A preliminary investigation of the hand-held fan and the Calming Hand for the management of chronic refractory breathlessness in patients with advanced malignant and non-malignant diseases.

Short title Non-pharmacological interventions for chronic refractory breathlessness

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Abstract

Background Chronic breathlessness is a devastating symptom of advanced cardio-respiratory diseases, with extensive consequences for patients and their family carers. Despite optimal management of the underlying disease, problems may persist. Non-pharmacological interventions such as the hand-held fan and the Calming Hand may offer benefits, however there is little supportive evidence.

Aim To gain preliminary data about the effectiveness of the hand-held fan and the Calming Hand for the management of exertion-induced breathlessness in people with chronic breathlessness.

Methods Mixed method study with integrated findings; Systematic literature review and meta-analyses of airflow; feasibility 2x2 factorial, randomised controlled trial of the hand-held fan and/or Calming Hand for the relief of exertion-induced acute-on-chronic breathlessness. Qualitative interviews of patients and carers.

Findings Review findings indicate that airflow delivered from the hand-held fan at rest provides discernible breathlessness relief. The "2x2 factorial, pragmatic phase II trial of the Calming Hand and hand-held fan was feasible in terms of recruitment, data completion and trial acceptability. These preliminary results supported use of the fan for exertion-induced breathlessness including for time and rate of recovery after exertion-induced breathlessness. Qualitative data indicated that faster recovery improved patient self-efficacy and confidence. Patients identified the fan as a helpful "medical" device that played a useful role as part of a complex intervention for breathlessness. Conversely, there was little indication from quantitative or qualitative data to signal worthwhile benefit from the Calming Hand. The best candidate primary outcome measure was judged to be recovery rate or recovery time from exertion-induced breathlessness.

Conclusion A future definitive trial is feasible to assess the benefits of the hand-held fan with exertion induced breathlessness. Breathlessness recovery rate and the recovery time are novel outcomes that may potentially reflect important patient improvements with exercise. The

hand-held fan represents a tool that helps to promote patient self-mastery of breathlessness. These data do not support the use of the Calming Hand.

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Author Declaration

"I confirm that this work is original and that if any passage (s) or diagram (S) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference (s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised".

Publications, presentations and prizes

Publication

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Chapter 1 Introduction to breathlessness

1.1 Background

Breathlessness is a devastating symptom at the end stage of cardio-respiratory diseases. It can be frightening and disabling for both the patient and the carer, intruding on their quality of life, psychological well-being and social functioning (1). Palliative approaches still have limited impact on breathlessness intensity (2), but even an apparently incremental improvement such as a 1 point change in a 0 to 10 numerical rating scale (0 = no breathlessness; 10 = worst possible breathlessness) can be discerned by patients as relevant (3, 4).

Research into breathlessness historically focused on breathlessness as a single dimensional symptom. This approach has changed over the last 30 years with the understanding that breathlessness shared the same multi-dimensional qualities as pain including a distinct affective component (5). A multi-factorial programme was developed for the management of breathlessness to target the different dimensions of the symptom using a mixture of non-pharmacological and pharmacological interventions (6, 7). The use of a combination of different interventions as part of a complex multi-factorial approach to breathlessness management is supported by randomised controlled trial evidence (7-9), although the contribution from individual components is not always known.

1.2 Definition

1.2.1 Breathlessness and dyspnoea

The most widely accepted definition of breathlessness, medically known as dyspnoea, from the American Thoracic Society (ATS) consensus statement is:

> "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, that derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses" (10).

The terms breathlessness and dyspnoea have both frequently been used as inter-changeable in clinical practice and the research literature to describe the symptomatic discomfort of breathing. However, more recently, it has been suggested that the medical word dyspnoea, although intended to refer to the patient-reported symptom of breathlessness may be used in practice more as a clinician-observed physical sign, while the term "breathlessness" may better encompass the individual personal experience (11). Therefore, the term breathlessness will be adopted throughout the text to describe and embrace all the factors that contribute to the patient's experience of the symptom.

1.2.2 Definitions of breathlessness

Chronic breathlessness has been variably defined within a time context as breathlessness which persists on a daily basis for longer than a month (12), or for at least three out of the last six months (13). In this thesis, the term, chronic is taken to mean breathlessness that lasts for longer than one month. Refractory breathlessness is defined as breathlessness that remains despite the optimal management of the underlying causal condition and full attention to all possible reversible complications of the condition (14).

