. Voronovich, and J.A. Carley, *A review of therapeutic uses of mirtazapine in psychiatric and medical conditions.* Prim Care Companion CNS Disord, 2013. **15**(5).
60. Ahmed, T., J.A. Steward, and M.S. O'Mahony, *Dyspnoea and mortality in older people in the community: a 10-year follow-up.* Age Ageing, 2012. **41**(4): p. 545-59.
61. Booth, S., *Science supporting the art of medicine: improving the management of breathlessness.* Palliat Med, 2013. **27**(6): p. 483-85.

62. Clemens, K.E., M. Faust, and E. Bruera, *Update on combined modalities for the management of breathlessness.* Curr Opin Support Palliat Care, 2012. **6**(2): p. 163-67.
63. Currow, D., *A randomised, double-blind multi-site parallel arm controlled trial to assess relief of refractory breathlessness in palliative care patients taking oral sertraline versus a placebo*. 2010, Australian New Zealand Clinical Trials Registry.
64. Doherty, D.E., et al., *Chronic Obstructive Pulmonary Disease: Consensus recommendations for early diagnosis and treatment.* Journal of Family Practice, 2006. **November 2006**.
65. Guralnik, J.M., et al., *A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission.* J Gerontol Med Sci, 1994. **49**(2): p. M85-M94.
66. Choi, H.C., et al., *An implication of the short physical performance battery (SPPB) as a predictor of abnormal pulmonary function in aging people.* Arch Gerontol Geriatr, 2012. **54**(3): p. 448-52.
67. Schwarzer, R. and M. Jerusalem, *Generalized Self-Efficacy Scale*, in *Measures in health psychology: A user's portfolio. Causal and control beliefs*, J. Weinman, S. Wright, and M. Johnston, Editors. 1995, NFER-NELSON: Windsor, England. p. 35-37. http://userpage.fu-berlin.de/~health/selfscal.htm
68. Abernethy, A.P., et al., *The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice.* BMC Palliat Care, 2005. **4**(7): p. 1-12.
69. Trotti, A., et al., *CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment.* Semin Radiat Oncol, 2003. **13**(3): p. 176-81.
70. NIfHaCE, N., *Chronic Obstructive Pulmonary Disease*. 2010, London: NICE.
71. NIfHaCE, N., *Idiopathic pulmonary fibrosis*. 2013, London: NICE.
72. Beecham, J. and M. Knapp, *Costing psychiatric interventions*, in *Measuring Mental Health Needs*, G. Thornicroft, Editor. 2001. p. 200-224.
73. Bausewein, C., et al., *Measurement of breathlessness in advanced disease: a systematic review.* Respir Med, 2007. **101**(3): p. 399-410.
74. Dorman, S., A. Byrne, and A. Edwards, *Which measurement scales should we use to measure breathlessness in palliative care? A systematic review.* Palliat Med, 2007. **21**(3): p. 177-91.
75. Booth, S., et al., *Developing a breathlessness intervention service for patients with palliative and supportive care needs, irrespective of diagnosis.* J Palliat Care, 2011. **27**(1): p. 28-36.
76. Bausewein, C., et al., *Development, effectiveness and cost-effectiveness of a new out-patient Breathlessness Support Service: study protocol of a phase III fast-track randomised controlled trial.* BMC Pulmonary Medicine, 2012. **12**(1): p. 58.
77. Puhan, M.A., et al., *Relative responsiveness of the Chronic Respiratory Questionnaire, St Georges Respiratory Questionnaire and four other health-related quality of life instruments for patients with chronic lung disease.* Respiratory Medicine, 2007. **101**(2): p. 308-16.
78. Guyatt, G.H., et al., *A measure of quality of life for clinical trials in chronic lung disease.* Thorax, 1987. **42**(10): p. 773-78.
79. Siegert, R.J., et al., *Psychological well-being and quality of care: a factor-analytic examination of the palliative care outcome scale.* J Pain Symptom Manage, 2010. **40**(1): p. 67-74.
80. Hearn, J. and I.J. Higginson, *Development and validation of a core outcome measure for palliative care: the palliative care outcome scale.* Palliat Care Core Audit Project Advisory Group; Qual Health Care, 1999. **8**(4): p. 219-27.
81. Roberts, M.H., R.B. Fletcher, and P.L. Merrick, *Tha validity and clinical utlility of the hospital anxiety and depression scale (HADS) with older New Zealanders.* Int Psychogeriatr, 2014. **26**(2): p. 325-33.

82. Lancaster, G.A., S. Dodd, and P.R. Williamson, *Design and analysis of pilot studies: recommendations for good practice.* Journal of Evaluation in Clinical Practice, 2004. **10**(2): p. 307-312.
83. Bang, H., L. Ni, and C.E. Davis, *Assessment of blinding in clinical trials.* Control Clin Trials, 2004. **25**(2): p. 143-56.
84. Kurland, B.F., L.L. Johnson, and P.H. Diehr, *Accommodation of missing data in supportive and palliative care clinical trials.* Curr Opinion Support Palliat Care, 2012. **6**(4): p. 465-70.
85. . 2014, National Health Service.
86. Browne, R.H., *On the Use of a Pilot Sample for Sample-Size Determination.* Statistics in Medicine, 1995. **14**(17): p. 1933-1940.
87. Sturges, J. and K. Hanrahan, *Comparing telephone and face-to-face qualitative interviewing: a research note.* Qual Res, 2004. **4**(1): p. 107-18.
88. Novick, G., *Is there a bias against telephone interviews in qualitative research?* Res Nurs Health, 2008. **31**(4): p. 391-98.
89. Hewison, J. and A. Haines *Overcoming barriers to recruitment in health research*. BMJ, 2006. **333:300**, DOI: http://dx.doi.org/10.1136/bmj.333.7562.300.
90. Gysels, M., C. Shipman, and I.J. HIgginson, *"I will do it if it will help others": motiviations among patients taking part in qualitative studies in palliative care.* J Pain Symptom Manage, 2008. **35**(4): p. 347-55.
91. Gysels, M.H., C. Evans, and I.J. Higginson, *Patient, care-giver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature.* BMC Med Res Methodol, 2012. **12**(123).
92. Shipman, C., et al., *The views of patients with advanced cancer regarding participation in serial questionnaire studies.* Palliat Med, 2008. **22**(8): p. 913-20.
93. Newington, L. and A. Metcalfe, *Researchers' and clinicians' perceptions of recruiting participants to clinical research: a themtic meta-synthesis.* J Clin Med Res, 2014. **6**(3): p. 162-72.
94. Newington, L. and A. Metcalfe, *Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams.* BMC Med Res Methodol, 2014. **14**(10).
95. Corbin, J. and J. Morse, *The unstructured interactive interview: issues of reciprocity and risks when dealing with sensitive topics.* Qual Inq, 2003. **9**(3): p. 335-554.

27. Appendix A: Modified Medical Research Council (mMRC) Dyspnoea Scale

This is the modified Medical Research Council (mMRC) scale[34] that uses the same descriptors as the original MRC scale, in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE (Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity) index.

Grade

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

[34] Dennis E. Doherty, MD, FCCP, Mark H. Belfer, DO, FAAFP, Stephen A. Brunton, MD Leonard Fromer, MD, Charlene M. Morris, MPAS, PA-C, Thomas C. Snader, PharmD, CGP, FASCP. Chronic Obstructive Pulmonary Disease: Consensus Recommendations for Early Diagnosis and Treatment. Journal of Family Practice, November, 2006.

28. Appendix B: Australia-modified Karnofsky Performance Scale (AKPS)

The Australia-modified Karnofsky Performance Scale (AKPS)[35] is a measure of the patient's overall performance status or ability to perform their activities of daily living. It is a single score between 10 and 100 assigned by a clinician based on observations of a patient's ability to perform common tasks relating to activity, work and self-care. A score of 100 signifies normal physical abilities with no evidence of disease. Decreasing numbers indicate a reduced performance status. The rating should be recorded as assessed (scores in increments of 10); in between scores such as 45, 55 or scores such as 50-60 are invalid.

Here are some examples of questions you might ask the potential participant in order to assess their AKPS score:

- "Have there been any changes today with your ability to attend to activities of daily living?"
- "Are you requiring more physical care today?"
- "How much time are you actually spending in bed?"

AKPS Assessment Criteria	Score
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor sign of symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Able to care for most needs; but requires occasional assistance	60
Considerable assistance and frequent medical care required	50
In bed more than 50% of the time	40
Almost completely bedfast	30
Totally bedfast and requiring extensive nursing care by professionals and/or family	20
Comatose or barely rousable	10
Dead	0

[35] Abernethy, A. P., Shelby-James, T., Fazekas, B. S., Woods, D. Currow, D. C. (2005). The Australia-modified Karnofsky Performance Status (AKPS) Scale: A Revised Scale for Contemporary Palliative Care Clinical Practice [Electronic Version]. BioMed Central Palliative Care, 4, 1-12

29. Appendix C: New York Heart Association (NYHA)

Doctors usually classify patients' heart failure according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification[36]. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

[36] http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp; accessed on 08/10/2015.

30. Appendix D: Qualitative Sub-study

30.1 Background

A qualitative sub-study will run alongside the BETTER-B Feasibility trial to explore participants' views of the trial, aspects that affect their willingness to participate and remain in the trial, and views of the most common effects of the treatment. This sub-study will involve qualitative interviews held with a purposively selected sample of 12-15 patients.

This sub-study will be conducted by research nurses at the participating trial sites and supported by the BETTER-B Research Associate based at Kings College London, under the supervision of the Chief Investigator Prof Higginson.

Patients may feel uncomfortable with the use of a placebo-control, or the randomisation process. Understanding why patients choose not to participate or do not take up their treatment allocation will be crucial demonstrating that recruiting to a larger scale trial is feasible. We will explore what patients understand, perceive and feel about, how the BETTER-B trial was presented to them and their expectations of trial burden. We will include those participants who have declined participation; those who agreed to participate in the trial but do not take up their treatment allocation after being randomised into a particular trial arm, and those who agree to take part. Recruitment and retention of participants is essential to demonstrate our ability to perform a definitive trial in this setting, and so this work will explore the factors influencing recruitment from the patients' perspective.

30.2 Aim

To qualitatively explore patient acceptability of the trial and recruitment processes to assist in optimisation of recruitment and follow-up strategies employed for a future large-scalerandomised controlled trial.

Objectives

- To explore patients' reasons for acceptance or refusal to participate in the BETTER-B trial
- To determine ways in which the BETTER-B trial can be improved
- To explore participants' views of the placebo-control
- To explore participants' views of the randomisation process
- To identify methods and measures to be used to help generate specific recommendations for improvement

30.3 Patient Interview Eligibility Criteria

Patient Inclusion Criteria

1. Approached to consider entry into the BETTER-B Feasibility trial and **either**:
   - Agreed to participate in the trial; **or**
   - Decided against participation after randomisation; **or**
   - Decided against participation when study presented to them.
2. Willing and able to comply with requirements of this sub-study
3. Written informed consent obtained to participate in this sub-study

Patient Exclusion criteria

1. Decline participation in this sub-study
2. Unable to comply with requirements of this sub-study protocol

30.4 Sampling

We will conduct qualitative interviews with up to 15 patients (subject to data saturation). We will aim to include diverse experiences, including patients (or their families if the patients are not available) who consent and (where possible) do not consent to trial enrolment, completers and non-completers, across patients with different diseases (cancer, heart failure, COPD), different ages and ethnic groups. This sub-study will be open to patients from all BETTER-B trial sites.

Interviews will be collected after the end of the participation for patients who complete, or after non-consent or withdrawal (where ethically feasible).

30.5 Consent Process

Approaching patients who have consented to the main BETTER-B Feasibility trial

Patients who consent to the main BETTER-B Feasibility trial will be asked if they would be happy to be approached about this sub-study at the time of consent into the main trial – this is an optional consent item on the main trial's Informed Consent Form (ICF).

Approaching patients who have declined to the main BETTER-B Feasibility trial

Patients who decline to participate in the main BETTER-B Feasibility trial will be provided with a BETTER-B Feedback Questionnaire at the time of refusal. The last question on this questionnaire is about the qualitative sub-study and patients can indicate whether or not they would like to be approached about the sub-study. This questionnaire is entirely optional however, so we anticipate that some patients will complete this and therefore be able to indicate their willingness to know more about the sub-study, whereas other patients will not

wish to complete the questionnaire, but may still be willing to speak to a research nurse as part of this sub-study.

For those patients who decline to participate in the main trial and agree to complete the BETTER-B Feedback Questionnaire, they can indicate that they would be happy to be approached about this qualitative sub-study by answering the last question on the Feedback Questionnaire.

For those patients who decline to participate in the main trial and also decline to complete the BETTER-B Feedback Questionnaire, they will be asked at the time of refusal if they would be happy to be approached about this qualitative sub-study.

Consent to the qualitative sub-study

Those who do consent to be approached regarding the qualitative sub-study will be contacted by a member of their trial site's BETTER-B research team who will briefly describe this sub-study, go over its objectives, and answer any questions. The patient will also be provided with a sub-study Participant Information Sheet (PIS) and ICF. If patients give their consent to be interviewed, suitable arrangements will be made. The interview will be conducted at a time and place agreeable to the patient – this may be in the patient's home, or other location of their choice.

If patients change their mind following consent, they can withdraw from the sub-study at any time (including during the conduct of the interview). In these cases, no further contact will be made by the qualitative research team.

If the patient requires more time for consideration, they may contact their trial site's research team at a later time and arrange an interview.

30.6 Interview Procedure

Since several studies [87, 88] have pointed out that there are no major differences in the results of telephone and face-to-face interviews, the participants will be invited to be interviewed either over the phone or in person, to accommodate family and professional obligations. We selected this recruitment strategy because research shows that on one hand there is no evidence that potential participants object to such a system, while on the other hand such an approach minimises response bias and potentially increases the methodological rigour of the research [89].

Interviews will be audio-recorded and interviews are expected to last 30 to 45 minutes. Interviewers will follow a topic guide and probe specifically in areas of interest, including: why they agreed to participate or not, what might increase or reduce this, views of placebo control

arm, frequency of follow up interviews, best mode of contact, views of the trial, views of method and location of interviews, view of methods of data collection. The research nurses will be trained by the Qualitative sub-study Researcher (based at King's College London) in the conduct of these qualitative interviews, and the Researcher will monitor the quality of the interviews and will conduct the analysis.

The research nurses will be supported in the conduct of the qualitative interviews by the Researcher under the supervision of Prof Higginson. Qualitative data will be transcribed as soon as it is received, and prepared for analysis. The Researcher will monitor the progress of qualitative interviews and recruitment of the sub-sample according to the matrix and identify and follow up on any aspects that need to be explored further. Qualitative interviews will be completed by the end of the BETTER-B Feasibility trial's recruitment period to allow adequate time for analysis and integration.

30.7 Data analysis

The qualitative data will be audio recorded, transcribed verbatim and analysed following the framework method established by Ritchie and Spencer to identify key themes. The framework matrix will be developed using NVivo 10 software (QSR) and incorporate the interview topic guide, ideas from the existing literature [90-94] and prominent themes identified from a preliminary review of the transcripts. The transcripts will be coded line by line and additional themes entered into the matrix where necessary. The matrix will then be populated with summarised data according to participant and theme, and used to identify common and divergent issues.

30.8 Endpoints

Issues related to trial design and conduct that may be responsible for poor recruitment will be discussed with the research team to inform recruitment for the definitive trial. This may include re-design of study information, recruitment strategy, advice about presenting the study, or discussions about equipoise.

Feedback relating to the importance and timing of candidate primary and secondary endpoints and the acceptability of and feasibility of intervention blinding will be provided to the research team to inform any subsequent large-scale trial.

30.9 Ethical Considerations

"Lone worker" policy

Interviews are being conducted on a one-to-one basis between a participant and the research nurse. As the participants can choose the time and place of the interview and can

opt to be interviewed in their own homes, there is some risk to the research nurse. For this reason the research teams will follow their local "lone worker" policies.

Potential distress

Recent evidence suggests that qualitative interviewing, even when using unstructured interview guides (i.e. those which are not pre-approved by the ethics committees) does not have long-term negative effect which would require psychological treatment. In fact, the participants are far more likely to experience relief after discussing distressing experiences [95]. However, it is nevertheless possible that the participant will experience distress while remembering the nature of their illness. To address this issue we will make sure that the researcher working on the sub-study will have considerable experience in qualitative research in healthcare and working with vulnerable patient populations and (s)he will be able to handle these issues sensitively.

If the researcher is not able to address participant's distress then they will follow their local "distress protocol" which may involve the patient being referred to the local recruiting site's counselling service.

Distress may also be cause to the researcher themselves. Where this occurs, they should again follow the local "distress protocol".

30.10 Confidentiality

All participants in this sub-study will sign Informed Consent Forms (ICFs) – these will be held securely at trial sites (copies will not be sent to the Qualitative sub-study Researcher at King's College London). Sub-study participants will also have their interviews audio-recorded. This electronic data will be held securely at trial sites initially and then sent to King's College London using encrypted electronic transfer, where the recordings will then be transcribed. All data (electronic and paper) will be held securely at King's College London in accordance with the 1998 Data Protection Act.

Appendix 7 -Case Report Form

BETTER-B

ISRCTN32236160

FORM 90

Page 1 of 3

Patient Screening

Screening number

- **To be completed for every potential Better-B trial patient THAT DOES NOT GO ON to be randomised**
- **Potential participants include those who have been diagnosed with cancer, COPD / ILD or chronic heart failure and severe breathlessness (i.e. anticipated mMRC score of Grade 3 or 4)**

Site code C

Date patient considered Day Month Year

Where was the patient initially identified for potential participation in the Better-B trial?

- ☐ Outpatient
- ☐ Inpatient
- ☐ Community services
- ☐ Direct contact from patient
- ☐ Other, please specify

Patient age

- ☐ 30 or under
- ☐ 31–50
- ☐ 51–60
- ☐ 61–70
- ☐ 71–80
- ☐ 81 and over

Underlying condition

- ☐ Cancer
- ☐ Lung disease → Please specify
  - ☐ COPD
  - ☐ ILD
- ☐ Chronic heart failure

Completed by | Date Day Month Year | Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised		Verified/Checked	
	Date	Initials	Date	Initials

Version 0.5 12/05/2016

Screening number | | | | | | |

Has the participant been considered for participation in the Better-B trial?

☐ Yes ☐ No

If no, please give reason(s) patient was not considered:

☐ Patient ineligible (checks not requiring any trial intervention only). Please tick all the reasons that apply on the **ineligible** list on page 3

☐ Other, please specify

• Please sign & date the form and return to CTRU

Was the patient approached for the Better-B trial?

☐ Yes ☐ No

If no, please give reason(s) patient was not approached:

• Please sign & date the form and return to CTRU

Method of approach

Did the patient consent to the Better-B trial?

☐ Yes ☐ No

If no, please give reason(s) patient was not consented:

☐ Patient declined. Please tick all the reasons that apply on the **declined** list on page 3

☐ Patient too ill to consent

Why wasn't the patient randomised?

Please give reason(s) for non-randomisation

☐ Subsequently found to be ineligible. Please tick all the reasons that apply on the **ineligible** list on page 3

☐ Patient became too ill to randomise

☐ Other, please specify

• Please sign & date the form and return to CTRU

Completed by | Date Day Month Year

Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

Screening number

Ineligible list
(Please tick all that apply)

- ☐ Patient under 18 years old
- ☐ Currently taking antidepressants
- ☐ Known contraindication to mirtazapine
- ☐ Hypersensitivity to mirtazapine/placebo
- ☐ AKPS of 40 or less
- ☐ Acute cardiac event within last 3 months
- ☐ Hepatic impairment
- ☐ Renal impairment
- ☐ Uncontrolled blood pressure
- ☐ Uncontrolled diabetes mellitus
- ☐ Uncontrolled seizures, epilepsy or organic brain syndrome
- ☐ Severe depression / suicidal thoughts
- ☐ History of psychotic illness
- ☐ Not on optimal treatment for underlying condition
- ☐ Management of underlying condition changed within last week
- ☐ Reversible causes of breathlessness not optimally treated
- ☐ Prognosis less than 2 months
- ☐ Female of child-bearing potential not willing to use adequate contraception
- ☐ Pregnant or breast-feeding
- ☐ Other, please specify

Patient declined list
(Please tick all that apply)

- ☐ Travel costs
- ☐ Did not like the thought of clinical trials
- ☐ Did not like the thought of antidepressants
- ☐ Did not want to complete trial visits/call
- ☐ Did not want to complete Quality of Life booklets
- ☐ Did not want to take additional medication
- ☐ Did not like the thought of a blinded trial
- ☐ Did not think their breathlessness was bad enough
- ☐ Other, please specify

Completed by | Date Day Month Year | Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 01 Initial Eligibility Checklist

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- **To be completed prior to randomisation**
- **Participants must fulfil ALL eligibility criteria in order to be randomised into the trial**

Section A – Inclusion Criteria

Please tick yes / no / N/A for all questions. If any shaded boxes are ticked, the participant is ineligible

	Yes	No	N/A	
1. Is the participant aged over 18 years old?	☐	■		
2. Has the participant been diagnosed with any of the following conditions: • Cancer • Lung disease – Chronic Obstructive Pulmonary Disease (COPD) OR Interstitial Lung Disease (ILD) • Chronic heart failure – NYHA class III or IV	☐	■		
3. Does the participant have a modified MRC dyspnoea scale grade of 3 or 4? *(I.e. stops for breath after walking about 100 yards or after a few minutes on level ground, or is too breathless to leave to house, or is breathless whilst dressing)*	☐	■		
4. Is the participant on optimal treatment for their underlying condition in the opinion of the identifying clinician? *(See eligibility process section of the protocol for guidance)*	☐	■		
5. Has the management of the participant's underlying condition remained unchanged for the previous 1 week?	☐	■		
6. Have the reversible causes of breathlessness been optimally treated in the opinion of the identifying clinician? *(According to current appropriate national society guidance)*	☐	■		
7. Is the participant's expected prognosis at least 2 months or more?	☐	■		
8. If the participant is female and of child-bearing potential, has she agreed to use adequate contraception during her participation in the trial? *(See eligibility section of the protocol for guidance)*	☐	■	☐	*(The participant is either a male or a female not of childbearing potential)*
9. Is the participant able to complete questionnaires and trial assessments?	☐	■		
10. Has the participant provided written informed consent before any trial-specific procedures?	☐	■		

Completed by		Date	Day Month Year
Investigator signature		Date	Day Month Year

Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 01 Initial Eligibility Checklist

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section B – Exclusion Criteria

Please tick yes / no for all questions. If any shaded boxes are ticked, the participant is ineligible

		Yes	No	N/A	
1.	Is the participant currently taking antidepressants, linezolid or St John's wort? *(If previously on antidepressants, the participant must have stopped taking them at least 14 days prior to randomisation)*	☐	☐		
2.	Does the participant have a known contraindication to mirtazapine?	☐	☐		
3.	Does the participant have hypersensitivity to the active substance or any of the components of the mirtazapine or placebo (e.g. lactose intolerance)?	☐	☐		
4.	Does the participant have an Australia-modified Karnofsky Performance Scale of 40 or less? *(I.e. is the participant in bed more than 50% of time due to association with short survival)*	☐	☐		
5.	Is the participant pregnant or breast-feeding? *(All women of childbearing potential must have a pregnancy test within 7 days prior to randomisation)*	☐	☐	☐	*(The participant is either a male or a female not of childbearing potential)*
6.	Has the participant had an acute cardiac event within 3 months of randomisation (myocardial infarction, unstable angina pectoris, or significant cardiac conduction disturbance)?	☐	☐		
7.	Does the participant have known hepatic impairment?	☐	☐		
8.	Does the participant have known renal impairment?	☐	☐		
9.	Does the participant have uncontrolled blood pressure?	☐	☐		
10.	Does the participant have uncontrolled diabetes mellitus?	☐	☐		
11.	Does the participant have uncontrolled seizures, epilepsy or organic brain syndrome?	☐	☐		
12.	Does the participant have severe depression or suicidal thoughts?	☐	☐		
13.	Does the participant have a history of psychotic illness (bipolar disorder, mania, hypomania, schizophrenia, or other psychotic disturbances)?	☐	☐		

Section C – Eligibility Queries

Has an eligibility query been raised with the CTRU? ☐ Yes ☐ No

If yes, please state the number(s) of the checklist that have been queried

Query raised

Completed by Date Day Month Year

Investigator signature Date Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 02

Page 1 of 3

Baseline Assessments

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed following obtaining written informed consent and confirmation of eligibility but prior to starting treatment

Section A – Participant Details

Gender ☐ Male ☐ Female

NHS number

Section B – Underlying Disease

Please indicate the underlying disease(s) by **ticking yes or no for each**:

	Yes	No	If yes, please give details	
Cancer	☐	☐	Please indicate primary type	☐ Breast ☐ Prostate ☐ Lung ☐ Bowel ☐ Other, please specify
Lung disease	☐	☐	Specify type	☐ COPD ☐ ILD
Chronic heart failure	☐	☐	Provide NYHA class *(Ineligible if class I or II)*	☐ Class I ☐ Class II ☐ Class III ☐ Class IV

Section C – Recruitment Setting

Where was this participant initially identified for potential participation in this trial?

☐ Outpatient setting
☐ Inpatient setting
☐ Community Services setting
☐ Direct contact from participant
☐ Other, please provide details

Completed by | Date Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section D – Baseline Assessments

- **All assessments must be completed prior to randomisation in order to confirm eligibility**
- **Any assessment performed more than 7 days prior to treatment start must be repeated**

AKPS

Date of test: Day Month Year

Score *(See reverse for definitions)*: *(A score of 40 or less would mean the participant is ineligible)*

mMRC

Date of test: Day Month Year

Grade *(See reverse for definitions)*: *(An assessment of Grade 0, 1 or 2 would mean that the participant is ineligible)*

SPPB

Was the SPPB (**Form 60**) performed? ☐ Yes ☐ No

If no, give reason SPPB not performed

Pregnancy Test

Date of test: Day Month Year OR ☐ N/A – *The participant is male or is not a female of childbearing potential*

If performed, result ☐ Positive → **This participant is not eligible for Better B**

☐ Negative

Section E – NRS Assessment

- **The NRS assessment must be performed within 7 days prior to trial treatment start**

Date of test: Day Month Year

Please ask the participant...

How bad has your breathlessness felt **on average** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

How bad has your breathlessness felt **at its worst** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

Completed by | Date: Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised		Verified/Checked	
	Date	Initials	Date	Initials

AKPS Score

A score of 40 or less would mean the participant is ineligible

0	(Dead)
10	(Comatose or barely rousable)
20	(Totally bedfast and requiring extensive nursing care by professionals and/or family)
30	(Almost completely bedfast)
40	(In bed more than 50% of the time)

50	(Considerable assistance and frequent medical care required)
60	(Able to care for most needs; but requires occasional assistance)
70	(Cares for self; unable to carry on normal activity or to do active work)
80	(Normal activity with effort; some signs or symptoms of disease)
90	(Able to carry on normal activity; minor sign of symptoms of disease)
100	(Normal; no complaints; no evidence of disease)

mMRC Grades

An assessment of Grade 0, 1 or 2 would mean that the participant is ineligible

Grade 0	(“I only get breathlessness with strenuous exercise”)
Grade 1	(“I get short of breath when hurrying on the level or walking up a slight hill”)
Grade 2	(“I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”)

Grade 3	(“I stop for breath after walking about 100 yards or after a few minutes on the level”
Grade 4	(“I am too breathless to leave the house" or "I am breathless when dressing”)

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section F – Treatment of Underlying Disease

Did the treatment of the participant's underlying disease change in the 2 weeks prior to eligibility being assessed? ☐ Yes ☐ No

Please note: if the treatment changed within one week prior to eligibility assessment, the participant would be ineligible for the trial

Section G – Opioid Medication

Is the participant receiving any opioid medications? ☐ Yes ☐ No

If yes, please complete the table below

Name of medication	Start date
	Day Month Year
	Day Month Year
	Day Month Year
	Day Month Year

Section H – Other Concomitant Medication

Is the participant receiving any of the following concomitant medications?
Please tick yes or no for each

	Yes	No
Potent CYP3A4 inhibitors (e.g. ketoconazole), cimetidine, HIV protease inhibitors, azole antifungals, erythromycin, or nefazodone	☐	☐
CYP3A4 inducers (e.g. carbamazepine, phenytoin or rifampicin)	☐	☐

Section I – Participant Questionnaire Booklet

Was the participant able to complete the whole baseline booklet? ☐ Yes ☐ No

If no, give reason

Did the participant require any help completing the booklet? ☐ Yes ☐ No

If yes, please specify
☐ Questions read out to participant
☐ Helped to complete answers
☐ Other, please provide further information

Completed by | Date Day Month Year | *Last Page* ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

BETTER-B

ISRCTN32236160

FORM 03

Page 1 of 2

Randomisation

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- **To be completed following obtaining written informed consent and confirmation of eligibility**
- **The information on page 1 of this form is required to randomise the participant; please ensure this section has been fully completed and that you have the form to hand when phoning to randomise the participant**

Section A – Trial Site Details

Trial site code C

Trial site name

Name of caller

Section B – Participant Details

Initials

Date of birth Day Month Year

Does the participant satisfy ALL of the eligibility criteria? ☐ Yes ☐ No

Has the participant provided written informed consent? ☐ Yes ☐ No

Both answers must be **YES** to proceed with the randomisation

Have all baseline assessments, including the Quality of Life booklet, been completed? ☐ Yes ☐ No → **All assessments must be completed prior to treatment start**

Section C – Stratification Factors

Is the participant's underlying disease cancer? ☐ Yes ☐ No

If the participant suffers from more than one disease (e.g. cancer and COPD/ILD or cancer and chronic heart failure), please tick yes only if cancer is considered to be the **primary** disease.

HADS score ☐ 0–14 ☐ 15 or above

(Score should be obtained from baseline participant booklet)

Is the participant currently receiving any opioid medication? ☐ Yes ☐ No

Once all the information on page 1 has been completed, please call the CTRU's office hours (9:00 to 17:00 Monday to Friday) randomisation service on 0113 343 8090 to randomise the participant.

Completed by Date Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date Initials	*Verified/Checked* Date Initials

BETTER-B

ISRCTN32236160

FORM 03

Page 2 of 2

Randomisation

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section D – Randomisation Result

This information will be provided by CTRU at time of randomisation

Participant ID: C [Trial site] / [Trial number]

Kit code number: [ ]

Date of randomisation: [Day Month Year]

Immediately after randomisation, please fax this form and the participant's consent form to CTRU on 0113 343 6774

All participants must commence trial treatment within 7 days of eligibility

Completed by [ ] Date [Day Month Year] *Last Page* ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

BETTER-B

ISRCTN32236160

FORM 04

Page 1 of 4

Day 7 Call

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed for all participants on day 7 of trial treatment (+/− 1 working day)

Section A – Call Details

Was contact made with the participant? ☐ Yes ☐ No

If yes, date of call: Day Month Year

If no, please give reason:

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Other, please specify

Date of last contact: Day Month Year

Section B – BETTER-B Trial Drug Compliance

Date trial treatment started
(I.e. the date the first capsule was taken): Day Month Year

Has the participant taken 1 capsule of trial drug every day since treatment started? ☐ Yes ☐ No

If no, how many capsules have been **omitted?** ☐

Why have capsules been omitted?
Tick all applicable and give further details

	Details
☐ Participant choice	
☐ Clinician choice	
☐ Participant error	
☐ Other reason	

Is the participant continuing on treatment? ☐ Yes ☐ No

If no, please provide reason:

- ☐ Death
- ☐ Participant choice → Please complete **F12 Participant Withdrawal Request**
- ☐ Clinical choice → Please complete **F12 Participant Withdrawal Request**
  (e.g. toxicity)

Date of last dose: Day Month Year

Have unused capsules been collected? ☐ Yes ☐ No

Completed by | Date: Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

Version 0.10 29/06/2016

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section C – Opioid Medication

Has the participant started / changed dose / stopped any opioid medications since the baseline assessment? ☐ Yes ☐ No

If yes, please complete the table below

Name of medication	Started	Dose increased	Dose decreased	Stopped
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Section D – Other Concomitant Medication

Has the participant received any of the following concomitant medications since the baseline assessment?
Please tick yes or no for each

	Yes	No
Potent CYP3A4 inhibitors (e.g. ketoconazole), cimetidine, HIV protease inhibitors, azole antifungals, erythromycin, or nefazodone	☐	☐
CYP3A4 inducers (e.g. carbamazepine, phenytoin or rifampicin)	☐	☐

Completed by | Date Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section E – Adverse Events *(Since starting trial treatment)*

Please enter the worst CTCAE grades experienced by the participant **since they began trial treatment**.
Please refer to CTCAE v4.0 for guidance (see reverse of page 3).

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Increased appetite	☐	☐	☐
Weight gain	☐	☐	☐
Somnolence	☐	☐	☐
Sedation	☐	☐	☐
Lethargy	☐	☐	☐
Diarrhoea	☐	☐	☐
Nausea	☐	☐	☐
Vomiting	☐	☐	☐
Symptomatic orthostatic hypotension *(E.g. dizziness)*	☐	☐	☐

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Fatigue	☐	☐	☐
Insomnia	☐	☐	☐
Confusion	☐	☐	☐
Anxiety	☐	☐	☐
Other clinically significant events (Please specify)			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

**The nurse should seek clinical advice/input if any event is assessed as Grade 2 or above*

If any event meets the criteria of an SAE/SSAR/SUSAR please fax a report to the CTRU within 24 hours using F09/F10

Section F – Ongoing Participant Monitoring

All participants should be reviewed according to the Ongoing Participant Monitoring guidance (see reverse of page 4), including review of any con meds, as part of ongoing risk management

As a result of the Ongoing Participant Monitoring and AE assessment (Section E), have any issues been raised which required clinical review? ☐ Yes ☐ No

If yes, please specify

Completed by		Date	Day Month Year	*Form continues on next page ►►*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

CTCAE Grade Reference List

Side effect	CTCAE grade 1	2	3	4	5
Increased appetite	Unwanted increase in appetite without change in eating habits	Unwanted increase in appetite with increase in oral intake but no significant weight increase	Unwanted increase in appetite with increase in oral intake and significant weight increase	–	–
Weight gain	5–<10% from baseline	10–<20% from baseline	≥20% from baseline	–	–
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Sedation *(Decreased level of consciousness)*	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	–	–	–
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Symptomatic orthostatic hypotension *(E.g. dizziness) (hypotension)*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section G – NRS Assessment

Was the NRS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Please ask the participant...

How bad has your breathlessness felt **on average** over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not breathless at all										The worst possible breathlessness

Answer ☐

How bad has your breathlessness felt **at its worst** over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not breathless at all										The worst possible breathlessness

Answer ☐

If no, please provide reason

Completed by Date Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Ongoing Participant Monitoring Guidance

Ongoing Participant Monitoring consists of a nurse assessment of:

1. Concomitant medications
2. Tolerability of the trial drug

1. Concomitant medications

The following concomitant medications are prohibited during the duration of the trial:

- MAO inhibitors
- Linezolid
- Other anti-depressant medication *(e.g. L-trytophan, SSRIs, venlafaxine, lithium)*
- St John's wort

Either trial treatment or the medication should be stopped – please refer to the mirtazapine SPC and seek clinical input

Caution is advised and clinical input should be sought (particularly in relation to dose escalation) if the participant is taking any of the following:

- Inhibitors or inducers of CYP3A4
- Benzodiazepines or other sedatives *(e.g. antipsychotics, antihistamine H1 antagonists, opioids)*
- Serotonergic active substances *(e.g. triptans, tramadol)*
- Alcohol
- Warfarin

2. Tolerability of the trial drug since the last trial visit/call

If there are concerns for the participant's tolerability based on any Grade 2 or above noted in the CTCAE assessment in Section E and/or specific risks associated with mirtazapine (see guidance below), clinical advice/input should be sought by the nurse.

Further close-monitoring of the participant should be considered.

1. Indications of depression, unusual feelings or suicidal thoughts

2. Indications of epilepsy or organic brain syndrome
(Symptoms include tingling sensation in arms/legs, unusual taste/smell, unusual bod ily behaviour.)

3. Indications of liver problems
(Symptoms include jaundice, abdominal pain/swelling, swelling of arms/legs, itchy skin, change in colour of urine or stools, nausea/vomiting.)
Please note, where jaundice occurs, the mirtazapine SPC recommends discontinuation of treatment.

4. Indications of kidney problems
(Symptoms include swollen ankles/feet/hands, blood in urine.)

5. Indications of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis
(Symptoms includefever, sore throat, stomatitis, other signs of infection.)
Please note, where signs do occur, the mirtazapine SPC recommends discontinuation of treatment and blood counts to be taken.

6. Indications of hyponatraemia
(Symptoms include nausea/vomiting, headache, confusion, loss of energy/fatigue, restlessness/irritability, muscle weakness/spasms/cramps, seizures.)

7. Indications of akathisia or psychomotor restlessness
This is particularly important for the BETTER-B Day 14 assessment visit.
(Symptoms include unpleasant or distressing restlessness, need to move often accompanied by an inability to stand/sit still.)
Please note, where signs do occur, the mirtazapine SPC recommends that dose-escalation should be carefully considered as increasing the dose may be detrimental.

BETTER-B

ISRCTN32236160

FORM 05

Day 14 Visit

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed for all participants on day 14 of trial treatment (+/− 1 working day)

Section A – Visit Details

Did the participant attend the visit? ☐ Yes ☐ No

If yes, date of visit: Day Month Year

If no, please give reason:

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Other, please specify

Date of last contact: Day Month Year

Section B – BETTER-B Trial Drug Compliance

Has the participant taken 1 capsule of trial drug every day since the Day 7 assessment call? ☐ Yes ☐ No

If no, how many capsules have been **omitted?** ☐

Why have capsules been omitted?
Tick all applicable and give further details

	Details
☐ Participant choice	
☐ Clinician choice	
☐ Participant error	
☐ Other reason	

Is the participant continuing on treatment? ☐ Yes ☐ No

If no, please provide reason:

- ☐ Death
- ☐ Participant choice → Please complete **F12 Participant Withdrawal Request**
- ☐ Clinical choice → Please complete **F12 Participant Withdrawal Request** *(e.g. toxicity)*

Date of last dose: Day Month Year

Have unused capsules been collected? ☐ Yes ☐ No

Completed by | Date: Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section C – Opioid Medication

Has the participant started / changed dose / stopped any opioid medications since the Day 7 call? ☐ Yes ☐ No

If yes, please complete the table below

Name of medication	Started	Dose increased	Dose decreased	Stopped
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Section D – Other Concomitant Medication

Has the participant received any of the following concomitant medications since the Day 7 call?
Please tick yes or no for each

	Yes	No
Potent CYP3A4 inhibitors (e.g. ketoconazole), cimetidine, HIV protease inhibitors, azole antifungals, erythromycin, or nefazodone	☐	☐
CYP3A4 inducers (e.g. carbamazepine, phenytoin or rifampicin)	☐	☐

Completed by | Date Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section E – Adverse Events *(Since the Day 7 call)*

Please enter the worst CTCAE grades experienced by the participant **since the Day 7 call**.
Please refer to CTCAE v4.0 for guidance (see reverse of page 3).

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Increased appetite	☐	☐	☐
Weight gain	☐	☐	☐
Somnolence	☐	☐	☐
Sedation	☐	☐	☐
Lethargy	☐	☐	☐
Diarrhoea	☐	☐	☐
Nausea	☐	☐	☐
Vomiting	☐	☐	☐
Symptomatic orthostatic hypotension *(E.g. dizziness)*	☐	☐	☐

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Fatigue	☐	☐	☐
Insomnia	☐	☐	☐
Confusion	☐	☐	☐
Anxiety	☐	☐	☐
Other clinically significant events (Please specify)			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

**The nurse should seek clinical advice/input if any event is assessed as Grade 2 or above*

If any event meets the criteria of an SAE/SSAR/SUSAR please fax a report to the CTRU within 24 hours using F09/F10

Section F – Ongoing Participant Monitoring

All participants should be reviewed according to the Ongoing Participant Monitoring guidance (see reverse of page 4), including review of any con meds, as part of ongoing risk management. Vital signs (blood pressure and blood oxygen levels) should be performed at this visit.

As a result of the Ongoing Participant Monitoring and AE assessment (Section E), have any issues been raised which required clinical review? ☐ Yes ☐ No

If yes, please specify

Completed by _____ Date Day Month Year *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

CTCAE Grade Reference List

Side effect	CTCAE grade 1	2	3	4	5
Increased appetite	Unwanted increase in appetite without change in eating habits	Unwanted increase in appetite with increase in oral intake but no significant weight increase	Unwanted increase in appetite with increase in oral intake and significant weight increase	–	–
Weight gain	5–<10% from baseline	10–<20% from baseline	≥20% from baseline	–	–
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Sedation *(Decreased level of consciousness)*	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	–	–	–
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Symptomatic orthostatic hypotension *(E.g. dizziness) (hypotension)*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section G – Clinical Assessments

AKPS Assessment

Was the AKPS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Score *(See reverse for definitions)*

If no, please provide the reason

NRS Assessment

Was the NRS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Please ask the participant...

How bad has your breathlessness felt **on average** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

How bad has your breathlessness felt **at its worst** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

If no, please provide reason

Completed by Date Day Month Year

Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Ongoing Participant Monitoring Guidance

Ongoing Participant Monitoring consists of a nurse assessment of:

1. Concomitant medications
2. Tolerability of the trial drug

1. Concomitant medications

The following concomitant medications are prohibited during the duration of the trial:

- MAO inhibitors
- Linezolid
- Other anti-depressant medication *(e.g. L-trytophan, SSRIs, venlafaxine, lithium)*
- St John's wort

Either trial treatment or the medication should be stopped – please refer to the mirtazapine SPC and seek clinical input

Caution is advised and clinical input should be sought (particularly in relation to dose escalation) if the participant is taking any of the following:

- Inhibitors or inducers of CYP3A4
- Benzodiazepines or other sedatives *(e.g. antipsychotics, antihistamine H1 antagonists, opioids)*
- Serotonergic active substances *(e.g. triptans, tramadol)*
- Alcohol
- Warfarin

2. Tolerability of the trial drug since the last trial visit/call

If there are concerns for the participant's tolerability based on any Grade 2 or above noted in the CTCAE assessment in Section E and/or specific risks associated with mirtazapine (see guidance below), clinical advice/input should be sought by the nurse.

Further close-monitoring of the participant should be considered.

1. **Indications of depression, unusual feelings or suicidal thoughts**
2. **Indications of epilepsy or organic brain syndrome**
   (Symptoms include tingling sensation in arms/legs, unusual taste/smell, unusual bod ily behaviour.)
3. **Indications of liver problems**
   (Symptoms include jaundice, abdominal pain/swelling, swelling of arms/legs, itchy skin, change in colour of urine or stools, nausea/vomiting.)
   Please note, where jaundice occurs, the mirtazapine SPC recommends discontinuation of treatment.
4. **Indications of kidney problems**
   (Symptoms include swollen ankles/feet/hands, blood in urine.)
5. **Indications of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis**
   (Symptoms includefever, sore throat, stomatitis, other signs of infection.)
   Please note, where signs do occur, the mirtazapine SPC recommends discontinuation of treatment and blood counts to be taken.
6. **Indications of hyponatraemia**
   (Symptoms include nausea/vomiting, headache, confusion, loss of energy/fatigue, restlessness/irritability, muscle weakness/spasms/cramps, seizures.)
7. **Indications of akathisia or psychomotor restlessness**
   This is particularly important for the BETTER-B Day 14 assessment visit.
   (Symptoms include unpleasant or distressing restlessness, need to move often accompanied by an inability to stand/sit still.)
   Please note, where signs do occur, the mirtazapine SPC recommends that dose-escalation should be carefully considered as increasing the dose may be detrimental.

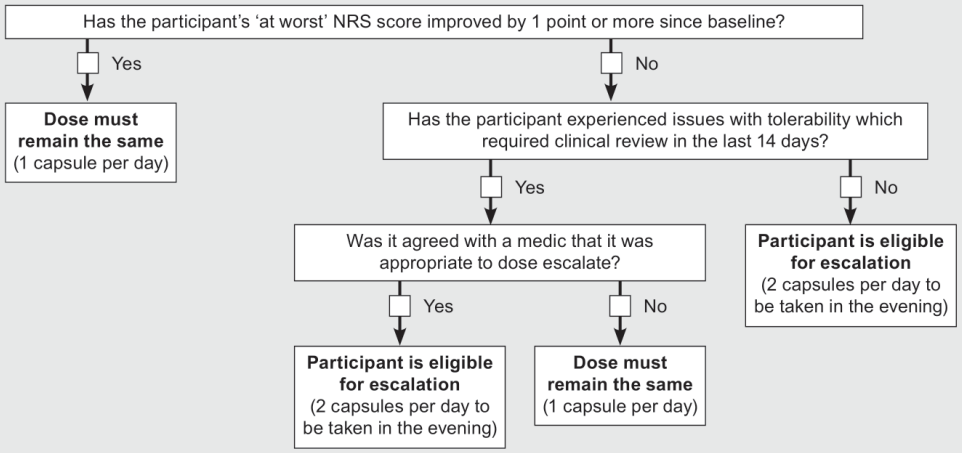
AKPS Score

0	(Dead)
10	(Comatose or barely rousable)
20	(Totally bedfast and requiring extensive nursing care by professionals and/or family)
30	(Almost completely bedfast)
40	(In bed more than 50% of the time)
50	(Considerable assistance and frequent medical care required)
60	(Able to care for most needs; but requires occasional assistance)
70	(Cares for self; unable to carry on normal activity or to do active work)
80	(Normal activity with effort; some signs or symptoms of disease)
90	(Able to carry on normal activity; minor sign of symptoms of disease)
100	(Normal; no complaints; no evidence of disease)

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section H – Dose Escalation

Please refer to the protocol for guidance on dose escalation at day 14



If the participant was eligible for dose escalation, did they increase their daily dose to 2 capsules from this point on? ☐ Yes ☐ No

If no, please provide the reason

Section I – Participant Questionnaire Booklet

Was the participant given the Day 14 Participant Booklet? ☐ Yes ☐ No

If no, give reason

Was the participant able to complete the whole booklet? ☐ Yes ☐ No

If no, give reason

Did the participant require any help completing the booklet? ☐ Yes ☐ No

If yes, please specify
- ☐ Questions read out to participant
- ☐ Helped to complete answers
- ☐ Other, please provide further information

Completed by | Date Day Month Year | *Last Page* ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 06

Day 21 Call

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed for all participants on day 21 of trial treatment (+/− 1 working day)

Section A – Call Details

Was contact made with the participant? ☐ Yes ☐ No

If yes, date of visit: Day Month Year

If no, please give reason:

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Other, please specify

Date of last contact: Day Month Year

Section B – BETTER-B Trial Drug Compliance

Non-dose escalated participants: Has the participant taken 1 capsule of trial drug every day since the Day 14 visit? ☐ Yes ☐ No

Dose escalated participants: Has the participant taken 2 capsules of trial drug every day since the Day 14 visit? ☐ Yes ☐ No

If no, how many capsules have been **omitted?** ☐

Why have capsules been omitted?
Tick all applicable and give further details

	Details
☐ Participant choice	
☐ Clinician choice	
☐ Participant error	
☐ Dose reduction	Date: Day Month Year — Reason:
☐ Other reason	

Is the participant continuing on treatment? ☐ Yes ☐ No

If no, please provide reason:

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Clinical withdrawal *(e.g. toxicity)* → Please complete **F12 Participant Withdrawal Request**

Date of last dose: Day Month Year

Have unused capsules been collected? ☐ Yes ☐ No

Completed by: Date: Day Month Year *Form continues on next page* ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised		Verified/Checked	
	Date	Initials	Date	Initials

Version 0.10 09/05/2016

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section C – Opioid Medication

Has the participant started / changed dose / stopped any opioid medications since the Day 14 visit? ☐ Yes ☐ No

If yes, please complete the table below

Name of medication	Started	Dose increased	Dose decreased	Stopped
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Section D – Other Concomitant Medication

Has the participant received any of the following concomitant medications since the Day 14 visit?
Please tick yes or no for each

	Yes	No
Potent CYP3A4 inhibitors (e.g. ketoconazole), cimetidine, HIV protease inhibitors, azole antifungals, erythromycin, or nefazodone	☐	☐
CYP3A4 inducers (e.g. carbamazepine, phenytoin or rifampicin)	☐	☐

Completed by | Date Day Month Year | *Form continues on next page ►►*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section E – Adverse Events *(Since the Day 14 visit)*

Please enter the worst CTCAE grades experienced by the participant **since the Day 14 visit**.
Please refer to CTCAE v4.0 for guidance (see reverse of page 3).

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Increased appetite	☐	☐	☐
Weight gain	☐	☐	☐
Somnolence	☐	☐	☐
Sedation	☐	☐	☐
Lethargy	☐	☐	☐
Diarrhoea	☐	☐	☐
Nausea	☐	☐	☐
Vomiting	☐	☐	☐
Symptomatic orthostatic hypotension *(E.g. dizziness)*	☐	☐	☐

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Fatigue	☐	☐	☐
Insomnia	☐	☐	☐
Confusion	☐	☐	☐
Anxiety	☐	☐	☐
Other clinically significant events (Please specify)			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

**The nurse should seek clinical advice/input if any event is assessed as Grade 2 or above*

If any event meets the criteria of an SAE/SSAR/SUSAR please fax a report to the CTRU within 24 hours using F09/F10

Section F – Ongoing Participant Monitoring

All participants should be reviewed according to the Ongoing Participant Monitoring guidance (see reverse of page 4), including review of any con meds, as part of ongoing risk management

As a result of the Ongoing Participant Monitoring and AE assessment (Section E), have any issues been raised which required clinical review? ☐ Yes ☐ No

If yes, please specify

Completed by | Date Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

CTCAE Grade Reference List

Side effect	CTCAE grade 1	2	3	4	5
Increased appetite	Unwanted increase in appetite without change in eating habits	Unwanted increase in appetite with increase in oral intake but no significant weight increase	Unwanted increase in appetite with increase in oral intake and significant weight increase	–	–
Weight gain	5–<10% from baseline	10–<20% from baseline	≥20% from baseline	–	–
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Sedation *(Decreased level of consciousness)*	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	–	–	–
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Symptomatic orthostatic hypotension *(E.g. dizziness) (hypotension)*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section G – NRS Assessment

Was the NRS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Please ask the participant...

How bad has your breathlessness felt **on average** over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not breathless at all										The worst possible breathlessness

Answer ☐

How bad has your breathlessness felt **at its worst** over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not breathless at all										The worst possible breathlessness

Answer ☐

If no, please provide reason ☐

Completed by ☐ Date Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Ongoing Participant Monitoring Guidance

Ongoing Participant Monitoring consists of a nurse assessment of:

1. Concomitant medications
2. Tolerability of the trial drug

1. Concomitant medications

The following concomitant medications are prohibited during the duration of the trial:

- MAO inhibitors
- Linezolid
- Other anti-depressant medication *(e.g. L-trytophan, SSRIs, venlafaxine, lithium)*
- St John's wort

Either trial treatment or the medication should be stopped – please refer to the mirtazapine SPC and seek clinical input

Caution is advised and clinical input should be sought (particularly in relation to dose escalation) if the participant is taking any of the following:

- Inhibitors or inducers of CYP3A4
- Benzodiazepines or other sedatives *(e.g. antipsychotics, antihistamine H1 antagonists, opioids)*
- Serotonergic active substances *(e.g. triptans, tramadol)*
- Alcohol
- Warfarin

2. Tolerability of the trial drug since the last trial visit/call

If there are concerns for the participant's tolerability based on any Grade 2 or above noted in the CTCAE assessment in Section E and/or specific risks associated with mirtazapine (see guidance below), clinical advice/input should be sought by the nurse.

Further close-monitoring of the participant should be considered.

1. Indications of depression, unusual feelings or suicidal thoughts

2. Indications of epilepsy or organic brain syndrome
(Symptoms include tingling sensation in arms/legs, unusual taste/smell, unusual bod ily behaviour.)

3. Indications of liver problems
(Symptoms include jaundice, abdominal pain/swelling, swelling of arms/legs, itchy skin, change in colour of urine or stools, nausea/vomiting.)
Please note, where jaundice occurs, the mirtazapine SPC recommends discontinuation of treatment.

4. Indications of kidney problems
(Symptoms include swollen ankles/feet/hands, blood in urine.)

5. Indications of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis
(Symptoms includefever, sore throat, stomatitis, other signs of infection.)
Please note, where signs do occur, the mirtazapine SPC recommends discontinuation of treatment and blood counts to be taken.

6. Indications of hyponatraemia
(Symptoms include nausea/vomiting, headache, confusion, loss of energy/fatigue, restlessness/irritability, muscle weakness/spasms/cramps, seizures.)

7. Indications of akathisia or psychomotor restlessness
This is particularly important for the BETTER-B Day 14 assessment visit.
(Symptoms include unpleasant or distressing restlessness, need to move often accompanied by an inability to stand/sit still.)
Please note, where signs do occur, the mirtazapine SPC recommends that dose-escalation should be carefully considered as increasing the dose may be detrimental.

BETTER-B

ISRCTN32236160

FORM 07

Day 28 Visit

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed for all participants on day 28 of trial treatment (− 1 working day)

Section A – Visit Details

Did the participant attend the visit? ☐ Yes ☐ No

If yes, date of visit: Day Month Year

If no, please give reason

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Other, please specify

Date of last contact: Day Month Year

Section B – BETTER-B Trial Drug Compliance

Non-dose escalated participants: Has the participant taken 1 capsule of trial drug every day since the Day 21 call? ☐ Yes ☐ No

Dose escalated participants: Has the participant taken 2 capsules of trial drug every day since the Day 21 call? ☐ Yes ☐ No

If no, how many capsules have been **omitted?** ☐

Why have capsules been omitted?
Tick all applicable and give further details

	Details
☐ Participant choice	
☐ Clinician choice	
☐ Participant error	
☐ Dose reduction	Date: Day Month Year — Reason:
☐ Other reason	

Completed by | Date: Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date / Initials	*Verified/Checked* Date / Initials

Version 0.12 30/06/2016

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section C – Trial Drug Reconcilliation

To be completed after the last trial treatment dose is taken

Date of last trial treatment dose: Day Month Year

Once the participant has completed trial treatment, any unused trial drug capsules must be collected and returned to pharmacy for reconciliation.