1.3 Prevalence

Breathlessness is a very common symptom in patients with severe chronic obstructive pulmonary disease and other non-malignant lung diseases, (15) advanced cancer, and the end-stages of heart or renal failure (16). Breathlessness worsens with advanced disease (17), and may represent a core component of the symptomatology experienced by patients with palliative needs (16). A similar conclusion was reached in a cross sectional study of symptom burden and palliative care needs in chronic obstructive pulmonary disease (COPD) and cancer, which identified comparable prevalence of breathlessness and other individual symptoms (18). Further, the vast majority (97%) of COPD patients ranked shortness of breath as the most prevalent symptom (18). This is consistent with previous work that found 95% breathlessness prevalence in people with COPD (16). Prevalence in people with cancer ranges between 49% in all cancer types (19), to nearly 90% of people just prior to death due to lung cancer (20). It is also important to note that breathlessness may be a result of cancer cachexia, even in those with no lung involvement. Fatigue and weakness of the muscles of ventilation and lower limb muscle deconditioning may all perpetuate breathlessness (21). A

similar picture is also found with other diseases; end stage heart and renal failure presenting with a prevalence estimated to be as high as 88% and 62% respectively (16). These studies demonstrate that patients with breathlessness, irrespective of diagnosis or disease stage, represent a group with a high symptom burden, frequently experienced over years due to extended survival (18).

An epidemiological study in Australia, found that nearly 10% of the community-based population had chronic breathlessness, with chronicity defined as experiencing breathlessness for most days for more than three months in the last six months (22). Within this population group, multivariate analysis found a strong association between breathlessness and the elderly, and a prevalence of 16.9% in the over 65 years old category suggesting, that breathlessness becomes more of a significant problem as people age (22). Figures from Health Survey for England (HSE), 2010 indicate an even higher prevalence (23). Breathlessness was measured with the Medical Research Council (MRC) dyspnoea scale (24) and defined as breathlessness experienced in the last 12 months. The data identified that 21% of men and 28% of women were breathlessness when not doing strenuous exercise, and 15% of men and 23% of women were graded two to five on the MRC breathlessness scale indicating that there was some impact on their ability to take exercise (23). The MRC dyspnoea scale is an assessment tool that categorises breathlessness in relation to activity (24), and is displayed in Table 1.

Table 1 Medical Research Council Dyspnoea Scale (24)

1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or walking up a slight hill
3	Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
4	Stops for breath after about 100 m or after a few minutes on the level
5	Too breathless to leave the house, or breathless when dressing or undressing

The significant association between age and breathlessness is of particular interest, as populations all over the world are aging with those in the over 60 years category increasing faster than any other group (25). This indicates that breathlessness represents a serious and potentially worsening problem for the future, as a cumulative incidence of breathlessness occurs, correlating to growing numbers in an aging population, and proportionally higher figures experiencing chronic diseases associated with an increased longevity. A final complication is that patients suffer an even greater risk of becoming breathless in the terminal stage of many diseases, therefore, many patients could experience the symptom before death occurs and when there is little chance of improvement from disease modifying treatments (16, 20).

1.4 Causes of breathlessness

The causes of breathlessness are numerous both in malignant and non-malignant advanced diseases. For example, in cancer the causes may be directly related to the disease; such as ascites, airway obstruction by tumour, or indirectly from the manifestations of problems such as cachexia, anaemia, or potentially resulting from the side-effects of chemotherapy, surgical or radiation treatment. The causes of breathlessness in cancer have been categorised with a list of over 20 different aetiologies for malignancy and a further ten identified as unrelated to cancer such as COPD, pneumothorax and anxiety (19). These causes are listed in Table 2;

Table 2 Causes of breathlessness due to diseases and complications of diseases (19)

Breathlessness directly due to cancer	**Breathlessness unrelated to cancer**
Pulmonary Parenchymal involvement (primary or metastatic) Lymphangitic carcinomatosis Intrinsic or extrinsic airway obstruction by tumour Pleural effusion Pleural tumour Pericardial effusion Ascites Hepatomegaly Phrenic nerve paralysis Multiple tumour micro emboli Pulmonary leukostasis Superior vena cava syndrome	Chronic Obstructive Pulmonary Disease Asthma Congestive heart failure Interstitial lung disease Pneumothorax Anxiety Chest wall deformity Obesity Neuromuscular disorders Pulmonary vascular disease
Breathlessness indirectly due to cancer	**Breathlessness due to cancer treatment**
Cachexia Electrolyte Abnormalities Anaemia Pneumonia Pulmonary aspiration Pulmonary emboli Neurologic Paraneoplastic syndromes	Surgery Radiation pneumonitis/fibrosis Radiation-induced pericardial disease Chemotherapy-induced pulmonary disease Chemotherapy-induced cardiomyopathy