Have all unused capsules been collected? ☐ Yes ☐ No ☐ N/A – No unused capsules
(Applies to dose-escalated participants only)

If no, please give reason
☐ The participant has lost the unused capsules
☐ Other, please specify

Section D – Opioid Medication

Has the participant started / changed dose / stopped any opioid medications since the Day 21 call? ☐ Yes ☐ No

If yes, please complete the table below

Name of medication	Started	Dose increased	Dose decreased	Stopped
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

Section E – Other Concomitant Medication

Has the participant received any of the following concomitant medications since the Day 21 call?
Please tick yes or no for each

	Yes	No
Potent CYP3A4 inhibitors (e.g. ketoconazole), cimetidine, HIV protease inhibitors, azole antifungals, erythromycin, or nefazodone	☐	☐
CYP3A4 inducers (e.g. carbamazepine, phenytoin or rifampicin)	☐	☐

Completed by | Date: Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section F – Adverse Events *(Since the Day 21 call)*

Please enter the worst CTCAE grades experienced by the participant **since the Day 21 call**.
Please refer to CTCAE v4.0 for guidance (see reverse of page 3).

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Increased appetite	☐	☐	☐
Weight gain	☐	☐	☐
Somnolence	☐	☐	☐
Sedation	☐	☐	☐
Lethargy	☐	☐	☐
Diarrhoea	☐	☐	☐
Nausea	☐	☐	☐
Vomiting	☐	☐	☐
Symptomatic orthostatic hypotension *(E.g. dizziness)*	☐	☐	☐

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Fatigue	☐	☐	☐
Insomnia	☐	☐	☐
Confusion	☐	☐	☐
Anxiety	☐	☐	☐
Other clinically significant events (Please specify)			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

**The nurse should seek clinical advice/input if any event is assessed as Grade 2 or above*

If any event meets the criteria of an SAE/SSAR/SUSAR please fax a report to the CTRU within 24 hours using F09/F10

Section G – Ongoing Participant Monitoring

All participants should be reviewed according to the Ongoing Participant Monitoring guidance (see reverse of page 4), including review of any con meds, as part of ongoing risk management. Vital signs (blood pressure and blood oxygen levels) should be performed at this visit.

As a result of the Ongoing Participant Monitoring and AE assessment (Section F), have any issues been raised which required clinical review? ☐ Yes ☐ No

If yes, please specify

Completed by _____ Date Day Month Year

Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

CTCAE Grade Reference List

Side effect	CTCAE grade 1	2	3	4	5
Increased appetite	Unwanted increase in appetite without change in eating habits	Unwanted increase in appetite with increase in oral intake but no significant weight increase	Unwanted increase in appetite with increase in oral intake and significant weight increase	–	–
Weight gain	5–<10% from baseline	10–<20% from baseline	≥20% from baseline	–	–
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Sedation *(Decreased level of consciousness)*	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	–	–	–
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Symptomatic orthostatic hypotension *(E.g. dizziness) (hypotension)*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section H – Clinical Assessments

AKPS

Was the AKPS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Score *(See reverse for definitions)*

If no, please provide the reason

NRS

Was the NRS assessment performed? ☐ Yes ☐ No

If yes, date of test Day Month Year

Please ask the participant...

How bad has your breathlessness felt **on average** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

How bad has your breathlessness felt **at its worst** over the past 24 hours?

0 1 2 3 4 5 6 7 8 9 10

Not breathless at all — The worst possible breathlessness

Answer

If no, please provide reason

SPPB

Was the SPPB (**Form 60**) performed? ☐ Yes ☐ No

If no, please provide the reason

Completed by | Date Day Month Year | *Form continues on next page ▶▶*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

Ongoing Participant Monitoring Guidance

Ongoing Participant Monitoring consists of a nurse assessment of:

1. Concomitant medications
2. Tolerability of the trial drug

1. Concomitant medications

The following concomitant medications are prohibited during the duration of the trial:

- MAO inhibitors
- Linezolid
- Other anti-depressant medication *(e.g. L-trytophan, SSRIs, venlafaxine, lithium)*
- St John's wort

Either trial treatment or the medication should be stopped – please refer to the mirtazapine SPC and seek clinical input

Caution is advised and clinical input should be sought (particularly in relation to dose escalation) if the participant is taking any of the following:

- Inhibitors or inducers of CYP3A4
- Benzodiazepines or other sedatives *(e.g. antipsychotics, antihistamine H1 antagonists, opioids)*
- Serotonergic active substances *(e.g. triptans, tramadol)*
- Alcohol
- Warfarin

2. Tolerability of the trial drug since the last trial visit/call

If there are concerns for the participant's tolerability based on any Grade 2 or above noted in the CTCAE assessment in Section F and/or specific risks associated with mirtazapine (see guidance below), clinical advice/input should be sought by the nurse.

Further close-monitoring of the participant should be considered.

1. **Indications of depression, unusual feelings or suicidal thoughts**
2. **Indications of epilepsy or organic brain syndrome**
   (Symptoms include tingling sensation in arms/legs, unusual taste/smell, unusual bod ily behaviour.)
3. **Indications of liver problems**
   (Symptoms include jaundice, abdominal pain/swelling, swelling of arms/legs, itchy skin, change in colour of urine or stools, nausea/vomiting.)
   Please note, where jaundice occurs, the mirtazapine SPC recommends discontinuation of treatment.
4. **Indications of kidney problems**
   (Symptoms include swollen ankles/feet/hands, blood in urine.)
5. **Indications of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis**
   (Symptoms includefever, sore throat, stomatitis, other signs of infection.)
   Please note, where signs do occur, the mirtazapine SPC recommends discontinuation of treatment and blood counts to be taken.
6. **Indications of hyponatraemia**
   (Symptoms include nausea/vomiting, headache, confusion, loss of energy/fatigue, restlessness/irritability, muscle weakness/spasms/cramps, seizures.)
7. **Indications of akathisia or psychomotor restlessness**
   This is particularly important for the BETTER-B Day 14 assessment visit.
   (Symptoms include unpleasant or distressing restlessness, need to move often accompanied by an inability to stand/sit still.)
   Please note, where signs do occur, the mirtazapine SPC recommends that dose-escalation should be carefully considered as increasing the dose may be detrimental.

AKPS Score

0	(Dead)
10	(Comatose or barely rousable)
20	(Totally bedfast and requiring extensive nursing care by professionals and/or family)
30	(Almost completely bedfast)
40	(In bed more than 50% of the time)
50	(Considerable assistance and frequent medical care required)
60	(Able to care for most needs; but requires occasional assistance)
70	(Cares for self; unable to carry on normal activity or to do active work)
80	(Normal activity with effort; some signs or symptoms of disease)
90	(Able to carry on normal activity; minor sign of symptoms of disease)
100	(Normal; no complaints; no evidence of disease)

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section H – Clinical Assessments *(Continued)*

Pregnancy Test

Was a pregnancy test performed? ☐ Yes ☐ No ☐ N/A – The participant is male or is not a female of childbearing potential

If yes, date of test: Day Month Year

Result: ☐ Positive → Please complete **F14 Notification of Pregnancy**
☐ Negative

If no, please provide the reason:

Section I – Participant Questionnaire Booklet

Was the participant given the Day 28 Participant Booklet? ☐ Yes ☐ No

If no, give reason:

Was the participant able to complete the whole booklet? ☐ Yes ☐ No

If no, give reason:

Did the participant require any help completing the booklet? ☐ Yes ☐ No

If yes, please specify:
☐ Questions read out to participant
☐ Helped to complete answers
☐ Other, please provide further information

Section J – Further Dose Escalation

- **Please note, this section is for information only**
- **No further trial treatment is to be provided beyond Day 28**

Would the participant be eligible for further dose escalation? ☐ Yes ☐ No

If yes, please provide the reason:

If no, please provide the reason:
☐ Improvement in NRS score
☐ Participant is not tolerating treatment
☐ Other, please provide further information

Completed by: Date: Day Month Year

Form continues on next page ▶▶

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed by a member of the team involved in the participant's clinical care during the trial period

Section K – Blinding Assessment

Role of person completing this section

Please ensure the following questions regarding treatment blinding are not discussed with or revealed to the participant

Has this participant been unblinded?

- ☐ Yes → Is the CTRU aware?
  - ☐ Yes
  - ☐ No → **The CTRU must be notified within 24 hours**
- ☐ No → Please continue completing the rest of this section

Which treatment do you think this participant has received?

- ☐ Mirtazapine
- ☐ Placebo

→ What is the reason for your choice?

- ☐ Treatment appeared to have no benefit
- ☐ Treatment appeared to benefit participant
- ☐ The participant had adverse event(s), please specify
- ☐ Appearance of capsules
- ☐ Other reason, please specify

- ☐ No idea

Completed by | Date Day Month Year | Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 08

Page 1 of 2

End of Treatment Follow-up Call

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed 7 days after last dose of trial drug taken (+1 working day)

Section A – Call Details

Was contact made with the participant? ☐ Yes ☐ No

If yes, date of call: Day Month Year

If no, please give reason:

- ☐ Death → Please complete **F11 Notification of Death**
- ☐ Participant withdrawal → Please complete **F12 Participant Withdrawal Request**
- ☐ Other, please specify

Date of last contact: Day Month Year

Completed by | Date: Day Month Year | *Form continues on next page ►►*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Version 0.10 30/06/2016

CTCAE Grade Reference List

Side effect	CTCAE grade 1	2	3	4	5
Increased appetite	Unwanted increase in appetite without change in eating habits	Unwanted increase in appetite with increase in oral intake but no significant weight increase	Unwanted increase in appetite with increase in oral intake and significant weight increase	–	–
Weight gain	5–<10% from baseline	10–<20% from baseline	≥20% from baseline	–	–
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Sedation *(Decreased level of consciousness)*	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	–	–	–
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	–	–
Vomiting	1–2 episodes (separated by 5 minutes) in 24 hrs	3–5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Symptomatic orthostatic hypotension *(E.g. dizziness) (hypotension)*	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	–	–
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death

BETTER-B

ISRCTN32236160

FORM 08

Page 2 of 2

End of Treatment Follow-up Call

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Section B – Adverse Events *(Since the Day 28 visit)*

Please enter the worst CTCAE grades experienced by the participant **since the Day 28 visit**.
Please refer to CTCAE v4.0 for guidance (see reverse of page 1).

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Increased appetite	☐	☐	☐
Weight gain	☐	☐	☐
Somnolence	☐	☐	☐
Sedation	☐	☐	☐
Lethargy	☐	☐	☐
Diarrhoea	☐	☐	☐
Nausea	☐	☐	☐
Vomiting	☐	☐	☐
Symptomatic orthostatic hypotension *(E.g. dizziness)*	☐	☐	☐

Event	CTCAE grade*	If experienced: Does this event meet the criteria of an SAE/SSAR/SUSAR? Yes	No
Fatigue	☐	☐	☐
Insomnia	☐	☐	☐
Confusion	☐	☐	☐
Anxiety	☐	☐	☐
Other clinically significant events (Please specify)			
	☐	☐	☐
	☐	☐	☐
	☐	☐	☐

**The nurse should seek clinical advice/input if any event is assessed as Grade 2 or above*

If any event meets the criteria of an SAE/SSAR/SUSAR please fax a report to the CTRU within 24 hours using F09/F10

Section C – Ongoing Participant Monitoring

All participants should be reviewed according to the Ongoing Participant Monitoring guidance (see reverse), including review of any con meds, as part of ongoing risk management (see reverse of page 2)

As a result of the Ongoing Participant Monitoring and AE assessment (Section B), have any issues been raised which required clinical review? ☐ Yes ☐ No

If yes, please specify

Completed by | Date Day Month Year | Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Ongoing Participant Monitoring Guidance

Ongoing Participant Monitoring consists of a nurse assessment of:

1. Concomitant medications
2. Tolerability of the trial drug

1. Concomitant medications

The following concomitant medications are prohibited during the duration of the trial:

- MAO inhibitors
- Linezolid
- Other anti-depressant medication *(e.g. L-trytophan, SSRIs, venlafaxine, lithium)*
- St John's wort

Either trial treatment or the medication should be stopped – please refer to the mirtazapine SPC and seek clinical input

Caution is advised and clinical input should be sought (particularly in relation to dose escalation) if the participant is taking any of the following:

- Inhibitors or inducers of CYP3A4
- Benzodiazepines or other sedatives *(e.g. antipsychotics, antihistamine H1 antagonists, opioids)*
- Serotonergic active substances *(e.g. triptans, tramadol)*
- Alcohol
- Warfarin

2. Tolerability of the trial drug since the last trial visit/call

If there are concerns for the participant's tolerability based on any Grade 2 or above noted in the CTCAE assessment in Section B and/or specific risks associated with mirtazapine (see guidance below), clinical advice/input should be sought by the nurse.

Further close-monitoring of the participant should be considered.

1. Indications of depression, unusual feelings or suicidal thoughts

2. Indications of epilepsy or organic brain syndrome
(Symptoms include tingling sensation in arms/legs, unusual taste/smell, unusual bod ily behaviour.)

3. Indications of liver problems
(Symptoms include jaundice, abdominal pain/swelling, swelling of arms/legs, itchy skin, change in colour of urine or stools, nausea/vomiting.)
Please note, where jaundice occurs, the mirtazapine SPC recommends discontinuation of treatment.

4. Indications of kidney problems
(Symptoms include swollen ankles/feet/hands, blood in urine.)

5. Indications of bone marrow depression, usually presenting as granulocytopenia or agranulocytosis
(Symptoms includefever, sore throat, stomatitis, other signs of infection.)
Please note, where signs do occur, the mirtazapine SPC recommends discontinuation of treatment and blood counts to be taken.

6. Indications of hyponatraemia
(Symptoms include nausea/vomiting, headache, confusion, loss of energy/fatigue, restlessness/irritability, muscle weakness/spasms/cramps, seizures.)

7. Indications of akathisia or psychomotor restlessness
This is particularly important for the BETTER-B Day 14 assessment visit.
(Symptoms include unpleasant or distressing restlessness, need to move often accompanied by an inability to stand/sit still.)
Please note, where signs do occur, the mirtazapine SPC recommends that dose-escalation should be carefully considered as increasing the dose may be detrimental.

BETTER-B

ISRCTN32236160

FORM 09

Page 1 of 2

Serious Adverse Event (SAE) Report

Report Type: ☐ Initial ☐ Follow-up	Participant Initials	Date of Birth (Day Month Year)	Participant ID	Centre No	Trial No

- **Complete this form for SAEs occurring within the BETTER-B Feasibility trial from randomisation up until 7 days after the last dose of trial treatment and email immediately to the CTRU**
- **For SSARS/SUSARs complete F10 and email immediately to the CTRU**

a) SAE/Participant Information

a1) **Gender** ☐ Male ☐ Female

a2) **Date** of onset of first sign/symptom of the event (Day Month Year)

a3) **Date** event became serious (Day Month Year)

a4) **Date** trial team first aware of AE being serious (Day Month Year)

a5) **Country** where SAE occurred

a6) **Main diagnosis/symptom** — CTCAE grade (v4.0)

a7) **Associated symptoms** that caused main event to be serious *(if applicable)* — CTCAE grade (v4.0) ×3

a8) **Case description** of the SAE *(inc. signs/symptoms and any other relevant information)*

a9) **Seriousness criteria** *(Tick all that apply)*

☐ Participant died ☐ Life threatening ☐ Required/prolonged hospitalisation ☐ Persistent or significant disability/incapacity
☐ Congenital anomaly/birth defect ☐ Other important medical event ☐ Jeopardised participant/required intervention to prevent one of the above

a10) **Outcome** *(At the time of this report)*

☐ Recovered → Date of recovery (Day Month Year)
☐ Recovered with sequelae → Date of recovery (Day Month Year)
☐ Condition improving
☐ Condition still present & unchanged
☐ Condition deteriorated
☐ Ongoing at time of death
☐ Death *(Only applicable if participant died due to SAE)* → Date of death (Day Month Year)

Return **F11 Notification of Death** within 24 hrs

b) Trial Medicinal Information (IMPs)

☐ No trial medication received

Trial medication	Product form	Start date 1st trial dose	Date most recent dose received	Most recent: Number of capsules	Most recent: Frequency	Action taken as a result of the SAE: None	Dose reduced to 1 capsule	Treatment delayed	Treatment stopped	If treatment stopped: stop date
Mirtazapine/placebo	Capsule	Day Month Year	Day Month Year		Daily	☐	☐	☐	☐ →	Day Month Year

Completed by _____ Date (Day Month Year)

*Please email SAE a reports to the CTRU: **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and Sponsor, as appropriate. CTRU, University of Leeds (please see Investigator Site File for full contact details)*

Form continues on next page ►►

For office use only SAE code

Computerised		Verified/Checked	
Date	Initials	Date	Initials

BETTER-B

ISRCTN32236160

FORM 09

Page 2 of 2

Serious Adverse Event (SAE) Report

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

c) Causality & Expectedness of the SAE

c1) Is the event suspected to be related to mirtazapine?
- ☐ Yes → **Report on F10 SSAR / SUSAR Report and email immediately to CTRU**
- ☐ No

c2) Are any other causes thought to have played a role in the event?
- ☐ Yes
  - ☐ Concomitant medications *(name)* _____
  - ☐ Underlying disease – Lung disease
  - ☐ Underlying disease – Chronic heart failure
  - ☐ Underlying disease – Cancer
  - ☐ Other illness *(specify)* _____
  - ☐ Other *(specify)* _____
- ☐ No

d) Is there any additional information not reported above?
- ☐ Yes → Please provide details:
- ☐ No

e) Investigator Review

THIS SAE MUST BE REVIEWED AND THIS SECTION COMPLETED BY THE PRINCIPAL INVESTIGATOR OR AN AUTHORISED CLINICALLY QUALIFIED DELEGATE
Refer to the current approved SPC/IB for the trial

Reviewer name _____ Position _____

Signature _____ Date Day Month Year

Completed by _____ Date Day Month Year

*Please email SAE a reports to the CTRU: **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and Sponsor, as appropriate. CTRU, University of Leeds (please see Investigator Site File for full contact details)*

Last Page ■

f) Report handling (CTRU USE ONLY)

Is this event an SAE? ☐ Yes ☐ No

Date initial report received Day Month Year ☐ N/A (if follow-up report)

Date this report received Day Month Year

MedDRA/Body System code _____

SAE Code *(Please also add this code to the footer of Page 1)*

For office use only	*Computerised* Date Initials	*Verified/Checked* Date Initials	TEM41_T11_V10.0_150317 BETTER-B v0.5 02/03/2016

BETTER-B

ISRCTN32236160

SSAR/SUSAR Report
Concomitant Medications Supplemental Page

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No Trial No

EudraCT Number: 2015-004064-11 **Source of report: Clinical Trial**

ONLY RECORD CONCOMITANT MEDICATIONS: NON-STUDY MEDICATIONS TAKEN AT THE TIME OF THE ONSET OF THE SUSAR THAT HAVE A CAUSAL RELATIONSHIP WITH THE SSAR/SUSAR

Drug name

Reason for use

Dose	Units	Route	Frequency

Start date Day Month Year

Stop date Day Month Year

☐ Ongoing

Drug name

Reason for use

Dose	Units	Route	Frequency

Start date Day Month Year

Stop date Day Month Year

☐ Ongoing

Drug name

Reason for use

Dose	Units	Route	Frequency

Start date Day Month Year

Stop date Day Month Year

☐ Ongoing

Drug name

Reason for use

Dose	Units	Route	Frequency

Start date Day Month Year

Stop date Day Month Year

☐ Ongoing

Page ☐ **of** ☐ **Concomitant Medication Supplemental Pages**

Completed by

Date Day Month Year

Please email SSAR/SUSAR reports to the CTRU ***better-b@leeds.ac.uk****. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	Computerised *Date* *Initials*	Verified/Checked *Date* *Initials*	SAE code

BETTER-B

ISRCTN32236160

SSAR/SUSAR Report
Diagnostic Tests Supplemental Page

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

EudraCT Number: 2015-004064-11 **Source of report: Clinical Trial**

ONLY RECORD DIAGNOSTIC TESTS RELEVANT TO THE SSAR/SUSAR

Diagnostic test name	Date	Test value	Test units
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A

Page ☐ **of** ☐ **Diagnostic Tests Supplemental Page**

Completed by | Date Day Month Year

*Please email SSAR/SUSAR reports to the CTRU **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials	SAE code

BETTER-B

ISRCTN32236160

SSAR/SUSAR Report
Relevant Medical History Supplemental Page

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

EudraCT Number: 2015-004064-11 **Source of report: Clinical Trial**

ONLY RECORD THE PARTICIPANT'S RELEVANT MEDICAL HISTORY

Name of condition, including dates where relevant:

Page ☐ **of** ☐ **Relevant Medical History Supplemental Page**

Completed by | Date Day Month Year

*Please email SSAR/SUSAR reports to the CTRU **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	Computerised Date Initials	Verified/Checked Date Initials	SAE code

BETTER-B

ISRCTN32236160

Form 10

Page 1 of 4

SSAR/SUSAR Report

(Suspected Serious Adverse Reaction
Suspected Unexpected Serious Adverse Reaction)

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- **Complete this form for SSARS/SUSARs occurring within the BETTER-B Feasibility trial from first dose of trial treatment up until 90 days after the End of Trial and email immediately to the CTRU**
- **For SAEs complete F09 and email immediately to the CTRU**

EudraCT Number: 2015-004064-11 **Source of report: Clinical Trial**

Report type: ☐ Initial ☐ Follow-up

Country where SSAR/SUSAR occurred

a) Participant data

a1) Gender ☐ Male ☐ Female a2) Height ____ cm a3) Weight ____ . ____ kg

b) SSAR/SUSAR information

b1) Date of onset of first sign/symptom of event (Day Month Year)

b2) Date event became a SSAR/SUSAR (Day Month Year)

b3) Date trial team first aware of event being a SSAR/SUSAR (Day Month Year)

b4) **Main diagnosis/symptom** — CTCAE grade (v4.0)

b5) **Associated symptoms** that caused the main event to become serious *(if applicable)* — CTCAE grade (v4.0)

b6) **Brief description** of the SSAR/SUSAR *(Including signs/symptoms and any other relevant information)*

b7) Place where SSAR/SUSAR started ☐ Hospital ☐ Outpatient clinic ☐ Home ☐ Care home ☐ Nursing home ☐ Other *(specify)*

c) Seriousness criteria *(tick all that apply)*

- ☐ c1) Participant died
- ☐ c2) Life threatening
- ☐ c3) Required/prolonged hospitalisation
- ☐ c4) Persistent or significant disability/incapacity
- ☐ c5) Congenital anomaly/birth defect
- ☐ c6) Other important medical event
- ☐ c7) Jeopardised participant/required intervention to prevent one of the above

d) Outcome *(at the time of this report)*

- ☐ d1) Recovered → Date of recovery (Day Month Year)
- ☐ d2) Recovered with sequelae
- ☐ d3) Condition improving
- ☐ d4) Condition still present and unchanged
- ☐ d5) Condition deteriorated
- ☐ d6) Ongoing at time of death
- ☐ d7) Death *(only applicable if participant died due to the SSAR/SUSAR)*

Date of death (Day Month Year)

Post-mortem undertaken? ☐ Yes ☐ No

***If yes**, please send in an anonymised copy of the report*

Completed by ____ Date (Day Month Year) *Form continues on next page ►►*

*Please email SSAR/SUSAR reports to the CTRU **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	*Computerised* Date Initials	*Verified/Checked* Date Initials	SAE code

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

e) Participant's relevant medical history

e1) Does the participant have any other relevant medical conditions? *(Such as diseases, allergies or similar experiences)*

☐ Yes *(please give details)* ☐ Unknown
☐ No *(go to Section f)*

Name of condition, including dates where relevant:

Additional medical history may be provided on the RELEVANT MEDICAL HISTORY SUPPLEMENTAL PAGE ☐ *Tick if using*

f) Trial Medicinal Information

First trial medicinal information

First ever trial medication	Product form	Start date 1st ever trial dose	1st ever number of capsules	Frequency
Mirtazapine / placebo	Capsule	Day Month Year	One	Daily

Trial medicinal information at the time of the SSAR/SUSAR

Trial medication	Product form	Date most recent dose received	Most recent trial medication: Number of capsules	Most recent trial medication: Frequency	Action taken as a result of the SSAR/SUSAR: None	Dose reduced to 1 capsule	Treatment delayed	Treatment stopped*	*If treatment stopped: Stop date
Mirtazapine / placebo	Capsule	Day Month Year		Daily	☐	☐	☐	☐	Day Month Year

Completed by | Date Day Month Year | *Form continues on next page ►►*

*Please email SSAR/SUSAR reports to the CTRU **better-b@leeds.ac.uk**. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	Computerised Date Initials	Verified/Checked Date Initials	SAE code

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

g) Treatment for the SSAR/SUSAR

g1) Was treatment given for the SSAR/SUSAR? ☐ Yes *(please give details)* ☐ No *(go to Section h)*

Name of the treatment	Dose	Units	Route	Frequency
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A

Report additional treatment for the SSAR/SUSAR on the TREATMENT SUPPLEMENTAL PAGE ☐ *Tick if using*

h) Relevant Diagnostic Tests

Are there any test/laboratory findings to record? ☐ Yes *(please give details)* ☐ No *(go to Section i)*

Diagnostic test name	Date	Test value	Test units
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A
	Day Month Year		☐ N/A

Additional diagnostic tests may be reported on the DIAGNOSTIC TESTS SUPPLEMENTAL PAGE ☐ *Tick if using*

i) Relatedness and Expectedness *(To be completed by the Investigator or an authorised clinically qualified delegate)*

i1) Is the event suspected to be related to mirtazapine?
- ☐ Yes → ☐ Expected / ☐ Unexpected
- ☐ No → **This event is not a SSAR/SUSAR, please report on an F09 SAE Report**

i2) Are any other causes thought to have played a role in the event?
- ☐ Yes → ☐ Concomitant medications *(name)* _____
  - ☐ Underlying disease – Lung disease
  - ☐ Underlying disease – Chronic heart failure
  - ☐ Underlying disease – Cancer
  - ☐ Other illness *(specify)* _____
  - ☐ Other *(specify)* _____
- ☐ No

Completed by _____ Date Day Month Year

Form continues on next page ►►

Please email SSAR/SUSAR reports to the CTRU ***better-b@leeds.ac.uk****. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials	SAE code

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

j) Is there any additional information not reported above? ☐ Yes ☐ No

k) *THE SSAR/SUSAR MUST BE REVIEWED AND THIS SECTION COMPLETED BY THE INVESTIGATOR OR AN AUTHORISED, CLINICALLY QUALIFIED DELEGATE. Refer to the current approved SPC/IB appropriate to the trial.*

Reviewer name _____

Reviewer position _____

Reviewer telephone number _____

Reviewer signature _____ Date Day Month Year

Reviewer address

Completed by _____ Date Day Month Year

Last Page ■

Please email SSAR/SUSAR reports to the CTRU ***better-b@leeds.ac.uk****. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

I) Report Handling (CTRU USE ONLY)

Is this event a SSAR/SUSAR? ☐ Yes ☐ No

Is this event fatal or life-threatening? ☐ Yes → 7 day report ☐ No → 15 day report

Date of initial report Day Month Year ☐ N/A *(if follow-up report)*

Date this report received Day Month Year

SAE code *(Please also add to footer of previous and supplemental pages)*

Body system / MedDRA code

Date CTRU notified sponsor Day Month Year

Date CTRU reported full details to sponsor Day Month Year

Date sponsor reported to MHRA Day Month Year

Date CTRU reported to main REC Day Month Year

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

SSAR/SUSAR Report
Treatment Supplemental Page

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No Trial No

EudraCT Number: 2015-004064-11 **Source of report: Clinical Trial**

ONLY RECORD TREATMENT FOR THE SSAR/SUSAR

Name of the treatment	Dose	Units	Route	Frequency
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A
	☐ N/A	☐ N/A	☐ N/A	☐ N/A

Page ☐ **of** ☐ **Treatment Supplemental Page**

Completed by		Date	Day Month Year

Please email SSAR/SUSAR reports to the CTRU ***better-b@leeds.ac.uk****. The CTRU will notify the MHRA, main REC and sponsor, if applicable. CTRU, University of Leeds (please see Investigator Site File for full contact details).*

For office use only	*Computerised* *Date* *Initials*	*Verified/Checked* *Date* *Initials*	SAE code

BETTER-B

ISRCTN32236160

FORM 11 Notification of Death

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed by an authorised investigator and emailed to the CTRU at better-b@leeds.ac.uk within 7 days of the trial site team becoming aware

Date of death: Day Month Year

Cause of death *(Tick all that apply)*

- ☐ Cancer related
- ☐ COPD/ILD related
- ☐ Heart failure related
- ☐ BETTER-B trial treatment related toxicity → Please complete **F10 SSAR/SUSAR Report**, if within 7 days of last trial treatment
- ☐ Other, please specify

Place of death

- ☐ Home (own or family member)
- ☐ Hospital
- ☐ Hospice / Palliative Care Unit
- ☐ Nursing home
- ☐ Care home
- ☐ Other, please specify

Email to the CTRU at better-b@leeds.ac.uk within 7 days of the trial team becoming aware.
Where death is the result of an ongoing Serious Adverse Event, ensure F09 SAE Report is updated and emailed to CTRU within 24 hours.

Completed by: Date: Day Month Year

Investigator signature: Date: Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 12

Participant Withdrawal Request

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

- **Complete this form for any participant who requests to withdraw consent to the trial treatment / investigations or associated procedures, as detailed in the categories below**
- **This form should not be completed for participants who stop or change treatment for clinical reasons**
- **Ensure this form is returned to the CTRU within 7 days of the date of withdrawal**

Section A – Withdrawal Details

Date of withdrawal request: Day Month Year

Date of last trial drug dose: Day Month Year

Number of capsules being taken at last dose: ☐ 1 ☐ 2 (i.e. had been dose-escalated)

Has the participant been withdrawn from treatment by the **clinician**? ☐ Yes ☐ No

If yes, give reason

Has the participant withdrawn consent for collection of participant-reported questionnaires? ☐ Yes ☐ No

Has the participant withdrawn consent for further BETTER-B trial treatment? ☐ Yes – Participant wanted to permanently stop trial treatment ☐ No

Is the participant still willing to be followed up according to the BETTER-B trial follow-up schedule? ☐ Yes ☐ No

Is the participant still willing for further data to be collected from their medical records? ☐ Yes ☐ No

Section B – Reason for Withdrawal

Has the participant given a reason for their withdrawal? ☐ Yes ☐ No

If yes, give reason

Section C – Trial Results

Would the participant still like to receive information on the trial results? ☐ Yes ☐ No

Notify all withdrawals to the CTRU within 7 days of the date of withdrawal by emailing this form to better-b@leeds.ac.uk

Completed by: Date: Day Month Year

Investigator signature: Date: Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Version 0.3 02/03/2016

BETTER-B

ISRCTN32236160

FORM 13

Protocol Violations

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Please complete this form for breaches of eligibility criteria or drug administration errors relating to the Investigational Medicinal Products (IMPs) and email immediately to the CTRU at better-b@leeds.ac.uk.

If the error is associated with an event which meets the criteria of an SAE or SUSAR, this must also be reported using the trial SAE or SUSAR form.

Protocol Violations

Complete this section for violations relating to an INDIVIDUAL PARTICIPANT ONLY

Eligibility

Complete this section for participants who were found to breach eligibility criteria after randomisation

Breached eligibility criteria? ☐ Yes ☐ No

If yes, please specify which criteria and action taken

Unplanned Treatment Errors *(Over or Underdosing)*

Has the participant been **overdosed**? ☐ Yes ☐ No

If yes, please provide details of the treatment given

Reason for error

Other relevant information relating to this incident

Date first dosing error Day Month Year

Date last dosing error Day Month Year

Completed by Date Day Month Year

Investigator signature Date Day Month Year

Investigator print name

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

BETTER-B

ISRCTN32236160

FORM 13

Page 2 of 2

Protocol Violations

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Violation Identification and Reporting

Is this event medically significant? ☐ Yes ☐ No
(Considered to have compromised participant safety)

Assessed by
(Name of the clinician)

Is this event linked to an SAE or SUSAR? ☐ Yes ☐ No

If yes, date of onset Day Month Year

Date violation identified Day Month Year

Details of remedial action

Completed by

Date Day Month Year

Investigator signature

Date Day Month Year

Investigator print name

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For CTRU Use Only

If linked to an SAE or SUSAR, ID

Date SAE/SUSAR report received Day Month Year

Was this identified by: ☐ Site ☐ CTRU

Date reported to CI Day Month Year

CI comments

Date reported to QA Day Month Year ☐ N/A

Date reported to independent reviewer Day Month Year

Reviewer name

Independent reviewer comments

Date reported to sponsor Day Month Year ☐ N/A

Is the event a serious breach of GCP? ☐ Yes ☐ No

If yes, date reported to main REC Day Month Year

Date reported to MHRA Day Month Year

Reported by

For office use only	*Computerised* Date	Initials	*Verified/Checked* Date	Initials

BETTER-B

ISRCTN32236160

FORM 14 Notification of Pregnancy

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

To be completed by an authorised investigator and emailed to the CTRU at better-b@leeds.ac.uk within 7 days of the trial site team becoming aware of any confirmed or suspected pregnancies occurring from the date of randomisation to 7 days following permanent cessation of the trial drug

Details of Pregnancy

Date trial site aware: Day Month Year

Date of pregnancy test: Day Month Year

Expected date of delivery: Day Month Year ☐ Not available (please update when available)

Follow-up

☐ Live birth → Number of weeks ☐ → ☐ Healthy

☐ Congenital anomaly/ birth defect → Complete a **F09 Serious Adverse Event (SAE) Report**, or **F10 SSAR/SUSAR Report**

☐ Still birth → Number of weeks ☐

☐ Miscarriage → Number of weeks ☐

- **BETTER-B treament should cease immediately if a pregnancy occurs or is suspected**
- **Email to the CTRU at better-b@leeds.ac.uk within within 7 days of the trial site team becoming aware**

Completed by ☐ Date Day Month Year

Investigator signature ☐ Date Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Version 0.5 02/03/2016

BETTER-B

ISRCTN32236160

FORM 60

SPPB Staff-completed Booklet

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

The Short Physical Performance Battery (SPPB) assessment is performed at baseline and at the Day 28 visit

Date assessments performed: Day Month Year

Time point of assessment: ☐ Baseline ☐ Day 28

Please follow the guidance below and record the time taken for the participant to complete each activity.

1. Repeated Chair Stands

Instructions:

Please ask the participant the following questions and ask them to perform the following actions:

"Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch. Are you ready? Begin."

Begin the stopwatch when the participant begins to stand up. Count aloud each time the participant arises. Stop the stopwatch when the participant has straightened up completely for the fifth time. Also stop if the participant uses arms, or after 1 minute, if subject has not completed the rises, or if you are concerned about the participant's safety.

Record below the number of chair stands completed and, if 5 stands are achieved, the time (in seconds) the participant took to complete the activity.

To be completed by the trial staff

Number of stands completed: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

☐ Unable to attempt

Time (if five stands are completed) ___ seconds

Completed by _____ Date Day Month Year Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Version 0.1 03/02/2016

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Time point of assessment ☐ Baseline ☐ Day 28

2. Balance Testing

Begin with a semi-tandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semi-tandem position should be tested in the full tandem position.

a. Semi-tandem Stand

Instructions:

Please ask the participant to perform the following actions:

"Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate."

Stand next to the participant to help him or her into semi-tandem position. Allow participant to hold onto your arms to get balance. Begin timing when participant has the feet in position and lets go.

Record below how long the participant was able to hold the position.

To be completed by the trial staff

☐ Held for 10 seconds

☐ Held for less than 10 seconds; Number of seconds held: ☐☐

☐ Not attempted

Completed by ____ Date Day Month Year *Form continues on next page ►►*

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site. CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Time point of assessment ☐ Baseline ☐ Day 28

b. Side-by-Side stand

Instructions:

Please ask the participant to perform the following actions:

"I want you to try to stand with your feet together, side by side, for about 10 seconds. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop."

Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

To be completed by the trial staff

☐ Held for 10 seconds

☐ Held for less than 10 seconds; Number of seconds held: ☐☐

☐ Not attempted

c. Tandem Stand

Instructions:

Please ask the participant to perform the following actions:

"Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate."

Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when the participant has feet together and lets go.

To be completed by the trial staff

☐ Held for 10 seconds

☐ Held for less than 10 seconds; Number of seconds held: ☐☐

☐ Not attempted

Completed by _____ Date Day Month Year

Form continues on next page ►►

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Time point of assessment ☐ Baseline ☐ Day 28

3. 8' Walk (2.44 meters)

Instructions:

Please ask the participant to perform the following actions:

"This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course (a distance of 8 feet). Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?"

Press the start button to start the stopwatch as the participant begins walking.

To be completed by the trial staff

Time ___ seconds

☐ Not attempted

Completed by ____ Date Day Month Year

Last Page ■

Prior to returning this form to CTRU you must make a copy of the form and any amendments for retention at site.
CTRU, University of Leeds (please see Investigator Site File for full contact details).

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 80

Unblinding

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Trial name: Better-B Feasibility **Protocol/EudraCT number**: 2015-004064-11

- **To be completed following a request for unblinding or to notify CTRU in the event of an unblinding occurring in error**
- **When requests are made to CTRU, CTRU will complete this form**
- **When the request is made to the pharmacy department, the pharmacist must complete this form and email to CTRU within 1 working day of performing the unblinding at better-b@leeds.ac.uk**

Section 1 – Type of Request

Time of request Hours : Minutes *Please use 24 hr clock*

Type of request:
(Tick as appropriate)

☐ A request for CTRU to unblind → Please call the CTRU on 0113 343 8090 during office hours *(9 am – 5 pm Mon – Fri)* and a CTRU staff member will complete the form for you

☐ Notification to CTRU of an unblinding by the pharmacy department → Pharmacy to complete the whole form

☐ Notification to CTRU of an unblinding in error → Please give details below then complete sections 2 and 4 only

Date unblinded Day Month Year

Was the treatment allocation revealed to the research team? ☐ Yes ☐ No

Please give details:

Completed by: Date Day Month Year

Form continues on next page ▶▶

*If this form is completed by pharmacy, please retain the original in the relevant section of the Pharmacy Site File and email a copy to the Better-B Authorised Unblind Individual at **better-b@leeds.ac.uk***

For office use only	Computerised Date	Initials	Verified/Checked Date	Initials

BETTER-B

ISRCTN32236160

FORM 80

Unblinding

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Trial name: Better-B Feasibility **Protocol/EudraCT number**: 2015-004064-11

Section 2 – Requester Details

Has the request for unblinding been authorised by the Principal Investigator or most senior clinician available? ☐ Yes ☐ No

Name of caller	
Position of caller	
Location of caller	
Tel no.	
Fax no.	
E-mail address	

Note to CTRU staff:
When taking the call, please read the details back to ensure they are recorded correctly.
Unblinding result will be communicated to this tel/fax number.

Who has requested unblind?	
What is their position?	
What is their location?	
Tel no. & email address if known	

Participant kit number	Participant initials	Date of birth (Day Month Year)	Participant ID (Centre No / Trial No)

Section 3 – Details of Request

Date of request: Day Month Year

Reason for unblinding request:

☐ Emergency situation → Please submit an SAE/SSAR/SUSAR form as applicable

☐ Other, please specify:

Completed by: Date: Day Month Year Form continues on next page ►►

*If this form is completed by pharmacy, please retain the original in the relevant section of the Pharmacy Site File and email a copy to the Better-B Authorised Unblind Individual at **better-b@leeds.ac.uk***

CTRU Office use only:

Was the participant unblinded? ☐ Yes ☐ No

Computerised		Verified/Checked	
Date	Initials	Date	Initials

BETTER-B

ISRCTN32236160

FORM 80

Unblinding

Participant Initials		Date of Birth	Day Month Year	Participant ID	Centre No	Trial No

Trial name: Better-B Feasibility **Protocol/EudraCT number**: 2015-004064-11

Section 4 – Result of Request

Was the participant unblinded? ☐ Yes ☐ No

If yes, treatment allocation:

☐ Mirtazapine
☐ Placebo

Unblinding carried out by:

Name | Role

Signature | Date (Day Month Year)

Confirmed by:

Name | Role

Signature | Date (Day Month Year)

If no, action taken:

Please email this completed form to the Better-B Authorised Unblind Individual at *better-b@leeds.ac.uk*

Completed by: Date (Day Month Year) Last Page ■

*If this form is completed by pharmacy, please retain the original in the relevant section of the Pharmacy Site File and email a copy to the Better-B Authorised Unblind Individual at **better-b@leeds.ac.uk***

CTRU Office use only:

Allocation checked by Authorised Unblind Individual? ☐ Yes ☐ No

Initials Date (Day Month Year)

This section only needs to be completed if it was the pharmacy that carried out the unblinding.

Appendix 8 –Randomised, double-blind, multi-centre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility)

Brief communication

OPEN ACCESS

Randomised, double-blind, multicentre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility)

Irene J Higginson ,[1] Andrew Wilcock ,[2] Miriam J Johnson ,[3] Sabrina Bajwah,[1] Natasha Lovell,[1] Deokhee Yi,[1] Simon P Hart,[4] Vincent Crosby,[5] Heather Poad,[6] David Currow ,[7] Emma Best,[6] Sarah Brown,[6] on behalf of BETTER-B Feasibility Trial Group

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-213879).

For numbered affiliations see end of article.

Correspondence to
Professor Irene J Higginson, Cicely Saunders Institute of Palliative Care, Policy and Rehabilitation, Kings College London, London SE5 9PJ, UK; irene.higginson@kcl.ac.uk

Received 26 July 2019
Revised 1 November 2019
Accepted 18 November 2019
Published Online First 8 January 2020

To cite: Higginson IJ, Wilcock A, Johnson MJ, *et al*. *Thorax* 2020;**75**:176–179.

ABSTRACT

New treatments are required for severe breathlessness in advanced disease. We conducted a randomised feasibility trial of mirtazapine over 28 days in adults with a modified medical research council breathlessness scale score ≥3. Sixty-four patients were randomised (409 screened), achieving our primary feasibility endpoint of recruitment. Most patients had COPD or interstitial lung disease; 52 (81%) completed the trial. There were no differences between placebo and mirtazapine in tolerability or safety, and blinding was maintained. Worst breathlessness ratings at day 28 (primary clinical activity endpoint) were, 7.1 (SD 2.3, placebo) and 6.3 (SD 1.8, mirtazapine). A phase III trial of mirtazapine is indicated. Trial registration: ISRCTN 32236160; European Clinical Trials Database (EudraCT no: 2015-004064-11).

INTRODUCTION

Breathlessness is a prevalent and distressing symptom, associated with considerable disability, social isolation, emergency service use and poor survival.[1 2] It often persists despite optimum pharmacological treatment of the underlying medical condition and non-drug approaches.[1 3 4] Drug treatments are limited; opioids have the best evidence,[5 6] but concerns remain regarding long-term effects. New treatments are required. Antidepressants impact on neurotransmitters involved in various brain circuits potentially affecting breathlessness, and are worthy of consideration.[7] Data are mixed for selective serotonin reuptake inhibitors, with positive case series but a negative randomised controlled trial.[8 9] Mirtazapine is an antagonist at α2-adrenergic, H1, 5HT2A/C and 5HT3 receptors, resulting in serotonin, norepinephrine and dopamine release.[7]

Thus, we conducted a multicentre, randomised, placebo-controlled, double-blind, parallel-group, dose-escalating, mixed-methods, feasibility trial of mirtazapine for patients severely affected by breathlessness, to inform a potential phase III trial.

METHODS

For full details, see the Trial Protocol, online supplementary document S1.

Participants

Patients were recruited from three centres. Inclusion criteria were: consenting adults with a confirmed diagnosis (by hospitals/clinicians) of COPD, interstitial lung disease (ILD), cancer or chronic heart failure, plus clinician assessed modified medical research council (mMRC) breathlessness score of 3 or 4 despite optimal treatment of underlying disease(s) and prognosis of ≥2 months. Main exclusion criteria were: existing antidepressant use and contraindications to mirtazapine.

Trial design and procedures

Participants were randomised (1:1) to receive oral mirtazapine (15 mg/day (evening)) or placebo (capsules identical in appearance, smell and taste) for 28 days. Randomisation was stratified by disease (cancer vs non-cancer), Hospital Anxiety and Depression Scale (HADS) score (≥15 vs <15), and taking opioids (yes vs no).

The primary endpoint was number of patients recruited across three hospitals over 12 months, with a target of 60. Secondary endpoints, including proposed primary and secondary clinical activity outcomes for a main trial, are in online supplementary box S1. Assessments were at baseline and weekly thereafter, and included evaluation of breathlessness and related activity scales, toxicity, treatment adherence and quality of life. At 14 days, if the rating of worst breathlessness during the previous 24 hours had not improved ≥1 point on the 0–10 numerical rating scale (NRS) over baseline, the daily dose was increased to two capsules (placebo or 30 mg mirtazapine).

Semi-structured qualitative interviews with a purposive sample of participants, aiming to include a mix of diseases, experiences and backgrounds (subject to data saturation), explored motivations for trial participation and experiences of the intervention, procedures and study measures (see Trial Protocol, online supplementary document S1 page

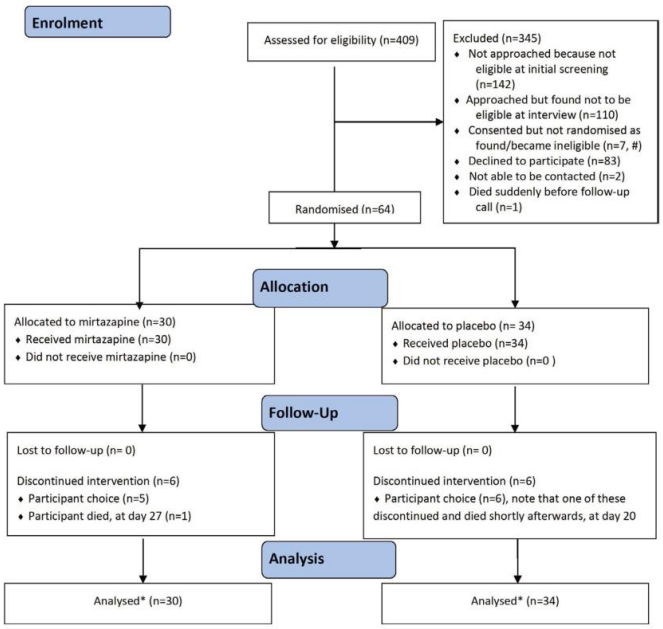


Figure 1 Consolidated Standards of Reporting Trials flow diagram of patients included in the trial, follow-up and analysis. #=reasons why seven patients were consented but not randomised were because they were found or became ineligible: started pulmonary rehabilitation (1); uncontrolled diabetes mellitus (2), started taking antidepressants (1), hepatic impairment (1), decided not on optimal treatment for underlying condition (1), and one missing. * Of those who discontinued intervention, patients were willing to continue data collection in all but one in the mirtazapine group and all but four in the placebo group, all available data were analysed.

77).

The trial received appropriate approvals from the Medicines and Healthcare products Regulatory Agency, London Central Research Ethics Committee (16/LO/0091), local research governance and registrations; International Standard Randomised Controlled Trial (32236160); EU Clinical Trials Register (2015-004064-11); adopted onto the National Institute for Health Research portfolio (30471).

Analysis

For the statistical analysis of the primary endpoint (feasibility), we predetermined 60 patients had to be recruited over 12 months across the centres. This sample size took into account the likely number required for a fully powered phase III trial, guidance on feasibility designs and number needed to estimate the overall SD for the phase III primary outcome of worst breathlessness.[10] As a feasibility trial, all quantitative endpoints were summarised descriptively, with no formal statistical comparisons between groups.

Qualitative data were audio recorded, transcribed verbatim and analysed following the framework method (see online supplementary document S1).

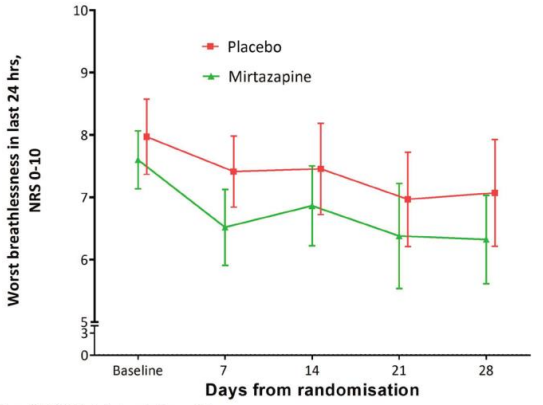


Figure 2 Mean (95% CI) breathlessness at worst and average over 24 hours during the 28 days of the study, by study arm.

RESULTS

Recruitment and progress through trial

Each centre opened for 12 months; 409 patients were screened for eligibility and 64 randomised (16% of those screened; mean 5.3 per month) achieving the primary outcome of feasibility (figure 1). Most participants had COPD (64%) or ILD (31%), and mMRC grade 4 (58%); 33% were taking opioids and HADS score was ≥15 in 24 (38%). Demographics and clinical characteristics were balanced between randomised groups (online supplementary tables S1, S2).

Main reasons for ineligibility were existing antidepressant use (38%), mMRC score <3 (27%). Eighty-three (20% of 409 screened) patients declined participation. Reasons were mainly not liking the idea of a clinical (18%) or a blinded (7%) trial, not wanting to take additional medicine (18%), already having too much to think about (17%) and not liking the thought of

(Statistician)—University of Oxford—Professor Trevor Sheldon (Health Services Research and Policy)—Non-independent member—University of York. Sylvia Bailey (Patient and Public Involvement Representative). We are grateful to our independent Patient and Public Involvement (PPI) team for their advice and support during the whole period of the study: Mandy Paine, Colleen Ewart, Gerry Bennison and Sylvia Bailey.

Collaborators We thank our collaborators for their help and advice during the project in particular: Dr Rohit Lal, Consultant Medical Oncologist; Dr Charles Reilly, Consultant Physiotherapist; Dr Matthew Maddocks, Senior Lecturer in Palliative care and Specialist Physiotherapist; Professor Surinder Birring, Professor of Respiratory Medicine; Dr Anna Gerratt, Dr Frank McCaughan, Dr Rachael Barton, Dr Irem Patel, Dr West, Wai Lam, Professor Charlotte Bolton, Dr William Chang, Professor Gisli Jenkins. Pharmacy (King's College Hospital): Stuart Chandler and Research project co-ordinator Deborah Tonkin.

Contributors BETTER-B Feasibility Trial Group: Chief Investigator: IJH, responsible for all aspects of the research, conduct, analysis and drafting of the paper. Coapplicants: Professor Julia Brown, SB, VC, DC, MJJ, Professor Trevor Sheldon and AW. Centre Principal Investigators: SB (London), SH (Hull) and AW (Nottingham). Research Nurses, Clinical Trial Manager and Project coordinator: Cathann Manderson, Sarah Farnan, Paramjote Kaler, Caty Pannell, Evelyne Burssens, Kayleigh Brindle, Caroline Wright, Anna Johnston and Maria Teixera. Researcher: NL. Health economist: DY. Statisticians: Hannah Buckley and SB. Clinical Trials Research Unit (Leeds): HP, EB, Victoria Hiley, Heather Cook and Helen Howard. Clinical Trials Office (KCL): Jackie Pullen, Helen Critchley and Hinna Mir. Lead paper writing group responsible for analysis interpretation and critical revisions of the paper: IJH, AW, MJJ, SB, NL, DY and SB. Other named authors provided critical revisions.

Funding We thank Marie Curie, Cicely Saunders International (CSI) and The Atlantic Philanthropies, Yorkshire Cancer Research whose funding made this study possible.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Irene J Higginson http://orcid.org/0000-0002-3687-1313
Andrew Wilcock http://orcid.org/0000-0002-3214-1188
Miriam J Johnson http://orcid.org/0000-0001-6204-9158
David Currow http://orcid.org/0000-0003-1988-1250

REFERENCES

1 Maddocks M, Lovell N, Booth S, *et al*. Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease. *The Lancet* 2017;390:988–1002.
2 Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. *BMC Palliat Care* 2011;10:15.
3 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. *The Lancet Respiratory Medicine* 2014;2:979–87.
4 Brighton LJ, Miller S, Farquhar M, *et al*. Holistic services for people with advanced disease and chronic breathlessness: a systematic review and meta-analysis. *Thorax* 2019;74:270–81.
5 Ekström M, Bajwah S, Bland JM, *et al*. One evidence base; three stories: do opioids relieve chronic breathlessness? *Thorax* 2018;73:88–90.
6 Simon ST, Higginson IJ, Booth S, *et al*. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016;10.
7 Lovell N, Wilcock A, Bajwah S, *et al*. Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. *Expert Rev Respir Med* 2019;13:173–80.
8 Lovell N, Bajwah S, Maddocks M, *et al*. Use of mirtazapine in patients with chronic breathlessness: a case series. *Palliat Med* 2018;32:1518–21.
9 Currow DC, Ekström M, Louw S, *et al*. Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial. *Eur Respir J* 2019;53.
10 Browne RH. On the use of a pilot sample for sample size determination. *Stat Med* 1995;14:1933–40.

Appendix 9: Confirmation that manuscript accepted for publication in Trials journal

Date: 01 Feb 2020
To: "Natasha Lovell" natasha.lovell@kcl.ac.uk
From: "Trials (TRLS)" krishna.vairamani@springer.com
Subject: Decision has been reached on your submission to Trials - TRLS-D-19-00438R3

TRLS-D-19-00438R3
What influenced people with chronic or refractory breathlessness and advanced disease to take part and remain in a drug trial? A qualitative study.
Natasha Lovell; Simon N Etkind; Sabrina Bajwah; Matthew Maddocks; Irene J Higginson
Trials

Dear Dr Lovell,

I am pleased to inform you that your manuscript "What influenced people with chronic or refractory breathlessness and advanced disease to take part and remain in a drug trial? A qualitative study." (TRLS-D-19-00438R3) has been accepted for publication in Trials.

Before publication, our production team will check the format of your manuscript to ensure that it conforms to the standards of the journal. They will be in touch shortly to request any necessary changes, or to confirm that none are needed.

Articles in this journal may be held for a short period of time prior to publication. If you have any concerns please contact the journal.

Any final comments from our reviewers or editors can be found, below. Please quote your manuscript number, TRLS-D-19-00438R3, when inquiring about this submission.

We look forward to publishing your manuscript and I do hope you will consider Trials again in the future.

Best wishes,

Sarah Cockayne, Msc
Trials
https://trialsjournal.biomedcentral.com/

Comments:

Reviewer #1: I am satisfied with the edits and responses from the authors. The paper is acceptable for publication.