This demonstrates that a multitude of causes may drive a patient's breathlessness and contribute to the complex underlying mechanisms that could be operating during the experience of breathlessness. The updated ATS consensus statement on the management of breathlessness highlights the numerous neurophysiological mechanisms both peripheral and central involved in the perception of breathlessness (26). This, in addition to the diversity of the different disease group processes, potential treatment side effects, or other co-morbidities makes the unravelling of a patient's breathlessness problem and the mechanisms at play an inherently difficult clinical task to assess and manage effectively.

1.4.1 Central mechanisms of breathlessness

The neurophysiological understanding of the central mechanisms of breathlessness has grown out of the concept that breathlessness comprises of multiple distinct and measurable dimensions or components (5).

1.4.2 Total breathlessness

The idea that there are at least two distinct dimensions of breathlessness, a sensory intensity and an affective unpleasantness has drawn authors to suggest similarities and an analogy with pain (5). *"Total breathlessness"* was proposed, a new conceptual model where similar to *"total pain"* the sensation and experience of breathlessness is described as embracing physical, psychological, social, and spiritual domains (27).

The concept is supported by the evidence emerging from neuroimaging studies investigating changes in blood flow to different regions of the brain in response to breathlessness. A recent updated consensus statement from the ATS identifies a sufficiently common theme in the results of these neuroimaging studies, despite the limitations to interpretation of cerebral blood flow, to conclude that breathlessness activates both cortical and sub-cortical central pathways, similar to, and overlapping with, the associated homeostatic responses seen during pain, thirst, fear or hunger (26).

Neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have specifically identified the amygdala, the right anterior insula, the prefrontal cortex and the dorsal anterior cingulate cortex (dACC) as key regions activated in both pain and breathlessness (28-30). The amygdala is known as the "hub of fear" and along with the dACC and anterior insula are associated as a centre responsible for the processing of fear, threat or danger related responses (31). This indicates that the sensations of breathlessness are processed by an important threat and emotion-related network and consequently these signals can be negatively interpreted by the patient resulting in adaptive behaviour. This could subsequently compromise how well the patient self-manages their symptoms, influence the perceived benefit of the different interventions used, or it could provide the motivation to seek medical help during a breathless episode.

The respiratory pattern generator also appears to be modifiable in response to continued respiratory threat. Breathing demands central adaptive solutions to accommodate longer lasting disturbances such as the physical changes associated with cardio-pulmonary diseases (32). Serotonin has been proposed as the driving element in several models of respiratory neuroplasticity (33, 34). Any increase in the ventilation rate that lasts over one hour produced by episodic hypoxia appears to be dependent on a serotonin central neural mechanism (35-37). The main central sources of sensation involved in breathlessness are listed in Table 3.

1.4.3 Model of breathlessness

The application of a common emotion-related homeostatic brain network for perceived threats such as breathlessness and pain has enabled researchers to explore a hypothetical model of breathlessness, (see Figure 1). This incorporates many of the same neurophysiological and psychological dimensions as pain (5). The key elements of the proposed model include the “Sensory dimension” (S), comprising of the sensory intensity, quality, location and time scale, and an “Affective dimension” (A), encompassing the initial unpleasantness and subsequent emotional response (5).