Comment from Associate Editor. Dear Dr Lovell, apologies for the delay in reviewing the final comments from the peer reviewer. I had two NIHR final reports due in within a month, hence my delay. I am pleased to now recommend the manuscript for publication. Best wishes Sarah

--
Please also take a moment to check our website at for any additional comments that were saved as attachments. Please note that as Trials has a policy of open peer review, you will be able to see the names of the reviewers.

Appendix 10: Wording of NRS Across Studies

Manuscript Title	Author/ Year/ Journal	NRS wording
No detail on wording in manuscript		
Fan Therapy Is Effective in Relieving Dyspnea in Patients With Terminally Ill Cancer: A Parallel-Arm, Randomized Controlled Trial.	Kako J, 2018, JPSM.	No detail on wording in manuscript
Low-Dose Morphine for Dyspnea in Terminally Ill Patients with Idiopathic Interstitial Pneumonias.	Matsuda Y, 2017, Journal of Palliative Medicine.	No detail on wording in manuscript
The Effect of Using an Electric Fan on Dyspnea in Chinese Patients With Terminal Cancer.	Wong SL, 2017, Am J Hosp Palliat Care.	No detail on wording in manuscript
Inspiratory High Frequency Airway Oscillation Attenuates Resistive Loaded Dyspnea and Modulates Respiratory Function in Young Healthy Individuals.	Morris T, 2014, PLoS One.	No detail on wording in manuscript
Dyspnea scales in the assessment of illiterate patients with chronic obstructive pulmonary disease.	Martinez JA, 2000, Am J Med Sci.	No detail on wording in manuscript
Breathlessness Now		
Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness.	Sandberg J, 2018, JPSM.	How is your breathlessness right now?
Verbal numerical scales are as reliable and sensitive as visual analog scales for rating dyspnea in young and older subjects.	Morris NR, 2007, Respir Physiol Neurobiol.	How short of breath are you right now
Effect of Prophylactic Fentanyl Buccal Tablet on Episodic Exertional Dyspnea: A Pilot Double-Blind Randomized Controlled Trial.	Hui D, 2017, JPSM.	Dyspnoea intensity now
Impact of Prophylactic Fentanyl Pectin Nasal Spray on Exercise-Induced Episodic Dyspnea in Cancer Patients: A Double-Blind, Randomized Controlled Trial.	Hui D, 2016, JPSM.	Dyspnoea intensity "now"
Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot.	Johnson MJ, 2015 BMJ Open.	Breathlessness intensity 'now', at maximal exertion, and then every minute during recovery.
Assessment of dyspnoea in the emergency department by numeric and visual scales: A pilot study.	Placido R, 2015, Anaesth Crit Care Pain Med.	Tell me on a scale of 0 to 10, what is the level of your shortness of breath.

Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: a preliminary double-blind, randomized, controlled trial.	Hui D, 2014, JPSM.	Intensity of dyspnoea "now"
High Flow Oxygen and Bilevel Positive Airway Pressure for Persistent Dyspnea in Patients With Advanced Cancer: A Phase II Randomized Trial.	Hui D, 2013, JPSM.	Intensity of dyspnoea "now"
Proposing a standardized method for evaluating patient report of the intensity of dyspnea during exercise testing in COPD.	Hareendran A, 2012, Int J Chron Obstruct Pulmon Dis.	Subjects asked to indicate how much shortness of breath they are having right now
Average and worst breathlessness		
Are within-person Numerical Rating Scale (NRS) ratings of breathlessness 'on average' valid in advanced disease for patients and for patients' informal carers?	Wade J, 2017, BMJ Open Respir Res.	What is the worst your breathlessness has been over the last 24 hours? How has your breathlessness been over the last 24 hours on average?
Assessment of Breathlessness in Lung Cancer: Psychometric Properties of the Dyspnea-12 Questionnaire.	Tan JY, 2017, JPSM.	Average breathlessness Worst breathlessness Breathlessness-related unpleasantness Breathlessness-related distress Patients' ability to cope with breathlessness
Practical Dyspnea Assessment: Relationship Between the 0–10 Numerical Rating Scale and the Four-Level Categorical Verbal Descriptor Scale of Dyspnea Intensity.	Wysham NG, 2015, JPSM.	How is your breathlessness right now? How has your breathlessness been over the last 24 hours, on average? What is the worst your breathlessness has been over the last 24 hours?
An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.	Higginson IJ, 2014, The Lancet Respiratory Medicine.	Indicate how much shortness of breath you are having on average over the last 24 hours? At worst at rest over the last 24 hours? On exertion over the last 24 hours?
A randomised controlled trial of three or one breathing technique training sessions for	Johnson MJ, 2015, BMC Med.	Worst breathlessness over the previous 24 hours

breathlessness in people with malignant lung disease.		Average intensity of breathlessness over the past 24 hours Distress due to breathlessness Coping with breathlessness Satisfaction with care of breathlessness
Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial.	Yorke J, 2015, Supportive Care in Cancer.	Average breathlessness in the past 24 hours Worst breathlessness in the past 24 hours Distress associated with breathlessness Unpleasantness associated with breathlessness Relief from breathlessness Ability to cope with breathlessness
Repeat dose opioids may be effective for breathlessness in chronic heart failure if given for long enough.	Oxberry SG, 2013, Journal of Palliative Medicine.	Average and worst breathlessness over the past 24 hours Distress, satisfaction, and coping with breathlessness
A randomised trial of high vs low intensity training in breathing techniques for breathless patients with malignant lung disease: a feasibility study.	Barton R, 2010, Lung Cancer.	Perceived severity of breathlessness (average and worst over the past 24 h, and “now”) Distress caused by breathlessness Ability to cope with breathlessness
The effect of resistance inspiratory muscle training in the management of breathlessness in patients with thoracic malignancies: a feasibility randomised trial.	Molassiotis A, 2015, Support Care Cancer.	Perceived severity of breathlessness (average and ‘worst’ over the past 24 h, and “now”) and distress caused by breathlessness Ability to cope with breathlessness
Minimally clinically important difference in chronic breathlessness: Every little helps.	Oxberry SG, 2012, Am Heart J.	Intensity of average breathlessness over the past 24 hours Worst breathlessness over the past 24 hours

Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial.	Oxberry SG, 2011, Eur J Heart Fail.	Severity of average breathlessness Worst breathlessness over the past 24 h Breathlessness 'now' Coping with breathlessness
Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial.	Abernethy AP, Lancet, 2010.	Breathlessness right now Average dyspnoea in the past 24 hours Worst breathlessness in the past 24 hours Relief of dyspnoea over the prior 24 hours
Average breathlessness		
Association of Descriptors of Breathlessness With Diagnosis and Self-Reported Severity of Breathlessness in Patients With Advanced Chronic Obstructive Pulmonary Disease or Cancer.	Chowienczyk S, 2016, JPSM.	How has your breathlessness been over the last 24 hours on average? How distressed are you by your breathlessness?
Worst breathlessness and breathlessness now		
Predictors of response to corticosteroids for dyspnea in advanced cancer patients: a preliminary multicenter prospective observational study.	Mori M, 2017, Support Care Cancer.	Dyspnoea worst Dyspnoea now
Distress due to breathlessness		
Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial.	Farquhar MC, 2014, BMC Med.	Patient distress due to breathlessness
The clinical and cost effectiveness of a Breathlessness Intervention Service for patients with advanced non-malignant disease and their informal carers: mixed findings of a mixed method randomised controlled trial.	Farquhar MC, 2016, Trials.	Patient distress due to breathlessness
Other		
Acupuncture for Dyspnea in Lung Cancer: Results of a Feasibility Trial.	Bauml J, 2016, Integr Cancer Ther.	Dyspnoea severity in the past 7 days
Morphine in the management of dyspnoea in ALS. A pilot study.	Clemens KE, 2008, Eur J Neurol.	Intensity of dyspnoea
Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study.	Currow DC, 2010, JPSM.	Intensity of dyspnoea

Appendix 11 -What is the evidence for mirtazapine in treating cancer-related

Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-05229-7

REVIEW ARTICLE

What is the evidence for mirtazapine in treating cancer-related symptomatology? A systematic review

Guillaume Economos [1,2] · Natasha Lovell [1] · Anna Johnston [1] · Irene J. Higginson [1]

Received: 17 July 2019 / Accepted: 5 December 2019

Abstract

Purpose Cancer patients often experience multiple distressing symptoms which are challenging to manage. It would therefore be helpful to find a treatment that alleviates more than one symptom, to avoid polypharmacy: mirtazapine has been used in several studies for this purpose. The objective of this study was to assess the effectiveness and safety of mirtazapine in alleviating one or more frequently encountered cancer-related symptoms.

Methods Systematic review of clinical trials in English or French. Eight databases were searched. Included studies assessed the effectiveness of mirtazapine in alleviating one or more frequently encountered cancer-related symptoms. Comparator and validated assessment tools were required. Studies were independently appraised by two investigators before data synthesis.

Results The search yielded 1898 references, from which we identified 12 relevant articles evaluating highly heterogeneous outcomes. These were two randomised-controlled (RCTs), three non-randomised controlled, and seven non-randomised non-controlled trials. In total, 392 participants were included and 185 were in RCTs. No study assessed the effectiveness of mirtazapine in alleviating symptoms at the same time, but some considered more than one symptom. Overall, the data was of poor quality, limited by small sample size and bias. However, mirtazapine showed effectiveness in treating depression, anxiety, sleep disorders, emesis and neuropathic pain. Across all studies, mirtazapine is safe to use, with drowsiness and dizziness the most common side-effects.

Conclusion Study design and small sample sizes limit the ability to interpret results. Trials to assess the impact of mirtazapine or other medicines in alleviating multiple symptoms would be valuable.

Keywords Mirtazapine · Neoplasms · Palliative care · Supportive care in cancer · Polysymptomatology

Introduction

Cancer patients often experience multiple distressing symptoms simultaneously [1]. The experience of multiple symptoms at the same time is referred to as polysymptomatology and requires multiple medications to mitigate their effect [2]. The most burdensome includes fatigue, pain, lack of energy, weakness and loss of appetite, affecting more than half of patients with advanced cancer [1, 3]. These symptoms are a challenge to assess and treat, and very few drugs are licenced for this purpose [4, 5]. In this frail and multimorbid population, polymedication increases the risk of drug interactions and side effects [6, 7]. One approach to tackle this is identifying a single medication which can effectively treat multiple symptoms.

Mirtazapine [8], a noradrenergic and specific serotonergic antidepressant, has proved effective in the treatment of depression in the cancer population [9]. It has also been

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-019-05229-7) contains supplementary material, which is available to authorized users.

✉ Guillaume Economos
economos.guillaume@gmail.com

Natasha Lovell
Natasha.lovell@kcl.ac.uk

Anna Johnston
Anna.johnston@kcl.ac.uk

Irene J. Higginson
Irene.higginson@kcl.ac.uk

[1] Cicely Saunders Institut, Departement Palliative Care Policy and Rehabilitation, King's College London, 10 Cutcombe Rd, Brixton, London SE5 9PJ, UK

[2] Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Palliative Care, 165 chemin du Grand Revoyet, 69310 Pierre-Bénite, France

Published online: 19 December 2019

symptomatology? A systematic review

evaluated in several studies to alleviate other cancer-related symptoms. This pre-synaptic α2adrenoreceptor antagonist increases the central noradrenergic and serotoninergic neurotransmission. Whilst the cause of its effectiveness as an antidepressant remains unclear, it is hypothesised to be due to a blockage of pre-synaptic α2 receptors leading to the release of norepinephrine, and a better availability of neurotransmitters in the synapse. It also antagonizes α2 heteroreceptors leading to an increment of serotonin release. Besides these central noradrenergic and serotoninergic effects, mirtazapine has an affinity to the anti-H1 receptor and is an 5-HT3 antagonist [10], which could be relevant in treating sleep disorders, appetite and breathlessness [11]. With this pharmacological profile, mirtazapine may be effective for the treatment of multiple symptoms, particularly those associated with cancer [5, 8, 12].

Mirtazapine is reported to be a safe antidepressant drug in the cancer population. It is almost completely metabolized by the liver and has a low-drug interaction risk, thus, allowing its use in advanced renal failure [10, 13]. However, some authors report drug-related symptoms such as dry-mouth, sedation, increased appetite and weight gain [14]. Sedation, increased appetite and weight gain are specific to mirtazapine, and could be useful in the cancer population who commonly experience poor sleep and a lack of appetite.

The effectiveness and safety of mirtazapine in alleviating multiple symptoms in cancer populations remain unclear. This review aims to address this question.

Material and methods

We performed a systematic review of the literature using eight different databases to identify studies relevant to our research question.

The full protocol is available in supplementary material 1.

Data sources

To identify relevant studies, we searched on Medline, Scopus, Web of Science, Central and EMBASE. We searched for grey literature on Clinical Trials, the WHO ICTRP and OpenGrey. Investigators were contacted by e-mail to request any unpublished study details identified using the clinical trial databases. Additional records were identified using related articles and references as well as by open searches. The inclusion time frame covered all databases until the 15th of January 2019.

Research algorithms were designed to fit with each database to improve the sensitivity of the search (supplementary material 2). The titles and abstracts (if available) of yielded records were screened for inclusion and exclusion criteria to evaluate their eligibility. Full text articles were then read and non-relevant articles excluded.

Article selection

We included only primary literature: randomized controlled trials (RCTs), cohort studies, case-controlled and non-randomised experimental studies, reporting original studies written in English or French languages. Experimental studies were required to use a control.

Included studies concerned patients diagnosed with cancer, excluding cancer survivors, with one or more of the following symptoms: depression, anxiety, sleep disorders, nausea, anorexia, weight loss, breathlessness, pain, constipation, fatigue and drowsiness. These symptoms were chosen based on the fact that they are the most frequently encountered symptoms in cancer [3] and could potentially be addressed using mirtazapine given its pharmacological profile [8]. The primary outcome of studies was improvement of one of the listed symptoms.

Data extraction

Data was extracted independently by two authors (GE, NL) regarding the effectiveness of mirtazapine (primary or secondary outcome) and the safety of its use. Authors extracted data on the year of publication and country of the study, number of participants, doses and modes of administration of mirtazapine and the comparator, follow-up completion rate, assessed symptoms and the tools used for assessment, results of the analysis, reported toxicity, adverse events and reasons for withdrawals.

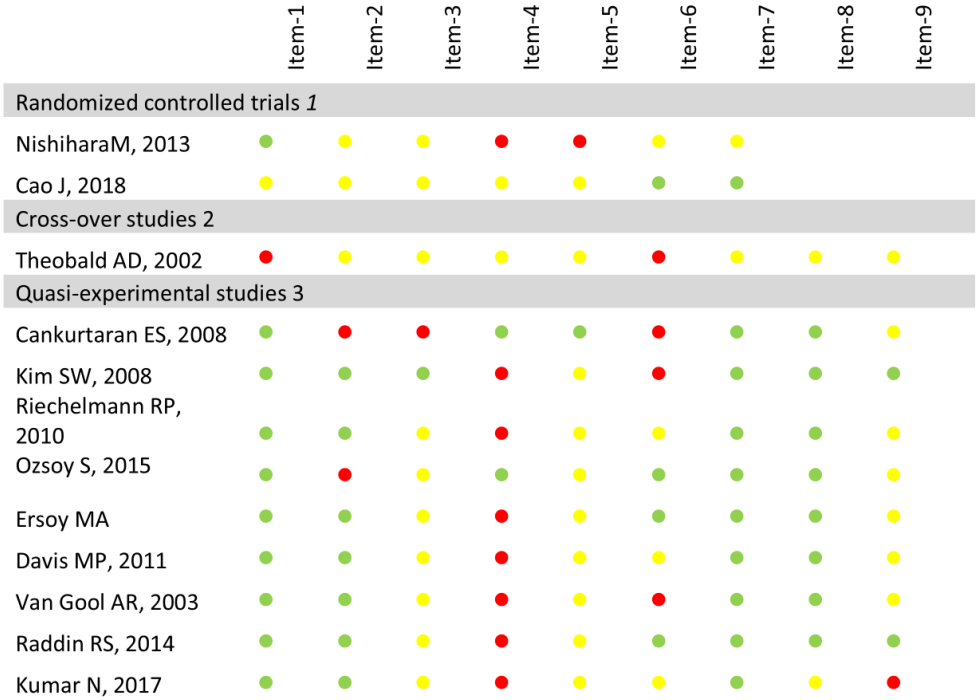
Data synthesis

Two authors (GE, NL) independently assessed the risk of bias and quality of studies using Cochrane Collaboration's tools for RCTs and crossover studies, and the checklist for non-randomised experimental studies provided by the Johanna Briggs Institute for non-randomised experimental studies (Table 1).

Data were summarized according to the level of evidence permitted within the study design (Table 2, supplementary material 3) and the risk of bias for each study (Table 1). Evidence for each symptom was assessed following the GRADE practice recommendations [15]. If the authors disagreed on data, an external opinion was sought.

Regarding the predictably high heterogeneity of studies, no meta-analysis has been planned.

Table 1 Assessment of the studies' risk of bias according to their designs



[1] Randomized controlled trials' risk of bias assessed using the Cochrane collaboration tool for assessing risk of bias: ● low risk of bias, ● unclear risk of bias, ● high risk of bias

Item 1 random sequence generation, *Item 2* allocation concealment, *Item 3* blinding participant and personnel, *Item 4* blinding outcome assessment, *Item 5* incomplete outcome data, *Item 6* selective reporting, *Item 7* other source of bias, *Items 8* and *Item 9* are not suitable for randomized controlled trials

[2] Cross-over trials' risk of bias assessed using the Cochrane collaboration tool for assessing risk of bias: ● low risk of bias, \● unclear risk of bias, ● high risk of bias

Item 1 appropriate crossover design, *Item2* randomized treatment order, *Item 3* carry-over effect, *Item 4* unbiased data, *Item 5* allocation concealment, *Item 6* blinding, *Item 7* incomplete outcome data, *Item 8* selective outcome reporting, *Item 9* other bias

[3] Quasi-experimental studies' risk of bias assessed using the Joanna Briggs Institute Checklist: ● adequate, ● unclear, ● inadequate

Item 1 causes and effects are clearly defined, *Item 2* similarity in participants, *Item 3* similarity in treatments, *Item 4* existing control group, *Item 5* multiple measurement, *Item 6* follow-up completion, *Item 7* outcome measurement comparable, *Item 8* outcome measurement reliable, *Item 9* appropriate statistics

Results

Search results

The electronic search yielded 1898 references overall, 582 from Medline, 477 from EMBASE, 293 from Central, 389 from Web of Science, 125 from Scopus, none from OpenGrey, 17 from Clinical Trials and 15 from the ICTRP. After this screening, 75 articles were identified as relevant. Of these, 50 were duplicates. From studies identified using clinical trials registries, five trials were ongoing, two had discontinued, six investigators did not answer our requests and one informed us that the study was currently under submission process. After this, 12 relevant studies remained with no additional records identified (Fig. 1). Three studies were presented as RCTs, including 53 [16], 25 [17] and 95 patients [18]. However, closer scrutiny of the designs revealed that, in one, the control group was made of people refusing to take antidepressant medications [16]. Therefore, this study has been considered a non-randomised experimental study for the purpose of this review.

One was a crossover trial [19], and nine were non-randomised experimental studies [5, 16, 20–25]. The longest duration of treatment was 6 months [20], and the shortest was 3 days [18]. All articles were in English.

Overall, the evidence was highly heterogeneous (Table 1 and supplementary material 3) and the quality of the studies'

Table 2 Summary of the main findings

	GRADE's quality of evidence	Symptom	Data summary
Targeted symptoms	Low	Nausea and vomiting	6 studies (236 patients) of which 1 RCT (95 patients) ☞ Could mitigate chemotherapy-induced emesis within 3 days of treatment in addition to other anti-emetic drugs. Has not been proven to mitigate radiotherapy induced emesis. No evidence available in other situations.
	Very low	Pain	4 studies (140 patients), of which 1 RCT (25 patients) ☞ Was more effective to treat neuropathic pain from day 14 than pregabalin alone.
		Depression	8 studies (249 patients) ☞ Could be effective earlier than with compared antidepressants.
		Anxiety	6 studies (214 patients) ☞ Could improve anxiety, could be effective from day 15.
		Sleep disorders	5 studies (155 patients) ☞ Could improve every stage of sleep, and extend the length of sleep. Could be efficient from week 1.
		Anorexia	3 studies (113 patients) ☞ Weak evidence in effectiveness of improving appetite.
		Loss of weight	4 studies (148 patients) ☞ Weak evidence in the effectiveness of weight gain.
	Not applicable	Breathlessness	1 study (17 patients) ☞ Studies are underpowered to make a statement.
Side effects	Very low	Drowsiness and fatigue	2 studies (35 patients). ☞ The studies did not report any changes in drowsiness and fatigue, however, these two are often reported as side effects.
	Not applicable	Dizziness	No study available; however, dizziness is often reported as a side effect.
		Constipation	No study available in this specific population, but a well-known side effect in the general population.

reported was poor, with important concerns about the risk of bias (Table 2).

Effectiveness of mirtazapine in cancer-related symptoms

Evidence from randomised-controlled trials

Two studies used randomised-controlled designs, although mirtazapine was not compared with a placebo in either. The studies assessed the effectiveness of mirtazapine on two different symptoms: emesis [18] and pain [17].

Cao et al.'s study aimed to assess the effectiveness of mirtazapine in addition to usual anti-emetic therapies in the treatment of chemotherapy-induced emesis [18]. The study included 95 breast cancer patients undergoing cisplatin chemotherapy. The intervention group received mirtazapine in addition to aprepitan, a 5HT3 receptor antagonist and dexamethasone 7.5 mg. The control group received the same medications except mirtazapine. Response was assessed as "complete response to vomiting" (no emesis and no rescue treatments) and "complete control" (defined as no emesis, no rescue treatment and no more than grade 1 nausea). In the first cycle, delayed and overall complete response rates were significantly higher with mirtazapine (78.3 versus 49% $p = 0.003$, and 58.7 versus 34.7% $p = 0.019$). Similar results were observed in the 3rd cycle. The study closed early due to slow enrolment, and the interpretation of results is limited by a small sample size.

Nishihara et al.'s study compared antidepressant drugs used as adjuvants with pregabalin and opioids for intractable painful bone metastases in mixed cancer types [17]. The authors compared pregabalin 50 mg three times daily, pregabalin 25 mg three times daily combined with mirtazapine 7.5 mg twice daily and pregabalin 25 mg three times daily combined with imipramine 5 mg twice daily. Authors also recorded the average use of opioids in the three arms. The trial included 25 patients treated for 15 days; a numerical rating scale was used to evaluate average intensity of pain and intensity of paroxysmal pain over the past 24 h. The results found a clinically important difference over 2 [26, 27] in the total pain score intensity and in the paroxysmal pain intensity from the 1st day of use in all 3 arms of the trial. This decrease was significantly higher in the arm with mirtazapine and imipramine than in the arm with pregabalin only, and results were higher in the mirtazapine arm than the

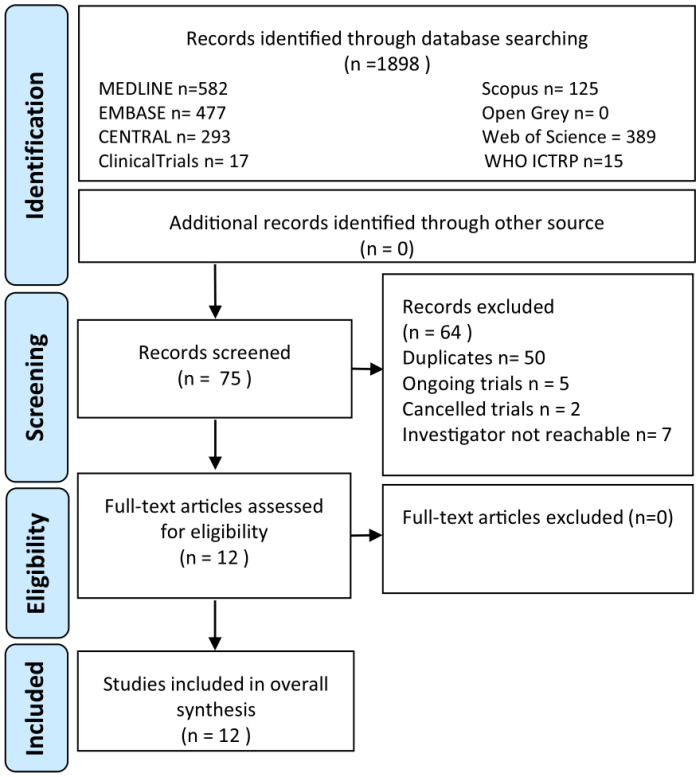


Fig. 1 Flow-chart (based on the CONSORT statement)

imipramine arm during the first day of treatment. There was no difference in the daily opioid dose for any of the arms.

Evidence from non-randomised controlled trials

Three non-randomised controlled trials were identified [16, 23, 24]. Two compared mirtazapine with other antidepressant drugs, one with imipramine and a control group [16], and the second with citalopram [24]. The last one compared mirtazapine with a non-interventional control group. The studies attempted to assess a wide range of symptoms including depression, anxiety, pain, appetite, emesis, insomnia, weight loss and fatigue using validated tools. Overall, the sample sizes were small (43.7 participants on average) with a high risk of bias (Table 1).

Cankurtaran et al. report a randomised-controlled trial; however, in this study, the control group was participants who had refused the intervention (mirtazapine) [16]. We have therefore considered this to be a non-randomised controlled trial. The study included 53 patients over a 6-week period with a follow-up completion rate of 0.66. Participants were cancer patients with various diagnoses. One arm received an unspecified dose of mirtazapine in addition to supportive therapy for 6 weeks, the second one received imipramine in addition to supportive therapy and the third (who had refused antidepressant treatment) received only supportive therapy. The evaluated outcomes were nausea, vomiting, reduced appetite, weight, sleep disorders, depression, anxiety and pain. Results did not show any difference in nausea or vomiting (using a single symptom scale). When assessing for pain, no difference was found between arms using a numerical rating scale. Anxiety and depression were assessed using a validated tool in cancer, the hospital anxiety and depression scale (HADS) [28, 29]. The study found a statistically and clinically significant difference [30] in anxiety (-3.7 points, $p = 0.025$) and depression (-4.7 points, $p = 0.003$) for patients taking mirtazapine, compared with imipramine and control. The effectiveness on sleep disorders was assessed using the Hamilton depression rating scale (HAM-D) which is validated in cancer [31]. For initial, middle and late insomnia, only the mirtazapine group showed improvement ($p = 0.001$, $p = 0.001$, $p = 0.003$). Using single symptom scales, no significant difference was found for appetite or

weight change in the mirtazapine group when compared with the other arms.

Raddin et al. report the results of a non-randomised controlled study including 18 patients over a 9-week period [24]. The follow-up completion rate was 0.86. Participants received mirtazapine (starting dose 7.5 mg, escalated to 15 and then 30 mg as appropriate) or citalopram (starting dose 10 mg, escalated to 20 and then 40 mg as appropriate). Allocation was not concealed and was decided by clinical experience. The authors assessed depression using the Patient Health Questionnaire 9 (PHQ-9) at baseline, weeks 1, 2, 3, 4, 6 and 9. In this study, depression did not significantly improve in the overall cancer sample when evaluated using the PHQ-9. However, a sub-analysis which excluded actively dying patients showed a significant and clinically important difference [32] of 7.6 (95% CI = [2.9–12.2]) after 9 weeks of treatment. The quality of sleep was evaluated using the Pittsburgh Sleep Quality Index (PSQI) [33]. The study reports a non-significant improvement in sleep quality when assessed using the PSQI score (11.0 versus 8.6, 95% CI = [− 2.2–6.9]) and a non-significant improvement of the hours of sleep (5.9 versus 7.5, 95% CI = [− 0.3–3.5]). The study did not find any significant difference for weight or fatigue across the different arms.