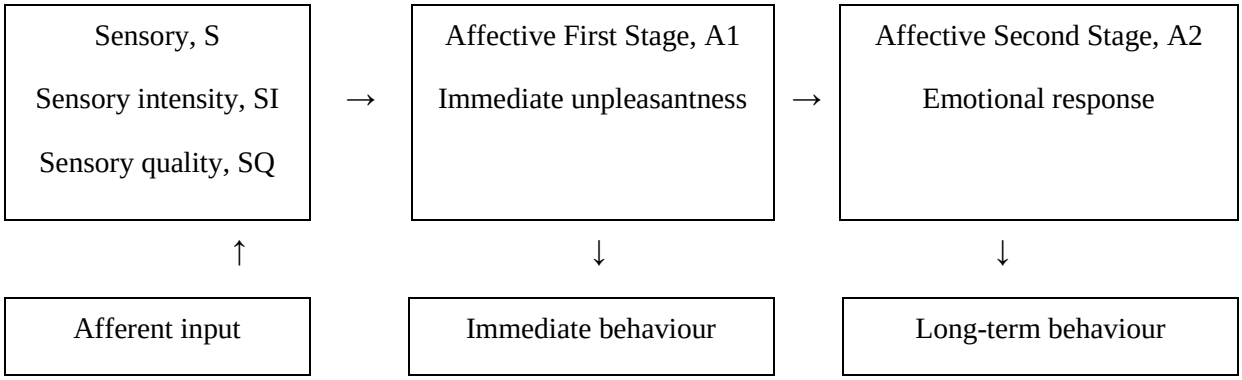


Figure 1 Modified hypothetical model of breathlessness (5)

Therefore, the patient's experience of pain or the sensation of breathlessness is driven by the patient's perception of the symptom and their reaction to the sensory experience (38). However, most studies have not tried to separate these dimensions, working often with single scales that combine both the sensory intensity, (SI) and the affective unpleasantness, (A1), so that when the patient is asked to report on their breathlessness it is not understood if the answer represents “How bad?” or “How much?” breathlessness they perceive (5).

1.4.4 Affective response and anxiety

The concept of a ratio between the sensory intensity and the affective unpleasantness, SI/A1 (39), means that theoretically it is possible to show differences in the relationship or changes between SI and A1, with breathlessness in different conditions. Psychological studies have used varying affective images to alter the emotional state of normal subjects during resistive work breathing demonstrating a decrease in the perceived breathlessness or A1, affective unpleasantness, but no change in the sensory intensity, SI (40). An earlier study that used exercise training programmes also found that the relationship of the affective and sensory components can be altered as activity reduces anxiety, the affective emotional reaction, A2, more than it decreases the sensory intensity, SI (41). It is possible to propose that with chronic refractory breathlessness there could be an up-regulation of the affective component, A2 due to the recurring and persistent stimulation of the limbic system (30). The excessive stimulation of this emotional network may potentially lead to increased symptoms of anxiety or depression; problems that are known to be commonly associated with these patients groups (21, 42).

There are differences in the central perception of breathlessness in people with chronic, as distinct from acute breathlessness. A recent study that used fMRI to investigate the brain response to breathlessness word cues found that people with breathlessness due to COPD appear to process the perception using the emotional systems in the medial prefrontal cortex and anterior cingulate cortex (43). These results suggest increased engagement of the brain emotional network in the interpretation of breathlessness and a heightened response to salient cues, such as the prospect of going upstairs (43).

1.5 Peripheral mechanisms of breathlessness

The 2012 ATS consensus statement has highlighted numerous possible different sources of afferent respiratory sensation. The input from these various stimuli contribute to the peripheral mechanisms and experience of breathlessness in different patient groups (26). Potentially other unknown breathlessness sensations may also exist with corresponding afferent drivers. For example, limited evidence suggests that the J-receptors (pulmonary C-fibres) are implicated in the sensory pathway for breathlessness mediated by pulmonary vascular diseases such as congestive heart failure (44).The main known and potential sources of respiratory sensation and the corresponding stimuli are reproduced in Table 3.

Table 3 Known and potential central and peripheral sources of respiratory sensation modified from Parshall et al (26)

Central source of sensation	**Adequate stimulus**
Medullary respiratory corollary discharge	Drives to automatic breathing (hypercapnia, hypoxia, exercise)
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Medullary chemoreceptors	Hypercapnia
Peripheral sources of sensation	**Adequate stimulus**
Carotid and aortic bodies	Hypercapnia, hypoxemia, acidosis
Slow adapting pulmonary stretch receptors	Lung inflation
Fast adapting pulmonary stretch receptors	Airway collapse, sudden lung inflation/deflation
Pulmonary C-fibres (J-receptors)	Pulmonary vascular congestion
Vascular receptors (heart and lung)	Distension of vascular structures
Chest wall joint and skin receptors	Tidal breathing motion
Muscle spindles in respiratory pump muscles	Muscle length change with breathing motion
Tendon organs in respiratory pump muscles	Muscle active force with breathing motion
Metaboreceptors respiratory pump muscles	Metabolic activity of respiratory pump
Airway C-fibres	Irritant substances
Upper airway “flow” receptors	Cooling of airway mucosa
Trigeminal skin receptors	Facial skin cooling

Of these numerous aspects, the skeletal muscle appears to play a key pivotal role and is discussed in more detail below.