Oszoy et al. report an open-labelled study assessing the outcomes of radiotherapy-induced cachexia treated with mirtazapine 15-30 mg for 6 months in patients with head and neck cancer [23]. The interventional group was made of patients diagnosed with major depression using the Hamilton depression rating scale, and they were compared with a control group who did not have a diagnosis of cancer or depression. The primary outcome of this study was to assess the effectiveness of mirtazapine on the level of two hormones involved in the regulation of food intake (ghrelin and leptin); secondary outcomes were assessment of weight and body mass index. The results are challenging to analyse, and no conclusion can be reached as baseline characteristics highly differ between the groups.

Evidence from non-randomised non-controlled trials

We recorded seven non-randomised non-controlled trials which were all before and after designs [19–22, 25, 34, 35]. They assessed a number of symptoms including the following: depression, anxiety, emesis, insomnia, anorexia, weight loss, breathlessness, fatigue and pain. The studies had small sample sizes (on average 24.1 participants in each study) and a high risk of bias.

Theobald et al. report a 6-week open-label crossover trial comparing the effectiveness of mirtazapine 15 mg versus mirtazapine 30 mg in cancer patients experiencing pain [19]. Evaluated outcomes were pain, depression, nausea and appetite. The study included 20 patients over a 6-week period with a low follow-up completion rate (0.55). The authors assessed pain, appetite, and nausea and vomiting using a numeric rating scale and found no change for any symptom between baseline and end-point. However, patients did report feeling less concerned about their weight at week 4 ($F = 12.9$, $p < 0.01$) and week 7 ($F = 4.7$, $p < 0.05$) when compared with baseline. Depression was assessed using the Zung self-rating depression scale (ZSDS) which is validated for cancer [36]. The authors report a significant improvement in the ZSDS scores at week 7 ($F = 8.2$, $p < 0.05$).

Ersoy et al. report a before-after trial which followed up 19 patients treated with mirtazapine 15 mg daily for 6 months [20]. The study reports a clinically significant improvement in depression using the 17-item Hamilton rating scale with a drop from 21.4 ± 4.9 at baseline to 6.5 ± 3.2 at end-point ($p < 0.001$) [37, 38]. This improvement was significant for each sub-index of the scale rating anxiety, depression and the quality of sleep.

Riechelmann et al. report a before-after trial which followed up 21 participants for 8 weeks of treatment with mirtazapine 15-30 mg daily [21]. The primary outcome was a gain of at least 1 kg after 4 weeks of treatments and secondary outcomes were appetite and quality of life. At week 4, on intention to treat, 24% of participants had gained 1 or more kilogrammes with a median gain of 1.5 kg (ranging from 1 to 3.6); all respondents reported an improvement in their appetite (of more than 2 points) on the Edmonton Symptom Assessment Scale.

Kim et al. describe the results from a before-after trial which followed up 39 participants treated with mirtazapine 15 mg daily for 4 weeks [22]. The primary outcomes were the Chonnam National University Hospital Leeds Sleep Evaluation Questionnaire (C-LESQ) for the quality of sleep, and the Clinical Global Impression (CGI) scale for nausea. The amount of sleep increased from 3.6 at baseline to 6.8 h per day at end-point ($p < 0.001$), the ease of getting sleep improved from 4.2 to 2.4 ($p < 0.001$), the quality of sleep improved from 4.3 to 2.6 ($p < 0.001$) and the ease of waking in the morning improved from 3.2 to 2.5 ($p < 0.001$). In the sub-population of patients experiencing nausea at baseline ($n = 28$), the rating of nausea decreased from 4.6 ± 1.3 at baseline to 2.6 ± 1.9 at the end-point ($p < 0.001$).

Kumar et al. present the descriptive results for a before-after trial including 30 patients treated with mirtazapine 7.5 mg daily for 15 days [34]. Anorexia was a secondary outcome reported using a single symptom scale. At baseline 10.3% of participants experienced mild anorexia, 41.4% moderate anorexia and 62.1% severe anorexia. At end-point, 23.3% did not experienced anorexia anymore, 62.1% experienced mild anorexia, 13.8% moderate anorexia, and none experienced severe anorexia.

Mellar et al. report a before-after trial including 57 patients treated with mirtazapine 15 mg daily (increased to 30 mg daily after 1 week) for 15 days. They assessed insomnia, nausea and

anxiety using the EORTC QLQ-C30 sub-scales and considered a response if the difference was over 1 point on the subscale. In intention to treat, insomnia and anxiety had a response rate of 33%.

Safety of mirtazapine's use in cancer populations

Only two studies included a validated tool to evaluate side effects or the toxicity of mirtazapine in their design [22, 35]. Additionally, one study reported outcomes about fatigue and drowsiness using a validated scale [21] and one about the clinical global impression [25].

One open-labelled study including 42 participants with a follow-up completion rate of 0.4 used the UKU side effect rating scale [22] which has been developed to assess and rate the side effects of psychotropic treatments [39]. It has not however been validated in cancer. In this study, authors report that sleepiness/sedation was experienced after introduction in 36% of subjects. However, sleepiness/sedation appeared to decrease over the time, 19% of patients experienced increased sedation after the seven first days of treatment but they were only 8% after 14 days and none continued to experience an increased sedation on day 28. When compared with baseline; at day 7, 19% had a worst sleepiness/sedation, they were and 8% on day 14 and 0% on day 28.

Additionally, 48% of patients already had sleepiness/sedation before the medication. Sixty percent of those patients improved sleepiness when compared with baseline.

A non-randomised experimental study used the Common Terminology Criteria for Adverse Events to report adverse effects during the study period [35]. This tool has been developed to assess the side effects of treatments in cancer populations [40]. In this study, the author reports 4 patients experiencing grade 3 toxicity in the first week, 4 with a grade 3 toxicity in the second week and 1 with a grade 4 toxicity in the second week.

An open-labelled study including 17 participants evaluated fatigue and drowsiness using the ESAS subscales [21]. Whilst it did not find any difference in drowsiness, the ESAS fatigue subscale had a median decrease of 3.5 points, corresponding to a clinically important difference.

Overall, among all patients receiving mirtazapine and for whom the studies report the number of side effects ($n = 192$) [19–22, 24, 35], the most frequent side-effect was the somnolence/drowsiness experienced by 48% of patients ($n = 25$). This concurs with the comments made in several studies reporting that sedation was the most important side-effect, responsible for the largest amount of withdrawals [18, 25]. The second most frequent side effect was dizziness which occurred in 13.4% ($n = 7$) of the participants. The next was fatigue, experienced by 9.6% ($n = 5$) of the patients, which was also supported by several comments found in the studies [17, 24]. After these symptoms, by order of frequency, patients reported delirium and xerostomia, weight gain, nausea, intentional tremor, restless legs, insomnia and blurred vision. Among all studies, the withdrawals were mostly reported to be unrelated to adverse events.

Overall, only a few patients treated with mirtazapine had side effects important enough to withdraw from a study. The most frequent side effects were somnolence/drowsiness, dizziness and fatigue.

Discussion

The studies presented in this review provide low level evidence for treating polysymptomatology, limited by sample size with a high risk of bias. It is therefore not possible to recommend the use of mirtazapine for multiple palliation. However, the results confirm the effectiveness of mirtazapine in psychiatric symptoms like depression and anxiety. They are also encouraging for its effectiveness in several other symptoms, in particular, the treatment of sleep disorders, pain and cancer-related emesis. These findings should inform future RCTs to better determine the effectiveness of mirtazapine in these symptoms.

Moreover, European populations are ageing and the problem of polypharmacy is now a main concern of geriatricians [41, 42]. With an ageing population, and cancer incidence increasing with age, we can expect a rise in the number of advanced cancer patients and palliative patients undergoing polypharmacy treatments. This represents a potential risk for safety as well as for the quality of life of these patients. A key to improving the management of ageing cancer populations would be to evaluate medications that decrease the risks related to polypharmacy whilst simultaneously improving quality of life and multiple symptoms [43]. Therefore, future RCTs should aim to determine the effectiveness of alleviating multiple symptoms and quality of life.

Whilst this review did not aim to assess the effectiveness of mirtazapine in improving quality of life, four studies evaluated this as a secondary outcome, and overall, they suggested an improvement in quality of life for patients taking mirtazapine [19, 21, 24, 35]. In addition, Van Gool et al.'s paper found an increase in the clinical global impression scale, which measures the perceived efficacy of the medication in improving the global clinical state of the patient. This improvement is suggestive of a treatment response and improvement in symptom severity. Global clinical improvement might also reflect an improvement in quality of life. It supports the importance of assessing the potential improvement in quality of life whilst using this medication to alleviate multiple symptoms.

Our findings suggest that mirtazapine could be of interest in alleviating symptoms strongly associated with depressive disorders, such as anxiety and sleep disorders [44]. The population of cancer patients is at high risk of psychiatric and sleep disorders [45, 46], and the use of mirtazapine to alleviate

more than one symptom could be a good alternative to multiple medications. However, effectiveness in treating these three symptoms might be explained through their categorisation as part of the same cluster of symptoms [47]. Therefore, experiencing one of these symptoms can have a worsening impact on the others [48]. For this reason, the effectiveness of mirtazapine in treating anxiety and sleep disorders could be an indirect consequence of a direct action on depressive disorders.

Regarding pain management, Nishihara's study results is informative for future research [17]. Despite a high risk of bias, the significant changes might reflect a benefit from mirtazapine in treating neuropathic pain. This effect on neuropathic pain could be of great interest in the cancer population. This population often experiences neuropathic pain, either because of a direct effect of the neoplasm or side effects of the treatments [49]. Moreover, chronic pain and especially chronic neuropathic pain are common risk factors for depressive disorders [50], and some authors suggest that, considering that they are part of the same symptom cluster, an improvement in neuropathic pain may lead to an improvement in sleep quality [51]. Therefore, the effectiveness of mirtazapine in chronic neuropathic pain management could be of interest in more ways than one by treating the underlying symptom cluster of pain-depression-sleep disorders. Serotonin noradrenaline reuptake inhibitors (SNRIs) are antidepressants approved to treat neuropathic pain. Their action on neuropathic pain is not fully understood; however, it might be mediated by enhancing serotonin and noradrenaline in the spinal and supraspinal structures [52]. Besides, tricyclic antidepressants are also approved in this indication. Like mirtazapine, tricyclic antidepressants inhibit serotonin and noradrenaline reuptake in the synapse, resulting in a central noradrenergic and serotoninergic neurotransmission increase [53]. These shared pharmacological pathways between mirtazapine and other medications licenced for treating neuropathic pain could explain the potential effectiveness of mirtazapine for this indication.

Mirtazapine may also be an interesting antidepressant to treat multiple symptoms because of its effects on appetite and weight [14]. Mirtazapine's side effects might be of great interest, particularly because malnutrition is a cause of treatment intolerance and shortens the life expectancy of advanced cancer patients [54]. For these reasons, mirtazapine may be the preferred option when treating depression in cancer patients. To date, evidence for the use of mirtazapine to improve weight gain and appetite is lacking but studies are currently ongoing to address this.

Another interesting symptom for which no treatment is licensed in Europe is breathlessness. Evidence is lacking to support the use of mirtazapine in alleviating breathlessness; however, some pilot studies have shown encouraging results in alleviating breathlessness in advanced lung disease conditions, including lung cancers [55]. Mirtazapine appears to be a promising candidate to pursue, but definitive randomized controlled trials are required to determine its efficacy and safety in this setting.

Limitations

Our review has several limitations. Whilst including grey literature, we cannot be certain that we have identified all studies. Some studies were excluded from the review because the data was not available. Publication bias is a common concern in interventional studies, especially in populations with life-threatening diseases, as many studies do not recruit or retain enough patients to have strong results, limiting their publication in peer-reviewed journals. Therefore, this review may have been impacted by publication bias. Additionally, we excluded studies that did not focus only on cancer patients. This decision was supported by the fact that most of these studies had "cancer-affected patients" as exclusion criteria. However, this choice potentially led to the neglect of relevant data.

Conclusion

Overall, there are limited studies which aim to assess the effectiveness of mirtazapine in alleviating multiple symptoms in the cancer population and no studies which assess the use of mirtazapine to treat polysymptomatology. The study designs are mostly too weak to support strong results and often only include a small sample size. However, these results should inform further large RCTs which are able to determine the effectiveness of mirtazapine in treating multiple symptoms in the cancer population.

Authors' contributions IJH had the original idea, supervised the design of the work, the acquisition and interpretation of the data and revised the article.

GE designed the protocol, acquired the data, interpreted the data and drafted the article.

NL acquired the data, interpreted the data and revised the article.

AJ interpreted the data and revised the article.

Funding information This systematic review has been funded by King's College London, the employer of the investigators.

Availability of data and material The datasets analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

References

1. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ (2010) Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. J Palliat Med 13:1109–1118. https://doi.org/10.1089/jpm.2010.0068
2. Kierner KA, Weixler D, Masel EK, Gartner V, Watzke HH (2016) Polypharmacy in the terminal stage of cancer. Support Care Cancer 24:2067–2074. https://doi.org/10.1007/s00520-015-3007-z
3. Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A (2007) Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manag 34:94–104. https://doi.org/10.1016/j.jpainsymman.2006.10.015
4. Currow DC, Abernethy AP, Allcroft P, Banzett RB, Bausewein C, Booth S, Carrieri-Kohlman V, Davidson P, Disler R, Donesky D, Dudgeon D, Ekstrom M, Farquhar M, Higginson I, Janssen D, Jensen D, Jolley C, Krajnik M, Laveneziana P, McDonald C, Maddocks M, Morelot-Panzini C, Moxham J, Mularski RA, Noble S, O'Donnell D, Parshall MB, Pattinson K, Phillips J, Ross J, Schwartzstein RM, Similowski T, Simon ST, Smith T, Wells A, Yates P, Yorke J, Johnson MJ (2016) The need to research refractory breathlessness. Eur Respir J 47:342–343. https://doi.org/10.1183/13993003.00653-2015
5. Davis MP, Khawam E, Pozuelo L, Lagman R (2002) Management of symptons associated with advanced cancer: olanzapine and mirtazapine. Expert Rev Anticancer Ther 2:365–376. https://doi.org/10.1586/14737140.2.4.365
6. Rougé Bugat M-E, Bourgouin M, Gérard S, Lozano S, Brechemier D, Cestac P, Cool C, Balardy L (2017) Drug prescription including interactions with anticancer treatments in the elderly: a global approach. J Nutr Health Aging 21:849–854. https://doi.org/10.1007/s12603-017-0946-8
7. Nightingale G, Skonecki E, Boparai MK (2017) The impact of polypharmacy on patient outcomes in older adults with cancer. Cancer J 23:211–218. https://doi.org/10.1097/PPO.0000000000000277
8. Lovell N, Ward J (2011) The role of mirtazapine in treating multiple symptoms in patients with cancer. Clin Focus Cancer Med 2:61–64
9. Kent JM (2000) SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. Lancet 355:911–918. https://doi.org/10.1016/S0140-6736(99)11381-3
10. Anttila SA, Leinonen EV (2001) A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev 7:249–264
11. Lovell N, Wilcock A, Bajwah S, Etkind SN, Jolley CJ, Maddocks M, Higginson IJ (2019) Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. Expert Rev Respir Med 13:173–180. https://doi.org/10.1080/17476348.2019.1563486
12. Zaini S, Guan NC, Sulaiman AH, Zainal NZ, Huri HZ, Shamsudin SH (2018) The use of antidepressants for physical and psychological symptoms in cancer. Curr Drug Targets 19:1431–1455. https://doi.org/10.2174/1389450119666180226125026
13. Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA (2016) The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother Psychosom 85:270–288. https://doi.org/10.1159/000447034
14. Biswas PN, Wilton LV, Shakir SAW (2003) The pharmacovigilance of mirtazapine: results of a prescription event monitoring study on 13 554 patients in England. J Psychopharmacol (Oxf) 17:121–126. https://doi.org/10.1177/0269881103017001716
15. Balshem H, Helfand M, Schunemann HJ et al (2011) GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015
16. Cankurtaran ES, Ozalp E, Soygur H, Akbiyik DI, Turhan L, Alkis N (2008) Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine. Support Care Cancer 16:1291–1298. https://doi.org/10.1007/s00520-008-0425-1
17. Nishihara M, Arai Y-CP, Yamamoto Y et al (2013) Combinations of low-dose antidepressants and low-dose pregabalin as useful adjuvants to opioids for intractable, painful bone metastases. Pain Phys 16:E547–E552
18. Cao J, Wang B, Wang Z et al (2018) Efficacy of mirtazapine in preventing delayed nausea and vomiting induced by highly emetogenic chemotherapy: an open-label, randomized, multicenter phase III trial. J Clin Oncol 36:1078–1078. https://doi.org/10.1200/JCO.2018.36.15_suppl.1078
19. Theobald DE, Kirsh KL, Holtsclaw E, Donaghy K, Passik SD (2002) An open-label, crossover trial of mirtazapine (15 and 30 mg) in cancer patients with pain and other distressing symptoms. J Pain Symptom Manag 23:442–447
20. Ersoy MA, Noyan AM, Elbi H (2008) An open-label long-term naturalistic study of mirtazapine treatment for depression in cancer patients. Clin Drug Investig 28:113–120. https://doi.org/10.2165/00044011-200828020-00005
21. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C (2010) Phase II trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Med 27:106–110. https://doi.org/10.1177/1049909109345685
22. Kim S-W, Shin I-S, Kim J-M, Kim YC, Kim KS, Kim KM, Yang SJ, Yoon JS (2008) Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression. Psychiatry Clin Neurosci 62:75–83. https://doi.org/10.1111/j.1440-1819.2007.01778.x
23. Ozsoy S, Besirli A, Unal D, Abdulrezzak U, Orhan O (2015) The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy. Gen Hosp Psychiatry 37:31–35. https://doi.org/10.1016/j.genhosppsych.2014.09.002
24. Raddin RS, Park EM, Hamer RM, Nelson KM, Mayer DK, Rosenstein DL, Bernard SA (2014) A pilot study to evaluate symptom-oriented selection of antidepressants in patients with cancer. J Palliat Med 17:167–175. https://doi.org/10.1089/jpm.2013.0412
25. Van Gool AR, Bannink M, Stronks DL, Vos MS (2003) Re: Mirtazapine in cancer patients. J Pain Symptom Manag 25:7–8
26. Farrar JT, Young JP, LaMoreaux L et al (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94:149–158. https://doi.org/10.1016/S0304-3959(01)00349-9
27. Farrar JT, Portenoy RK, Berlin JA et al (2000) Defining the clinically important difference in pain outcome measures. Pain 88:287–294. https://doi.org/10.1016/S0304-3959(00)00339-0

28. Hartung TJ, Friedrich M, Johansen C, Wittchen HU, Faller H, Koch U, Brähler E, Härter M, Keller M, Schulz H, Wegscheider K, Weis J, Mehnert A (2017) The hospital anxiety and depression scale (HADS) and the 9-item patient health questionnaire (PHQ-9) as screening instruments for depression in patients with cancer: depression screening in oncology. Cancer 123:4236–4243. https://doi.org/10.1002/cncr.30846
29. Vodermaier A, Millman RD (2011) Accuracy of the hospital anxiety and depression scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support Care Cancer 19:1899–1908. https://doi.org/10.1007/s00520-011-1251-4
30. Puhan MA, Frey M, Büchi S, Schünemann HJ (2008) The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. Health Qual Life Outcomes 6:46. https://doi.org/10.1186/1477-7525-6-46
31. Olden M, Rosenfeld B, Pessin H, Breitbart W (2009) Measuring depression at the end of life: is the Hamilton depression rating scale a valid instrument? Assessment 16:43–54. https://doi.org/10.1177/1073191108320415
32. Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, Monahan PO (2016) Patient health questionnaire anxiety and depression scale: initial validation in three clinical trials. Psychosom Med 78:716–727. https://doi.org/10.1097/PSY.0000000000000322
33. Lu T, Li Y, Pan J, Wu D (2013) Study on minimal important difference of the Pittsburgh sleep quality index based on clinical trial of traditional Chinese medicine. Chin J Integr Med
34. Kumar N, Barai S, Gambhir S, Rastogi N (2017) Effect of mirtazapine on gastric emptying in patients with cancer-associated anorexia. Indian J Palliat Care 23:335–337. https://doi.org/10.4103/IJPC.IJPC_17_17
35. Davis MP, Kirkova J, Lagman R, Walsh D, Karafa M (2011) Intolerance to mirtazapine in advanced cancer. J Pain Symptom Manag 42:e4–e7. https://doi.org/10.1016/j.jpainsymman.2011.05.002
36. Dugan W, McDonald MV, Passik SD, Rosenfeld BD, Theobald D, Edgerton S (1998) Use of the Zung self-rating depression scale in cancer patients: feasibility as a screening tool. Psychooncology 7:483–493. https://doi.org/10.1002/(SICI)1099-1611(199811/12)7:6<483::AID-PON326>3.0.CO;2-M
37. Zimmerman M, Posternak MA, Chelminski I (2005) Is the cutoff to define remission on the Hamilton rating scale for depression too high? J Nerv Ment Dis 193:170–175
38. Montgomery SA, Möller H-J (2009) Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Int Clin Psychopharmacol 24:111–118. https://doi.org/10.1097/YIC.0b013e32832a8eb2
39. Lingjærde O, Ahlfors UG, Bech P et al (1987) The UKU side effect rating scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand 76:1–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x
40. Trotti A, Colevas A, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN, Rubin P (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 13:176–181. https://doi.org/10.1016/S1053-4296(03)00031-6
41. Hajjar ER, Cafiero AC, Hanlon JT (2007) Polypharmacy in elderly patients. Am J Geriatr Pharmacother 5:345–351. https://doi.org/10.1016/j.amjopharm.2007.12.002
42. Wehling M (2011) Guideline-driven polypharmacy in elderly, multimorbid patients is basically flawed: there are almost no guidelines for these patients: letters to the editor. J Am Geriatr Soc 59:376–377. https://doi.org/10.1111/j.1532-5415.2011.03252.x
43. Rosini M (2014) Polypharmacology: the rise of multitarget drugs over combination therapies. Future Med Chem 6:485–487. https://doi.org/10.4155/fmc.14.25
44. Redeker NS, Lev EL, Ruggiero J (2000) Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. Sch Inq Nurs Pract 14:275–290 discussion 291-298
45. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR (2009) Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics 50:383–391. https://doi.org/10.1176/appi.psy.50.4.383
46. Otte JL, Carpenter JS, Manchanda S, Rand KL, Skaar TC, Weaver M, Chernyak Y, Zhong X, Igega C, Landis C (2015) Systematic review of sleep disorders in cancer patients: can the prevalence of sleep disorders be ascertained? Cancer Med 4:183–200. https://doi.org/10.1002/cam4.356
47. Fan G, Filipczak L, Chow E (2007) Symptom clusters in cancer patients: a review of the literature. Curr Oncol Tor Ont 14:173–179
48. Theobald DE (2004) Cancer pain, fatigue, distress, and insomnia in cancer patients. Clin Cornerstone 6:S15–S21. https://doi.org/10.1016/S1098-3597(05)80003-1
49. Fallon MT (2013) Neuropathic pain in cancer. Br J Anaesth 111:105–111. https://doi.org/10.1093/bja/aet208
50. Torta R, Ieraci V, Zizzi F (2017) A review of the emotional aspects of neuropathic pain: from comorbidity to co-pathogenesis. Pain Ther 6:11–17. https://doi.org/10.1007/s40122-017-0088-z
51. Enomoto T, Yamashita A, Torigoe K, Horiuchi H, Hirayama S, Nakahara K, Yanase M, Sakai H, Ikegami D, Nagase H, Suzuki T, Iseki M, Inada E, Narita M (2012) Effects of mirtazapine on sleep disturbance under neuropathic pain-like state. Synapse 66:483–488. https://doi.org/10.1002/syn.21532
52. Marks D, Shah M, Patkar A, Masand PS, Park GY, Pae CU (2009) Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. Curr Neuropharmacol 7:331–336. https://doi.org/10.2174/157015909790031201
53. Obata H (2017) Analgesic mechanisms of antidepressants for neuropathic pain. Int J Mol Sci 18:2483. https://doi.org/10.3390/ijms18112483
54. Argilés JM (2005) Cancer-associated malnutrition. Eur J Oncol Nurs 9:S39–S50. https://doi.org/10.1016/j.ejon.2005.09.006
55. ISRCTN - ISRCTN32236160: Better treatments for refractory breathlessness. http://www.isrctn.com/ISRCTN32236160. Accessed 25 Apr 2019

Appendix 12 -Patient information sheets

Leeds Institute of Clinical Trials Research

An Academic Health Sciences Centre for London

Pioneering better health for all

Delete this line, then print on Trust/Hospital headed paper or add logo

BETTER-B

BETTER-B (Feasibility):

BETTER TREATMENTS FOR REFRACTORY BREATHLESSNESS

Participant Information Sheet

A large-print version of this leaflet is available on request.

REC Reference: 16/LO/0091

We would like to invite you to take part in our research trial called "BETTER-B (Feasibility)".

Joining the trial is entirely up to you. Before you decide, we would like you to know why the research is being done, what it will involve for you and how we will use the information we have about you. Please read through this booklet carefully and discuss with others if you wish. If **anything** is not clear, or if you would like more information, please ask the researcher or doctor.

Once you have read this information, your <<enter Consultant, Doctor, Nurse, Researcher>> will talk to you about the trial again and you can ask any questions you like.

Take time to decide whether or not you wish to take part.

Thank you

What is the purpose of the trial?

Breathlessness is a common symptom affecting most people with cancer and non-cancer lung diseases. Even when all the causes for breathlessness are treated, breathlessness often continues; when this happens it is called "refractory" breathlessness. This can be very distressing, causes fear and panic, reduces quality of life, including social life, and can result in emergency hospital admissions.

There are few treatments for refractory breathlessness that have been proven to work. Morphine can help some people, but other treatments are needed. Because breathlessness causes anxiety, which in turn makes breathlessness worse, people have tried anti-anxiety drugs, but a recent review of trials found no evidence that these work.

In this BETTER-B (Feasibility) trial we are testing a drug called mirtazapine. Mirtazapine is a commonly used antidepressant. It is also used for panic and anxiety. It affects a brain chemical called serotonin, which is active when people are breathless. Reports involving small numbers of patients suggest that mirtazapine may help breathlessness. It also might help because it reduces panic. Mirtazapine is a drug used commonly in the UK to treat depression and anxiety and doctors are familiar with its use.

Before we can conduct a big trial to see if Mirtazapine helps breathlessness, we need to know whether such a big trial is possible to do. This trial is a preliminary trial to test the feasibility of a big trial. We plan to recruit 60 patients over 12 months from approximately three hospitals in the UK. We will find out two things. Firstly, are the trial methods and the trial drug acceptable to those participating and will enough people be prepared to take part? Secondly, how effective might mirtazapine be in treating breathlessness?

Why have I been invited to take part?

You have been invited to take part in the BETTER-B (Feasibility) trial because you have been diagnosed with either cancer or non-cancer lung or heart disease and still have problems with breathlessness despite having received treatment. The BETTER-B researcher will look at the information provided about you to ensure you meet the criteria for taking part in the trial.

Do I have to take part?

No. It is up to you to decide whether or not to take part in the trial. **Your decision will make no difference to your usual treatment and care.** If you decide to take part you are free to withdraw at any time without giving a reason. **This will not affect your usual care.**

If you decide not to take part, your <<enter Consultant, Doctor, Nurse >> will be happy to talk through alternative options. Your treatment and care will not be affected in any way.

If I want to, will I definitely be able to take part?

Unfortunately, no. Although the BETTER-B researcher thinks you might be suitable to take part, they will still need to carry out some tests and ask you some questions to make sure you are suitable. These are known as "eligibility" or "screening" assessments. If the eligibility/screening assessments show that it is not appropriate for you to take part in BETTER-B (Feasibility), your <<enter Consultant, Doctor, Nurse >> will discuss your alternative treatment options with you.

What will happen next?

If you decide to take part, you will be given this booklet to keep and asked to sign a consent form. A copy of the consent form will be put in your medical notes, a copy kept by the research team and a copy sent to the Clinical Trials Research Unit (CTRU) in Leeds. We will let your GP know and will keep them informed of your participating in this trial.

The best way of finding out whether mirtazapine helps people with refractory breathlessness is by comparing mirtazapine to a placebo (or dummy-drug) in a randomised trial. "Randomised" means that a computer will allocate you randomly (as if by the roll of dice) to receive either mirtazapine or a placebo.

After your initial assessment, a computer will assign you by chance to one of these two groups. Based on this, you will either be prescribed mirtazapine or a placebo. Neither you, nor your doctor will choose which treatment you receive.

What is the placebo?

The placebo capsule is a "dummy-drug" which looks the same as the mirtazapine capsules, but does not actually contain any mirtazapine. It is made up of lactose powder and a gelatine capsule.

Will I be told if I am having mirtazapine or the placebo?

No, neither you, nor your doctor will know if you are receiving mirtazapine or placebo. However, if you have any problems whilst receiving your treatment, your doctor will be able to find out which treatment you are receiving if this is important to know for your care.

What do I have to do if I decide take part?

If your screening tests confirm that you are able to enter the trial then you will be able to take part. The BETTER-B research team will then ask you some more questions. These are called the "baseline" assessments.

After these "baseline" assessments, you will be prescribed 28 days of the trial drug (either mirtazapine or placebo). The trial drug will be given to you as capsules and you should take one capsule every day at night time before going to bed. The capsules can be taken with or without food.

The capsules are made from bovine gelatine – these may not be suitable for you if you are a vegetarian.

If your breathlessness has not improved after 14 days the dose will be increased (to 2 capsules every day) for the remaining 14 days of your treatment. Otherwise you will continue on the same dose (one capsule) for the full 28 days of your treatment.

You should avoid alcohol whilst you are on treatment. The trial drug may also make you drowsy, so you should avoid any dangerous tasks which need you to be alert such as driving or operating heavy machinery if you are affected. You should also let the trial team know if you start to take any new medication at any point during the trial.

During your time on treatment, the BETTER-B research team will contact you a further five times and ask you some questions about your breathlessness and do some tests (blood pressure and blood oxygen levels). You will also be asked to complete some questionnaires; the research team can help you complete these, or complete them on

your behalf if you prefer. This will help us understand how your breathlessness changes over time.

- Day 7 of treatment – the research team will ask you some questions over the phone.
- Day 14 of treatment – the research team will see you in person, ask you some questions and do some tests. You will also be asked to complete a questionnaire pack. This can be in a place of your choice, for example at home or at the hospital.
- Day 21 of treatment – the research team will ask you some questions over the phone.
- Day 28 of treatment – the research team will see you in person, ask you some questions and do some tests (e.g. blood pressure and blood oxygen levels). You will also be asked to complete a questionnaire pack. This can be in a place of your choice, for example at home or at the hospital.
- Follow-up 7 days after you stop taking the trial drug (either mirtazapine or placebo) – the research team will ask you some questions over the phone.

If you decide to go to the hospital to see the research team on days 14 and 28, you will be reimbursed for reasonable travel expenses if you wish.

Additional research

A small number of people will be invited to talk more about their experiences in this trial. If you are chosen to be part of this group, the BETTER-B researcher will invite you to have a separate interview. This will be audio-recorded. This interview can be conducted in a place of your choice and will last around 45-60 minutes.

You can choose to end the interview at any time and not to answer any questions you don't want to.

If you would be happy to be approached for such an interview, there is an optional section on the trial consent form for you to complete. If you do not wish to be approached for these interviews, then you can still take part in the BETTER-B (Feasibility) trial.

Will the research benefit me?

The trial is designed to understand if this drug can benefit people with breathlessness. We don't know if mirtazapine will benefit you or not. By taking part you will be helping us to answer that question and we believe this will help people with conditions such as yours in the future.

Are there downsides to taking part?

Mirtazapine is a commonly used medication for depression. It has been tolerated well in patients with a wide range of illnesses, but there are some side effects. The most common are drowsiness, which usually settles over a few days, and an increased appetite with weight gain, dry mouth and headaches (1 in 10 patients experience these); patients may also experience jaundice.

Taking part in the trial will also involve time commitments for seeing and talking to the BETTER-B researcher, and completing questionnaires (the research team can help with this, or complete them on your behalf if you prefer). This can be done at your home or another location of your choice if this is easiest for you.

The trial drug might harm an unborn baby; therefore you should not take part in this trial if you are pregnant. You should not become pregnant during the trial treatment period or for a safety period of at least 7 days after taking your last trial treatment capsule. If you are a woman who may become pregnant, you will be asked to take a pregnancy test before taking part in the study and at the end of the study. You must also agree to use a reliable form of effective contraception during this time. If you do become pregnant during the trial, or you find out after you have finished treatment, then you must tell the trial research team at once. Your doctor will advise you on the potential risks to your unborn child and the options available to you.

What will happen if I decide to stop being in the trial?

If you withdraw consent for taking further trial medication, information will still be collected about you and will be included in the trial results, unless you request otherwise. If you withdraw consent for further data collection your data already collected will remain on file and will be included in the results. The BETTER-B trial team may need to collect some limited information about side effects you may have as a result of taking part in the trial. This will only be collected if required by the Regulatory Authorities.

At the end of the trial we are required to store you data securely for a minimum of 15 years. They will then be destroyed confidentially.

Care after the trial treatment has stopped

At the end of your participation in the trial you will remain under the care of your routine clinical team. At the completion of the trial a formal letter will be sent to you thanking you for your participation and offering you the opportunity to receive further information about the outcome of the trial.

If whilst participating in the trial you decide the medication has helped your symptoms, you can discuss this with the research team and ask them to contact your GP to see if s/he is happy for you to take mirtazapine outside of the trial.

Will my taking part in this trial be kept confidential?

If you decide to participate in BETTER-B (Feasibility) the information collected about you will be handled in accordance with the consent that you have given and also the 1998 Data Protection Act. Your hospital notes will however, be reviewed by representatives of the Sponsor and Regulatory Authorities and Clinical Trials Unit (CTRU) in Leeds. By signing the consent form you will be giving us permission to do this.

The information needed for trial purposes will be collected on paper forms and sent (usually using standard Royal Mail post but in some cases by fax or email) from the hospital to the Clinical Trials Research Unit (CTRU) in Leeds. You will be allocated a trial number, which will be used along with your date of birth and initials to identify you on each paper form. Your full name will be included on your consent form and a copy of this will be sent to the CTRU by fax, post or email. Every effort will be made to ensure that any further information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it; this information will usually be removed by a member of the trial team at your hospital, but may also be removed by the CTRU upon receipt.

Your data will be entered onto a secure database held at the CTRU in accordance with the 1998 Data Protection Act.

The information collected about you may also be shared with other research teams to answer new research questions in the future. Wherever possible, information will be anonymised (for example; your full name will not be disclosed).

What will happen to the results of the trial?

The findings from the trial will be used to help improve care for people with breathlessness. We hope the results will be made available to other health care professionals by a series of articles published in medical journals. None of the participants will be identifiable in these articles. If you would like to obtain a copy of the published results, please ask your trial researcher.

We will also produce a short summary of the trial results at the end of the trial and the BETTER-B research team can send this to you if you wish.

What if new information becomes available?

Sometimes during a trial new information becomes available. If this happens the researcher will discuss it with you. It may mean the trial finishes or you decide to stop participating in the trial. If you decide not to continue your <<enter Consultant, Doctor, Nurse >> will continue your care if this is necessary. If you decide to continue you may be asked to sign an updated consent form. Occasionally on receiving new information, the researcher may consider it to be in your best interest to withdraw you from further trial treatment.

Who is organising and supervising this trial, who has funded it and who has reviewed it?

The Chief Investigator is Professor Irene Higginson who is based at the Cicely Saunders Institute at King's College London. She is a medical consultant. This trial is being sponsored jointly by King's College London and King's College Hospital NHS Foundation Trust and is being organised on their behalf by the Clinical Trials Research Unit (CTRU) at the University of Leeds. It is supported by a grant from Marie Curie. All research is looked at by an independent committee of people called a Research Ethics Committee, to protect your interests. This trial has been reviewed and approved by London Central Research Ethics Committee.

If I have more questions, who can I ask?

Please feel free to ask your <<enter Consultant, Doctor, Nurse >>or the researcher any question about the trial. Contact details can be found on the last page on this booklet.

If you have any concerns:

Every care will be taken in the course of this clinical trial and we do not expect anything to go wrong but if you are harmed by taking part in this trial there are no special compensation arrangements. However, in the unlikely event that you are injured as a result of the managing organisation (University of Leeds), compensation may be available and you may have to pay your related legal costs.

This trial is co-sponsored by the King's College Hospital NHS Foundation Trust and King's College London. The Sponsor will at all times maintain adequate insurance in relation to the trial. The College through its own professional indemnity (Clinical Trials) and no fault compensation and the Trust having a duty of care to patients via NHS indemnity cover in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a trial patient.

Your hospital where you receive your treatment has a duty of care to you whether or not you agree to participate in the trial and the University of Leeds and Sponsors accept no liability for negligence on the part of your hospital's employees.

Any claims will be subject to UK law and must be brought in the UK. If you have private medical insurance, you should tell your insurer that you are taking part in research. They will let you know if it affects your policy.

Complaints

Regardless of this, if you wish to complain, or have concerns about any aspect of the way you have been approached or treated during the course of this trial the normal National Health Service complaints mechanisms should be available to you. Your <<enter Consultant, Doctor, Nurse >> will give you further information if necessary. If you are unhappy about anything to do with this research and wish to complain formally, you can do this at the Patient Advice and Liaison Service (PALS) at: XXXXXXXXXXXXX.

Contact details for the Researcher:

Name: <<enter>>

Telephone: <<enter>>

Email: <<enter>>

If you have any further questions about your illness or clinical trials, please discuss them with your <<enter Consultant, Doctor, Nurse >>. If you would like further information about clinical research, the UK Clinical Research Collaboration (a partnership of organisations working together on clinical research in the UK) have published a booklet entitled 'Understanding Clinical Trials'. Contact UKCRC: Tel: 0207 670 5452; website www.ukcrc.org

Thank you very much for taking the time to read this booklet.

Leeds Institute of Clinical Trials Research

An Academic Health Sciences Centre for London

Pioneering better health for all

Delete this line, then print on Trust/Hospital headed paper or add logo

BETTER-B

BETTER-B (Feasibility):
BETTER TREATMENTS FOR REFRACTORY BREATHLESSNESS:
Qualitative Interview Sub-study
(Main Trial Participants)

Participant Information Sheet

A large-print version of this leaflet is available on request.

REC no.: 16/LO/0091

You are invited to take part in a research sub-study which is interested in how patients perceive participation in clinical trials and their experiences of receiving information relating to the trial. Before you decide whether or not you want to be involved it is important for you to understand why the research is being done and what it will involve. We would be grateful if you would take the time to read this information sheet. Please ask us if there is anything that is not clear to you or if you would like more information.

Please take time to decide whether or not you wish to take part.

Thank you!

How to contact us
If you have any questions about this study, please talk to your *<enter consultant, doctor, nurse, researcher>* at
<<Enter PI, nurse name >>
<< Contact details for site>>

What is the purpose of the sub-study?

The main purpose of this sub-study is to explore patient's reasons for deciding to take part, or declining to take part, in the BETTER-B (Feasibility) trial. We recognise that there are different reasons that patients take part or decline. We are interested in why you made the choice you did, as this will help inform us how we deliver and design future research trials.

You have the right not to tell us why you chose to take part or declined to take part, however if you are happy to, we would be grateful if you would share your reasons with us. This is so that the research team can better understand your feelings about this trial, the recruitment process, the information provided to patients and the question the trial is trying to answer. The research team want to understand any concerns you have about this trial in order to help them improve their methods of recruiting patients in future trials. This information will help to ensure that the trial is discussed with patients in the most suitable, understandable and appropriate way.

Why have I been approached to take part in the sub-study?

You have been invited to take part in this sub-study as you have been identified as someone who has been offered information about the BETTER-B (Feasibility) trial.

What will happen to me if I take part?

If you agree to take part, you will be interviewed by a researcher from <Insert name of recruiting trial site>. You can choose to be interviewed face-to-face or over the phone. The interview is likely to take 45-60 minutes and will be digitally audio-recorded, with your permission. We will also ask you for your views about the BETTER-B (Feasibility) clinical trial, such as how we might present information to patients, how to reduce any difficulties taking part might have on patients, and what encouraged you or put you off taking part in this and other trials.

Will I be paid for taking part?

You will not be paid for taking part in this study, but we can reimburse you for reasonable travel expenses.

Do I have to take part?

Participation in this sub-study is entirely voluntary. You may refuse to take part and you do not have to tell the researchers why you do not want to take part. If you decide to take part you can choose to drop out at any time. If you agree to take part but during the interview you feel tired, or worried, you can stop the interview at any time – you don't have to give any explanation. If you decide not to take part, or decide to withdraw later on, the treatment and standard of care you receive and any of your legal rights will not be affected in any way.

Will my taking part be confidential?

If you agree to be interviewed, everything that you say will be kept confidential and the information collected about you will be handled strictly in accordance with the 1998 Data Protection Act. Any information about you will be stored securely at <enter recruiting site name> and at King's College London, where the sub-study Researcher is based. All interviews will be transcribed (writing down what has been said in the interview). While the interview is being typed up any personal details will be anonymised so your identity is protected. The recording of the interview will be destroyed after the data are analysed. The transcript of the interview will be stored securely for at least 15 years, in accordance with the rules of the Sponsor.

Some patients may discuss situations or potential tensions with doctors or nurses, and you may still be seeing these doctors/nurses as part of your ongoing treatment. In order to prevent identifying you from such circumstances and events, we will summarise the findings so you will not be identifiable. We may later discuss such events in academic papers, but in all cases, including these, we will use pseudonyms and anonymised accounts to protect your identity.

Even though we will protect your confidentiality at all times we do have a duty of care toward you. This means that if a researcher believes that you might be a danger to yourself (e.g. you are thinking about harming yourself) or others, we are obliged to alert appropriate services.

Your interview details may be inspected by authorised individuals from the research team, the Sponsors or Regulatory Authorities to ensure that the sub-study is being carried out correctly.

What will happen to the findings of this sub-study?

The sub-study will take 12 months to complete. The findings of the sub-study will be analysed by the sub-study Researcher and we hope they will inform a future large trial looking at the use of mirtazapine for refractory breathlessness. We also plan to present the results at academic conferences and publish the results in academic journals. This will help other health professionals learn more about how best to approach and present clinical trials to potential participants. A summary of the results will also be available to patient organisations. If you would like to obtain a copy of the results, please let the researchers know.

Who is organising and funding the study?

This sub-study is part of the BETTER-B (Feasibility) trial, which is funded by Marie Curie and co-sponsored by King's College London and King's College Hospital NHS Foundation Trust. The sub-study has been reviewed and approved by the National Research Ethics Committee16/LO/0091.

Contacts for further Information:

If you want further information about this sub-study please contact:

Name: <<enter>>

Telephone: <<enter>>

Email: <<enter>>

Thank you for taking the time to read this and if you do decide to take part, we very much appreciate your involvement.

Leeds Institute of Clinical Trials Research

An Academic Health Sciences Centre for London

Pioneering better health for all

Delete this line, then print on Trust/Hospital headed paper or add logo

BETTER-B

BETTER-B (Feasibility):
BETTER TREATMENTS FOR REFRACTORY BREATHLESSNESS:
Qualitative Interview Sub-study
(Main Trial Decliners)

Participant Information Sheet

A large-print version of this leaflet is available on request.

REC no.: 16/LO/0091

You are invited to take part in a research sub-study which is interested in how patients perceive participation in clinical trials and their experiences of receiving information relating to the trial. Before you decide whether or not you want to be involved it is important for you to understand why the research is being done and what it will involve. We would be grateful if you would take the time to read this information sheet. Please ask us if there is anything that is not clear to you or if you would like more information.

Please take time to decide whether or not you wish to take part.

Thank you!

How to contact us
If you have any questions about this study, please talk to your *<enter consultant, doctor, nurse, researcher>* at
<<Enter PI, nurse name >>
<< Contact details for site>>

What is the purpose of the sub-study?

The main purpose of this sub-study is to explore patient's reasons for deciding to take part, or declining to take part, in the BETTER-B (Feasibility) trial. We recognise that there are different reasons that patients take part or decline. We are interested in why you made the choice you did, as this will help inform us how we deliver and design future research trials.

You have the right not to tell us why you chose to take part or declined to take part, however if you are happy to, we would be grateful if you would share your reasons with us. This is so that the research team can better understand your feelings about this trial, the recruitment process, the information provided to patients and the question the trial is trying to answer. The research team want to understand any concerns you have about this trial in order to help them improve their methods of recruiting patients in future trials. This information will help to ensure that the trial is discussed with patients in the most suitable, understandable and appropriate way.

Why have I been approached to take part in the sub-study?

You have been invited to take part in this sub-study as you have been identified as someone who has been offered information about the BETTER-B (Feasibility) trial.

What will happen to me if I take part?

If you agree to take part, you will be interviewed by a researcher from <Insert name of recruiting trial site>. You can choose to be interviewed face-to-face or over the phone. The interview is likely to take 10-15 minutes and will be digitally audio-recorded, with your permission. We will also ask you for your views about the BETTER-B (Feasibility) clinical trial, such as how we might present information to patients, how to reduce any difficulties taking part might have on patients, and what encouraged you or put you off taking part in this and other trials.

Will I be paid for taking part?

You will not be paid for taking part in this study, but we can reimburse you for reasonable travel expenses.

Do I have to take part?

Participation in this sub-study is entirely voluntary. You may refuse to take part and you do not have to tell the researchers why you do not want to take part. If you decide to take part you can choose to drop out at any time. If you agree to take part but during the interview you feel tired, or worried, you can stop the interview at any time – you don't have to give any explanation. If you decide not to take part, or decide to withdraw later on, the treatment and standard of care you receive and any of your legal rights will not be affected in any way.

Will my taking part be confidential?

If you agree to be interviewed, everything that you say will be kept confidential and the information collected about you will be handled strictly in accordance with the 1998 Data Protection Act. Any information about you will be stored securely at <enter recruiting site name> and at King's College London, where the sub-study Researcher is based. All interviews will be transcribed (writing down what has been said in the interview). While the interview is being typed up any personal details will be anonymised so your identity is protected. The recording of the interview will be destroyed after the data are analysed. The transcript of the interview will be stored securely for at least 15 years, in accordance with the rules of the Sponsor.

Some patients may discuss situations or potential tensions with doctors or nurses, and you may still be seeing these doctors/nurses as part of your ongoing treatment. In order to prevent identifying you from such circumstances and events, we will summarise the findings so you will not be identifiable. We may later discuss such events in academic papers, but in all cases, including these, we will use pseudonyms and anonymised accounts to protect your identity.

Even though we will protect your confidentiality at all times we do have a duty of care toward you. This means that if a researcher believes that you might be a danger to yourself (e.g. you are thinking about harming yourself) or others, we are obliged to alert appropriate services.

Your interview details may be inspected by authorised individuals from the research team, the Sponsors or Regulatory Authorities to ensure that the sub-study is being carried out correctly.

What will happen to the findings of this sub-study?

The sub-study will take 12 months to complete. The findings of the sub-study will be analysed by the sub-study Researcher and we hope they will inform a future large trial looking at the use of mirtazapine for refractory breathlessness. We also plan to present the results at academic conferences and publish the results in academic journals. This will help other health professionals learn more about how best to approach and present clinical trials to potential participants. A summary of the results will also be available to patient organisations. If you would like to obtain a copy of the results, please let the researchers know.

Who is organising and funding the study?

This sub-study is part of the BETTER-B (Feasibility) trial, which is funded by Marie Curie and co-sponsored by King's College London and King's College Hospital NHS Foundation Trust. The sub-study has been reviewed and approved by the National Research Ethics Committee16/LO/0091.

Contacts for further Information:

If you want further information about this sub-study please contact:

Name: <<enter>>

Telephone: <<enter>>

Email: <<enter>>

Thank you for taking the time to read this and if you do decide to take part, we very much appreciate your involvement.

References

1. Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, 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(4):435-52.
2. Booth S, Bausewein C, Higginson I, Moosavi SH. Pharmacological treatment of refractory breathlessness. Expert Rev Respir Med. 2009;3(1):21-36.
3. Johnson MJ, Yorke J, Hansen-Flaschen J, Lansing R, Ekstrom M, Similowski T, et al. Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness. Eur Respir J. 2017;49(5).
4. Currow DC, Plummer JL, Crockett A, Abernethy AP. A community population survey of prevalence and severity of dyspnea in adults. J Pain Symptom Manage. 2009;38(4):533-45.
5. Moens K, Higginson IJ, Harding R. 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(4):660-77.
6. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. J Pain Symptom Manage. 2006;31(1):58-69.
7. Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Patel A, et al. Specialist palliative care is more than drugs: a retrospective study of ILD patients. Lung. 2012;190(2):215-20.
8. Currow DC, Smith J, Davidson PM, Newton PJ, Agar MR, Abernethy AP. 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(4):680-90.
9. Ekstrom M, Allingham SF, Eagar K, Yates P, Johnson C, Currow DC. Breathlessness During the Last Week of Life in Palliative Care: An Australian Prospective, Longitudinal Study. J Pain Symptom Manage. 2016;51(5):816-23.
10. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. Journal of Clinical Oncology. 2011;29(9):1151-8.
11. Bausewein C, Booth S, Gysels M, Kühnbach R, Haberland B, Higginson IJ. Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. Palliative Medicine. 2010;24(8):777-86.
12. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. BMC Palliat Care. 2011;10:15.
13. Currow DC, Dal Grande E, Ferreira D, Johnson MJ, McCaffrey N, Ekstrom M. Chronic breathlessness associated with poorer physical and mental health-related quality of life (SF-12) across all adult age groups. Thorax. 2017;72(12):1151-3.
14. Janssen DJ, Wouters EF, Spruit MA. Psychosocial consequences of living with breathlessness due to advanced disease. Curr Opin Support Palliat Care. 2015;9(3):232-7.
15. Gysels MH, Higginson IJ. Caring for a person in advanced illness and suffering from breathlessness at home: threats and resources. Palliat Support Care. 2009;7(2):153-62.
16. Malik FA, Gysels M, Higginson IJ. Living with breathlessness: a survey of caregivers of breathless patients with lung cancer or heart failure. Palliat Med. 2013;27(7):647-56.
17. Reddy SK, Parsons HA, Elsayem A, Palmer JL, Bruera E. Characteristics and correlates of dyspnea in patients with advanced cancer. Journal of palliative medicine. 2009;12(1):29-36.
18. Simon ST, Weingartner V, Higginson IJ, Voltz R, Bausewein C. Definition, categorization, and terminology of episodic breathlessness: consensus by an international Delphi survey. J Pain Symptom Manage. 2014;47(5):828-38.

19. Hutchinson A, Pickering A, Williams P, Bland JM, Johnson MJ. Breathlessness and presentation to the emergency department: a survey and clinical record review. BMC Pulm Med. 2017;17(1):53.
20. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015(2):Cd003793.
21. Bausewein C, Booth S, Gysels M, Higginson IJ. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database of Systematic Reviews. 2013(11).
22. Bouca-Machado R, Rosario M, Alarcao J, Correia-Guedes L, Abreu D, Ferreira JJ. Clinical trials in palliative care: a systematic review of their methodological characteristics and of the quality of their reporting. BMC Palliat Care. 2017;16(1):10.
23. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer. 2013;119(5):1098-105.
24. Smith AK, Currow DC, Abernethy AP, Johnson MJ, Miao Y, Boscardin WJ, et al. Prevalence and Outcomes of Breathlessness in Older Adults: A National Population Study. J Am Geriatr Soc. 2016;64(10):2035-41.
25. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988;93(3):580-6.
26. Mullerova H, Lu C, Li H, Tabberer M. Prevalence and burden of breathlessness in patients with chronic obstructive pulmonary disease managed in primary care. PLoS One. 2014;9(1):e85540.
27. Bausewein C, Booth S, Gysels M, Kuhnbach R, Haberland B, Higginson IJ. Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. J Palliat Med. 2010;13(9):1109-18.
28. Farquhar M, Penfold C, Benson J, Lovick R, Mahadeva R, Howson S, et al. Six key topics informal carers of patients with breathlessness in advanced disease want to learn about and why: MRC phase I study to inform an educational intervention. PLoS One. 2017;12(5):e0177081.
29. Goodridge D, Lawson J, Duggleby W, Marciniuk D, Rennie D, Stang M. Health care utilization of patients with chronic obstructive pulmonary disease and lung cancer in the last 12 months of life. Respir Med. 2008;102(6):885-91.
30. Booth S, Moosavi SH, Higginson IJ. The etiology and management of intractable breathlessness in patients with advanced cancer: a systematic review of pharmacological therapy. Nat Clin Pract Oncol. 2008;5(2):90-100.
31. Currow D, Johnson M, White P, Abernethy A. Evidence-based intervention for chronic refractory breathlessness: practical therapies that make a difference. Br J Gen Pract. 2013;63(616):609-10.
32. Bowden JA, To TH, Abernethy AP, Currow DC. Predictors of chronic breathlessness: a large population study. BMC Public Health. 2011;11:33.
33. Simon ST, Bausewein C, Schildmann E, Higginson IJ, Magnussen H, Scheve C, et al. Episodic breathlessness in patients with advanced disease: a systematic review. J Pain Symptom Manage. 2013;45(3):561-78.
34. Simon ST, Higginson IJ, Benalia H, Gysels M, Murtagh FE, Spicer J, et al. Episodic and continuous breathlessness: a new categorization of breathlessness. J Pain Symptom Manage. 2013;45(6):1019-29.
35. Horton R, Rocker G. Contemporary issues in refractory dyspnoea in advanced chronic obstructive pulmonary disease. Curr Opin Support Palliat Care. 2010;4(2):56-62.

36. Currow DC, Quinn S, Greene A, Bull J, Johnson MJ, Abernethy AP. The longitudinal pattern of response when morphine is used to treat chronic refractory dyspnea. J Palliat Med. 2013;16(8):881-6.
37. Johnson MJ, Currow DC. Chronic refractory breathlessness is a distinct clinical syndrome. Curr Opin Support Palliat Care. 2015;9(3):203-5.
38. Simon ST, Higginson IJ, Benalia H, Gysels M, Murtagh FE, Spicer J, et al. Episodes of breathlessness: types and patterns - a qualitative study exploring experiences of patients with advanced diseases. Palliat Med. 2013;27(6):524-32.
39. Mercadante S. Episodic Breathlessness in Patients with Advanced Cancer: Characteristics and Management. Drugs. 2018, Feb 22, e-publication ahead of print.
40. Mercadante S, Fusco F, Caruselli A, Cartoni C, Masedu F, Valenti M, et al. Background and episodic breathlessness in advanced cancer patients followed at home. Curr Med Res Opin. 2017;33(1):155-60.
41. Linde P, Hanke G, Voltz R, Simon ST. Unpredictable episodic breathlessness in patients with advanced chronic obstructive pulmonary disease and lung cancer: a qualitative study. Support Care Cancer. 2018;26(4):1097-104.
42. Moxham J, Jolley C. Breathlessness, fatigue and the respiratory muscles. Clinical medicine. 2009;9(5):448-52.
43. Jolley CJ, Moxham J. A physiological model of patient-reported breathlessness during daily activities in COPD. Eur Respir Rev. 2009;18(112):66-79.
44. Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. Neuroscience & Biobehavioral Reviews. 2017;74:185-203.
45. Pattinson KT, Johnson MJ. Neuroimaging of central breathlessness mechanisms. Curr Opin Support Palliat Care. 2014;8(3):225-33.
46. von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, et al. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. Am J Respir Crit Care Med. 2008;177(9):1026-32.
47. Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJ, Adams L. Breathlessness in humans activates insular cortex. Neuroreport. 2000;11(10):2117-20.
48. Peiffer C, Costes N, Herve P, Garcia-Larrea L. Relief of dyspnea involves a characteristic brain activation and a specific quality of sensation. Am J Respir Crit Care Med. 2008;177(4):440-9.
49. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, 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(12):979-87.
50. Brown TM, Hernandez AF, Bittner V, Cannon CP, Ellrodt G, Liang L, et al. Predictors of cardiac rehabilitation referral in coronary artery disease patients: findings from the American Heart Association's Get With The Guidelines Program. Journal of the American College of Cardiology. 2009;54(6):515-21.
51. Maddocks M, Kon SS, Canavan JL, Jones SE, Nolan CM, Labey A, et al. Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax. 2016;71(11):988-95.
52. Taylor DR, Murray SA. Improving quality of care for end-stage respiratory disease: Changes in attitude, changes in service. Chron Respir Dis. 2018;15(1):19-25.
53. Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE, 2nd, Marcello J, 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(9743):784-93.
54. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database Syst Rev. 2016;10:Cd007354.

55. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev. 2016;3:Cd011008.
56. Ekstrom M, Bajwah S, Bland JM, Currow DC, Hussain J, Johnson MJ. One evidence base; three stories: do opioids relieve chronic breathlessness? Thorax. 2018;73(1):88-90.
57. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. J Pain Symptom Manage. 2011;42(3):388-99.
58. Rocker G, Bourbeau J, Downar J. The New "Opioid Crisis": Scientific Bias, Media Attention, and Potential Harms for Patients with Refractory Dyspnea. J Palliat Med. 2018;21(2):120-2.
59. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols J, Datla S, Dirksen CD, Johnson MJ, et al. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. Eur Respir J. 2017;50(5).
60. Young J, Donahue M, Farquhar M, Simpson C, Rocker G. Using opioids to treat dyspnea in advanced COPD: attitudes and experiences of family physicians and respiratory therapists. Can Fam Physician. 2012;58(7):e401-7.
61. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Opioids for chronic refractory breathlessness: patient predictors of beneficial response. Eur Respir J. 2013;42(3):758-66.
62. Papp LA, Weiss JR, Greenberg HE, Rifkin A, Scharf SM, Gorman JM, et al. Sertraline for chronic obstructive pulmonary disease and comorbid anxiety and mood disorders. Am J Psychiatry. 1995;152(10):1531.
63. Smoller JW, Pollack MH, Systrom D, Kradin RL. Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics. 1998;39(1):24-9.
64. Currow DC, Ekstrom M, Louw S, Hill J, Fazekas B, Clark K, et al. Sertraline in symptomatic chronic breathlessness: a double blind, randomised trial. Eur Respir J. 2019;53(1).
65. Tank AW, Lee Wong D. Peripheral and central effects of circulating catecholamines. Compr Physiol. 2015;5(1):1-15.
66. Edmonds P, Karlsen S, Khan S, Addington-Hall J. A comparison of the palliative care needs of patients dying from chronic respiratory diseases and lung cancer. Palliat Med. 2001;15(4):287-95.
67. Donabedian A. The Definition of Quality and Approaches to Its Assessment [= Explorations in Quality Assessment and Monitoring, vol. 1]. Ann Arbor: Health Administration Press. 1980:8-11.
68. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. Jama. 2002;288(23):3027-34.
69. Fitzpatrick R, Davey C, Buxton MJ, Jones DR. Evaluating patient-based outcome measures for use in clinical trials. 1998.
70. Evans CJ, Benalia H, Preston NJ, Grande G, Gysels M, Short V, et al. The selection and use of outcome measures in palliative and end-of-life care research: the MORECare International Consensus Workshop. J Pain Symptom Manage. 2013;46(6):925-37.
71. Bausewein C, Farquhar M, Booth S, Gysels M, Higginson IJ. Measurement of breathlessness in advanced disease: a systematic review. Respir Med. 2007;101(3):399-410.
72. Dorman S, Jolley C, Abernethy A, Currow D, Johnson M, Farquhar M, et al. Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. Palliat Med. 2009;23(3):213-27.
73. Gift AG, Narsavage G. Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care. 1998;7(3):200-4.

74. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabilitation Nursing. 1989;14(6):323-5.
75. Borg GA. Psychophysical bases of perceived exertion. Med sci sports exerc. 1982;14(5):377-81.
76. Banzett RB, O'Donnell CR, Guilfoyle TE, Parshall MB, Schwartzstein RM, Meek PM, et al. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. European Respiratory Journal. 2015;45(6):1681-91.
77. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax. 1987;42(10):773-8.
78. Banzett RB, Moosavi SH. Measuring dyspnoea: new multidimensional instruments to match our 21st century understanding. Eur Respir J. 2017;49(3).
79. Williams MT, Johnston KN. Multidimensional measurement of breathlessness: recent advances. Curr Opin Support Palliat Care. 2019;13(3):184-92.
80. Bajwah S, Higginson IJ, Ross JR, Wells AU, Birring SS, Riley J, et al. The palliative care needs for fibrotic interstitial lung disease: a qualitative study of patients, informal caregivers and health professionals. Palliat Med. 2013;27(9):869-76.
81. Barnett M. Chronic obstructive pulmonary disease: a phenomenological study of patients' experiences. J Clin Nurs. 2005;14(7):805-12.
82. Duck A, Spencer LG, Bailey S, Leonard C, Ormes J, Caress AL. Perceptions, experiences and needs of patients with idiopathic pulmonary fibrosis. J Adv Nurs. 2015;71(5):1055-65.
83. Gysels M, Higginson IJ. Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. J Pain Symptom Manage. 2008;36(5):451-60.
84. Hasson F, Spence A, Waldron M, Kernohan G, McLaughlin D, Watson B, et al. I can not get a breath: experiences of living with advanced chronic obstructive pulmonary disease. International journal of palliative nursing. 2008;14(11):526-31.
85. Lai Y, Chan CW, Lopez V. Perceptions of dyspnea and helpful interventions during the advanced stage of lung cancer: Chinese patients' perspectives. Cancer Nursing. 2007;30(2):E1-E8.
86. Booth S, Silvester S, Todd C. Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. Palliat Support Care. 2003;1(4):337-44.
87. Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. Control and Context Are Central for People With Advanced Illness Experiencing Breathlessness: A Systematic Review and Thematic Synthesis. J Pain Symptom Manage. 2019;57(1):140-55.e2.
88. Higginson IJ, Evans CJ, Grande G, Preston N, Morgan M, McCrone P, et al. Evaluating complex interventions in end of life care: the MORECare statement on good practice generated by a synthesis of transparent expert consultations and systematic reviews. BMC Med. 2013;11:111.
89. Boland J, Currow DC, Wilcock A, Tieman J, Hussain JA, Pitsillides C, et al. A systematic review of strategies used to increase recruitment of people with cancer or organ failure into clinical trials: implications for palliative care research. J Pain Symptom Manage. 2015;49(4):762-72.e5.
90. Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. BMJ Support Palliat Care. 2013;3(3):318-23.
91. Rinck GC, van den Bos GA, Kleijnen J, de Haes HJ, Schade E, Veenhof CH. Methodologic issues in effectiveness research on palliative cancer care: a systematic review. J Clin Oncol. 1997;15(4):1697-707.

92. Hanson LC, Bull J, Wessell K, Massie L, Bennett RE, Kutner JS, et al. Strategies to support recruitment of patients with life-limiting illness for research: the Palliative Care Research Cooperative Group. J Pain Symptom Manage. 2014;48(6):1021-30.
93. Ewing G, Rogers M, Barclay S, McCabe J, Martin A, Todd C. Recruiting patients into a primary care based study of palliative care: why is it so difficult? Palliat Med. 2004;18(5):452-9.
94. McWhinney IR, Bass MJ, Donner A. Evaluation of a palliative care service: problems and pitfalls. Bmj. 1994;309(6965):1340-2.
95. Jordhoy MS, Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. Palliat Med. 1999;13(4):299-310.
96. Kearney A, Daykin A, Shaw ARG, Lane AJ, Blazeby JM, Clarke M, et al. Identifying research priorities for effective retention strategies in clinical trials. Trials. 2017;18(1):406.
97. Tudur Smith C, Hickey H, Clarke M, Blazeby J, Williamson P. The trials methodological research agenda: results from a priority setting exercise. Trials. 2014;15:32.
98. Brunsdon D, Biesty L, Brocklehurst P, Brueton V, Devane D, Elliott J, et al. What are the most important unanswered research questions in trial retention? A James Lind Alliance Priority Setting Partnership: the PRioRiTy II (Prioritising Retention in Randomised Trials) study. Trials. 2019;20(1):593.
99. Hussain JA, Bland M, Langan D, Johnson MJ, Currow DC, White IR. Quality of missing data reporting and handling in palliative care trials demonstrates that further development of the CONSORT statement is required: a systematic review. J Clin Epidemiol. 2017;88:81-91.
100. Skea ZC, Newlands R, Gillies K. Exploring non-retention in clinical trials: a meta-ethnographic synthesis of studies reporting participant reasons for drop out. BMJ Open. 2019;9(6):e021959.
101. Higginson IJ. Research challenges in palliative and end of life care. BMJ Support Palliat Care. 2016;6(1):2-4.
102. Visser C, Hadley G, Wee B. Reality of evidence-based practice in palliative care. Cancer Biol Med. 2015;12(3):193-200.
103. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract. 2004;10(2):307-12.
104. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. BMC Med Res Methodol. 2010;10:67.
105. Lancaster GA. Pilot and feasibility studies come of age! Pilot Feasibility Stud. 2015;1(1):1.
106. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10.
107. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Hewison J. What can qualitative research do for randomised controlled trials? A systematic mapping review. BMJ Open. 2013;3(6).
108. Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. Bmj. 2002;325(7367):766-70.
109. Creswell JW, Clark VLP. Designing and conducting mixed methods research: Sage publications; 2017.
110. Tashakkori A, Teddlie C. Sage handbook of mixed methods in social & behavioral research: sage; 2010.
111. O'Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: a mixed methods study. BMC Health Serv Res. 2007;7:85.

112. Greene JC. Is mixed methods social inquiry a distinctive methodology? Journal of mixed methods research. 2008;2(1):7-22.
113. Leech NL, Onwuegbuzie AJ. A typology of mixed methods research designs. Quality & Quantity. 2009;43(2):265-75.
114. Seymour J. Combined qualitative and quantitative research designs. Curr Opin Support Palliat Care. 2012;6(4):514-24.
115. O'Cathain A, Hoddinott P, Lewin S, Thomas KJ, Young B, Adamson J, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. Pilot Feasibility Stud. 2015;1:32.
116. Hussain JA, White IR, Langan D, Johnson MJ, Currow DC, Torgerson DJ, et al. Missing data in randomized controlled trials testing palliative interventions pose a significant risk of bias and loss of power: a systematic review and meta-analyses. J Clin Epidemiol. 2016;74:57-65.
117. Daveson BA, de Wolf-Linder S, Witt J, Newson K, Morris C, Higginson IJ, et al. Results of a transparent expert consultation on patient and public involvement in palliative care research. Palliat Med. 2015;29(10):939-49.
118. Price A, Albarqouni L, Kirkpatrick J, Clarke M, Liew SM, Roberts N, et al. Patient and public involvement in the design of clinical trials: An overview of systematic reviews. J Eval Clin Pract. 2018;24(1):240-53.
119. Crocker JC, Ricci-Cabello I, Parker A, Hirst JA, Chant A, Petit-Zeman S, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. Bmj. 2018;363:k4738.
120. Gysels MH, Evans C, Higginson IJ. Patient, caregiver, health professional and researcher views and experiences of participating in research at the end of life: a critical interpretive synthesis of the literature. BMC Med Res Methodol. 2012;12:123.
121. Browne RH. On the use of a pilot sample for sample size determination. Stat Med. 1995;14(17):1933-40.
122. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative research in psychology. 2006;3(2):77-101.
123. Komulainen E, Heikkila R, Meskanen K, Raij TT, Nummenmaa L, Lahti J, et al. A single dose of mirtazapine attenuates neural responses to self-referential processing. J Psychopharmacol. 2016;30(1):23-32.
124. Komulainen E, Glerean E, Meskanen K, Heikkila R, Nummenmaa L, Raij TT, et al. Single dose of mirtazapine modulates whole-brain functional connectivity during emotional narrative processing. Psychiatry Res Neuroimaging. 2017;263:61-9.
125. Ekstrom M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. Cochrane Database Syst Rev. 2016;11:Cd006429.
126. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010;10:1.
127. Higginson IJ, Wilcock A, Johnson MJ, Bajwah S, Lovell N, Yi D, et al. Randomised, double-blind, multicentre, mixed-methods, dose-escalation feasibility trial of mirtazapine for better treatment of severe breathlessness in advanced lung disease (BETTER-B feasibility). Thorax. 2020.
128. Fallon M, Hoskin PJ, Colvin LA, Fleetwood-Walker SM, Adamson D, Byrne A, et al. Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain. J Clin Oncol. 2016;34(6):550-6.
129. Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle. 2017;8(5):778-88.

130. Spathis A, Fife K, Blackhall F, Dutton S, Bahadori R, Wharton R, et al. Modafinil for the Treatment of Fatigue in Lung Cancer: Results of a Placebo-Controlled, Double-Blind, Randomized Trial. Journal of Clinical Oncology. 2014;32(18):1882-8.
131. Dorman S, Byrne A, Edwards A. Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. Palliat Med. 2007;21(3):177-91.
132. Johnson MJ, Oxberry SG, Cleland JG, Clark AL. Measurement of breathlessness in clinical trials in patients with chronic heart failure: the need for a standardized approach: a systematic review. Eur J Heart Fail. 2010;12(2):137-47.
133. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open. 2017;7(3):e015276.
134. Abernethy AP, Wheeler JL. Total dyspnoea. Curr Opin Support Palliat Care. 2008;2(2):110-3.
135. Clark D. 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958-1967. Soc Sci Med. 1999;49(6):727-36.
136. Ekstrom M, Currow DC, Johnson MJ. Outcome measurement of refractory breathlessness: endpoints and important differences. Curr Opin Support Palliat Care. 2015;9(3):238-43.
137. Williams JE, Singh SJ, Sewell L, Guyatt GH, Morgan MD. Development of a self-reported Chronic Respiratory Questionnaire (CRQ-SR). Thorax. 2001;56(12):954-9.
138. Lovell N, Etkind SN, Bajwah S, Maddocks M, Higginson IJ. To What Extent Do the NRS and CRQ Capture Change in Patients' Experience of Breathlessness in Advanced Disease? Findings From a Mixed-Methods Double-Blind Randomized Feasibility Trial. J Pain Symptom Manage. 2019;58(3):369-81.e7.
139. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik Hals EK, et al. Assessment of pain. British Journal of Anaesthesia. 2008;101(1):17-24.
140. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.
141. Atkinson TM, Rosenfeld BD, Sit L, Mendoza TR, Fruscione M, Lavene D, et al. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). J Pain Symptom Manage. 2011;41(3):558-65.
142. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med. 1994;330(9):592-6.
143. Cleeland CS, Nakamura Y, Mendoza TR, Edwards KR, Douglas J, Serlin RC. Dimensions of the impact of cancer pain in a four country sample: new information from multidimensional scaling. Pain. 1996;67(2-3):267-73.
144. Mendoza T, Mayne T, Rublee D, Cleeland C. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. Eur J Pain. 2006;10(4):353-61.
145. Atkinson TM, Mendoza TR, Sit L, Passik S, Scher HI, Cleeland C, 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(3):337-46.
146. Gelhorn HL, Eremenco S, Skalicky AM, Balantac Z, Cimms T, Halling K, et al. Content validity and ePRO usability of the BPI-sf and "worst pain" item with pleural and peritoneal mesothelioma. J Patient Rep Outcomes. 2017;2(1):16.
147. Bergh I, Jakobsson E, Sjostrom B. Worst experiences of pain and conceptions of worst pain imaginable among nursing students. J Adv Nurs. 2008;61(5):484-91.

148. Albers G, Echteld MA, de Vet HC, Onwuteaka-Philipsen BD, van der Linden MH, Deliens L. Evaluation of quality-of-life measures for use in palliative care: a systematic review. Palliat Med. 2010;24(1):17-37.
149. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Bmj. 2010;340:c332.
150. Wilson C, Rooshenas L, Paramasivan S, Elliott D, Jepson M, Strong S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. Trials. 2018;19(1):50.
151. Currow D, Louw S, Mccloud P, Fazekas B, Plummer J, Mcdonald C, et al. Regular extended release morphine for chronic breathlessness: a multi-centre double-blind RCT. European Respiratory Journal. 2018;52(suppl 62):OA1624.
152. Currow D, Louw S, McCloud P, Fazekas B, Plummer J, McDonald CF, et al. Regular, sustained-release morphine for chronic breathlessness: a multicentre, double-blind, randomised, placebo-controlled trial. Thorax. 2020;75(1):50-6.
153. Ferreira DH, Louw S, McCloud P, Fazekas B, McDonald CF, Agar MR, et al. Controlled-Release Oxycodone vs. Placebo in the Treatment of Chronic Breathlessness—A Multisite Randomized Placebo Controlled Trial. Journal of Pain and Symptom Management. 2019.
154. White C, Hardy J. Gatekeeping from palliative care research trials. Progress in Palliative Care. 2008;16(4):167-71.
155. Ross C, Cornbleet M. Atitudes of patients and staff to research in a specialist palliative care unit. Palliative Medicine. 2003;17(6):491-7.
156. Kars MC, van Thiel GJ, van der Graaf R, Moors M, de Graeff A, van Delden JJ. A systematic review of reasons for gatekeeping in palliative care research. Palliat Med. 2016;30(6):533-48.
157. Biedrzycki BA. Decision making for cancer clinical trial participation: a systematic review. Oncol Nurs Forum. 2010;37(6):E387-99.
158. Biedrzycki BA. Factors and outcomes of decision making for cancer clinical trial participation. Oncol Nurs Forum. 2011;38(5):542-52.
159. White CD, Hardy JR, Gilshenan KS, Charles MA, Pinkerton CR. Randomised controlled trials of palliative care - a survey of the views of advanced cancer patients and their relatives. Eur J Cancer. 2008;44(13):1820-8.
160. Gysels M, Shipman C, Higginson IJ. "I will do it if it will help others:" motivations among patients taking part in qualitative studies in palliative care. J Pain Symptom Manage. 2008;35(4):347-55.
161. Jenkins VA, Fallowfield LJ. For the Benefit of Others: Reasons Why Women with Breast Cancer Participate in RCTs. Breast Care (Basel). 2015;10(2):88-93.
162. Moorcraft SY, Marriott C, Peckitt C, Cunningham D, Chau I, Starling N, et al. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. Trials. 2016;17(1):17.
163. Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, et al. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. Trials. 2014;15:399.
164. Johnston B, Smith LN. Nurses' and patients' perceptions of expert palliative nursing care. J Adv Nurs. 2006;54(6):700-9.
165. Chhatre S, Jefferson A, Cook R, Meeker CR, Kim JH, Hartz KM, et al. Patient-centered recruitment and retention for a randomized controlled study. Trials. 2018;19(1):205.
166. Department of Health. Attributing the costs of health and social care Research & Development (AcoRD). 2012.

167. Daykin A, Clement C, Gamble C, Kearney A, Blazeby J, Clarke M, et al. 'Recruitment, recruitment, recruitment' - the need for more focus on retention: a qualitative study of five trials. Trials. 2018;19(1):76.
168. Brueton VC, Tierney J, Stenning S, Harding S, Meredith S, Nazareth I, et al. Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews. 2013(12).
169. Kane PM, Murtagh FE, Ryan K, Mahon NG, McAdam B, McQuillan R, et al. The gap between policy and practice: a systematic review of patient-centred care interventions in chronic heart failure. Heart Fail Rev. 2015;20(6):673-87.
170. Burton CD, Entwistle VA, Elliott AM, Krucien N, Porteous T, Ryan M. The value of different aspects of person-centred care: a series of discrete choice experiments in people with long-term conditions. BMJ Open. 2017;7(4):e015689.
171. Chenoweth L, Forbes I, Fleming R, King MT, Stein-Parbury J, Luscombe G, et al. PerCEN: a cluster randomized controlled trial of person-centered residential care and environment for people with dementia. Int Psychogeriatr. 2014;26(7):1147-60.
172. Wan M, Orlu-Gul M, Legay H, Tuleu C. Blinding in pharmacological trials: the devil is in the details. Arch Dis Child. 2013;98(9):656-9.
173. Anderson C, Kirkpatrick S, Ridge D, Kokanovic R, Tanner C. Starting antidepressant use: a qualitative synthesis of UK and Australian data. BMJ Open. 2015;5(12):e008636.
174. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007(4):Cd005454.
175. Lovell N, Wilcock A, Bajwah S, Etkind SN, Jolley CJ, Maddocks M, et al. Mirtazapine for chronic breathlessness? A review of mechanistic insights and therapeutic potential. Expert Rev Respir Med. 2019;13(2):173-80.
176. Economos G, Lovell N, Johnston A, Higginson IJ. What is the evidence for mirtazapine in treating cancer-related symptomatology? A systematic review. Supportive Care in Cancer. 2019.
177. Kwon JH, Kim MJ, Bruera S, Park M, Bruera E, Hui D. Off-Label Medication Use in the Inpatient Palliative Care Unit. J Pain Symptom Manage. 2017;54(1):46-54.
178. Carel H. Breathlessness: the rift between objective measurement and subjective experience. The Lancet Respiratory Medicine. 2018;6(5):332-3.
179. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Goode J, Hewison J. Maximising the value of combining qualitative research and randomised controlled trials in health research: the QUAlitative Research in Trials (QUART) study--a mixed methods study. Health Technol Assess. 2014;18(38):1-197, v-vi.
180. Eborall HC, Stewart MC, Cunningham-Burley S, Price JF, Fowkes FG. Accrual and drop out in a primary prevention randomised controlled trial: qualitative study. Trials. 2011;12:7.
181. Shilling V, Williamson PR, Hickey H, Sowden E, Smyth RL, Young B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. Health Technol Assess. 2011;15(15):1-116.
182. O'Cathain A, Murphy E, Nicholl J. Three techniques for integrating data in mixed methods studies. Bmj. 2010;341:c4587.
183. Richards DA, Bazeley P, Borglin G, Craig P, Emsley R, Frost J, et al. Integrating quantitative and qualitative data and findings when undertaking randomised controlled trials. BMJ Open. 2019;9(11):e032081.
184. Cooper C, O'Cathain A, Hind D, Adamson J, Lawton J, Baird W. Conducting qualitative research within Clinical Trials Units: avoiding potential pitfalls. Contemp Clin Trials. 2014;38(2):338-43.
185. Reid CM, Gooberman-Hill R, Hanks GW. Opioid analgesics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. Ann Oncol. 2008;19(1):44-8.

186. Whyte WF. Learning from the field. A guide from experience. London: Sage; 1984 1984//.
187. Guillemin M, Heggen K. Rapport and respect: negotiating ethical relations between researcher and participant. Medicine, Health Care and Philosophy. 2009;12(3):291-9.
188. Latkin CA, Mai NV, Ha TV, Sripaipan T, Zelaya C, Le Minh N, et al. Social Desirability Response Bias and Other Factors That May Influence Self-Reports of Substance Use and HIV Risk Behaviors: A Qualitative Study of Drug Users in Vietnam. AIDS Educ Prev. 2016;28(5):417-25.
189. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: challenges and potential solutions. Curr Med Res Opin. 2009;25(4):929-42.
190. Murray SA, Kendall M, Carduff E, Worth A, Harris FM, Lloyd A, et al. Use of serial qualitative interviews to understand patients' evolving experiences and needs. BMJ. 2009;339:b3702.
191. Noble H, Smith J. Issues of validity and reliability in qualitative research. Evidence Based Nursing. 2015;18(2):34-5.
192. Lovell N, Etkind, S., Johnston, A.,. Can you hear anxiety? 2020 [Available from: https://london.sciencegallery.com/blog/can-you-hear-anxiety.
193. Mitchell S, Tan A, Moine S, Dale J, Murray SA. Primary palliative care needs urgent attention. Bmj. 2019;365:l1827.
194. Johnson M. Morphine and BrEathLessness trial (MABEL) 2019 [Available from: http://www.isrctn.com/ISRCTN87329095.
195. Dimbleby C. BETTER-B: Better treatments for persistent breathlessness 2019 [Available from: http://www.isrctn.com/ISRCTN10487976.
196. Bone AE, Gomes B, Etkind SN, Verne J, Murtagh FEM, Evans CJ, et al. What is the impact of population ageing on the future provision of end-of-life care? Population-based projections of place of death. Palliat Med. 2018;32(2):329-36.
197. Finucane AM, Bone AE, Evans CJ, Gomes B, Meade R, Higginson IJ, et al. The impact of population ageing on end-of-life care in Scotland: projections of place of death and recommendations for future service provision. BMC Palliat Care. 2019;18(1):112.
198. Etkind SN, Bone AE, Gomes B, Lovell N, Evans CJ, Higginson IJ, et al. How many people will need palliative care in 2040? Past trends, future projections and implications for services. BMC Med. 2017;15(1):102.
199. Gysels M, Evans CJ, Lewis P, Speck P, Benalia H, Preston NJ, et al. MORECare research methods guidance development: recommendations for ethical issues in palliative and end-of-life care research. Palliat Med. 2013;27(10):908-17.
200. Farquhar M, Preston N, Evans CJ, Grande G, Short V, Benalia H, et al. Mixed methods research in the development and evaluation of complex interventions in palliative and end-of-life care: report on the MORECare consensus exercise. J Palliat Med. 2013;16(12):1550-60.