1.5.1 Skeletal Muscle

The peripheral mechanisms that cause breathlessness usually result from the manifestation of the underlying cardio-respiratory disease processes. For example, the abnormalities detected in the muscle strength and function with COPD patients may rapidly produce breathlessness on minimal exertion (45). The peripheral skeletal muscle changes identified in COPD show loss of aerobic type one fibres (46) and reduced oxidative enzymes (45) that correspond with a lower aerobic capacity, early onset of lactic acidosis and subsequent contractile fatigue (47). This decreases a patient's exercise tolerance and increases the ventilatory drive, which are important mechanisms in the development of breathlessness. It is known that patients with COPD are less active than healthy people, walking with reduced movement intensity that is not solely restricted to the end stages of the disease (48, 49). Therefore, the changes to muscle groups may occur subtly over time so that the patient is not aware of their decreasing exercise capacity and the increased potency for breathlessness. These processes are also found with cachexia, for example, in cancer this has a trajectory similar to the malignant disease occurring progressively as a continuum through three progressive stages until refractory to all treatment (50). The most recent consensus definition of cancer cachexia suggests that it is;

> "a multifactorial syndrome characterised by an on-going loss of skeletal muscle mass (with or without loss of fat mass) that cannot be full reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism"(50).

However, cachexia *per se* also presents as a complication of many other conditions including chronic heart failure, lung and neurological diseases. Evidence suggests that there are similar causal processes of breathlessness and fatigue occurring amongst these conditions (51). Research with cardiac cachexia suggests increased breathlessness from functional and metabolic abnormalities in the skeletal muscle (52). These peripheral changes assume even greater importance as a determinant of exercise limitation in severe chronic heart failure (53). Likewise a study that examined exercise performance in intra-thoracic cancer patients found that both the inspiratory muscle, and the peripheral muscle strength were significantly associated with and predictive of exercise performance (54). These results are consistent with a study of 62 patients with cancer and breathlessness on exertion admitted for symptom

control to a specialist palliative care unit. The study results identify the importance of muscle fatigue as an equally limiting symptom in patients experiencing breathlessness from different activities of living (55).

The normal biological effects of ageing are also likely to precipitate or influence the level of breathlessness (56). The main anatomical and functional changes occurring in elderly people cause a decrease in lung elasticity, increased chest wall stiffness and lower respiratory muscle strength. This is compounded by the co-morbidities, obesity and sedentary lifestyle that may accompany advancing age in Western countries (56).

1.5.2 Theory of mismatch

The hypothesis central to the model of mismatch is that due to corollary discharge the brain "expects" a particular pattern of ventilation and feedback for a given level of neural respiratory drive. However, if the afferent signal deviates from what is predicted it mediates a state of imbalance and intensifies the perception of breathlessness (57). Experiments have induced the mismatch activity between the automatic drive to breathe and ventilation rate by raising the spontaneous inspiratory drive under various conditions with normal subjects .This has been achieved in most studies through the stimulus of high intensity exercise, hypercapnia, acidosis or mild hypoxia (58-60) to induce the sensory quality, alternatively in combination with chest strapping (61), or a corset to limit the available tidal volume (62). The sensation appears not to be specific to any disease or stimulus (26), but the main sensory afferent sources of information that have been implicated in study results are the chest wall mechanoreceptors, pulmonary stretch receptors, and the chemoreceptors (63-66).

The evidence suggests that the sensory information about the automatic respiratory motor drive of the brainstem is conveyed as corollary output to the cerebral cortex (66). A copy of the corollary output that projects to the cortical sensory areas is thought to be responsible for the highly distressing and urgent nature of this type of breathlessness sensation (66). This mechanism of breathlessness is identified as independent to the sensation mediated by "work and effort" of breathing which involves an increased voluntary motor drive to the respiratory muscles originating from the cerebral cortex (67).

The underlying pathophysiological changes that occur for example in a COPD patient highlight how the central mechanisms of breathlessness are perpetuated. The key common physiological alterations are the chest hyperinflation causing diaphragm muscle shortening, abnormal respiratory and chest wall geometry, along with the neuro-mechanical dissociation, the increased ventilatory load and decreased ventilatory capacity (68). Figure 2 demonstrates how the interaction of the disordered ventilatory mechanics in COPD drives the mismatch and leads to the breathlessness experience.

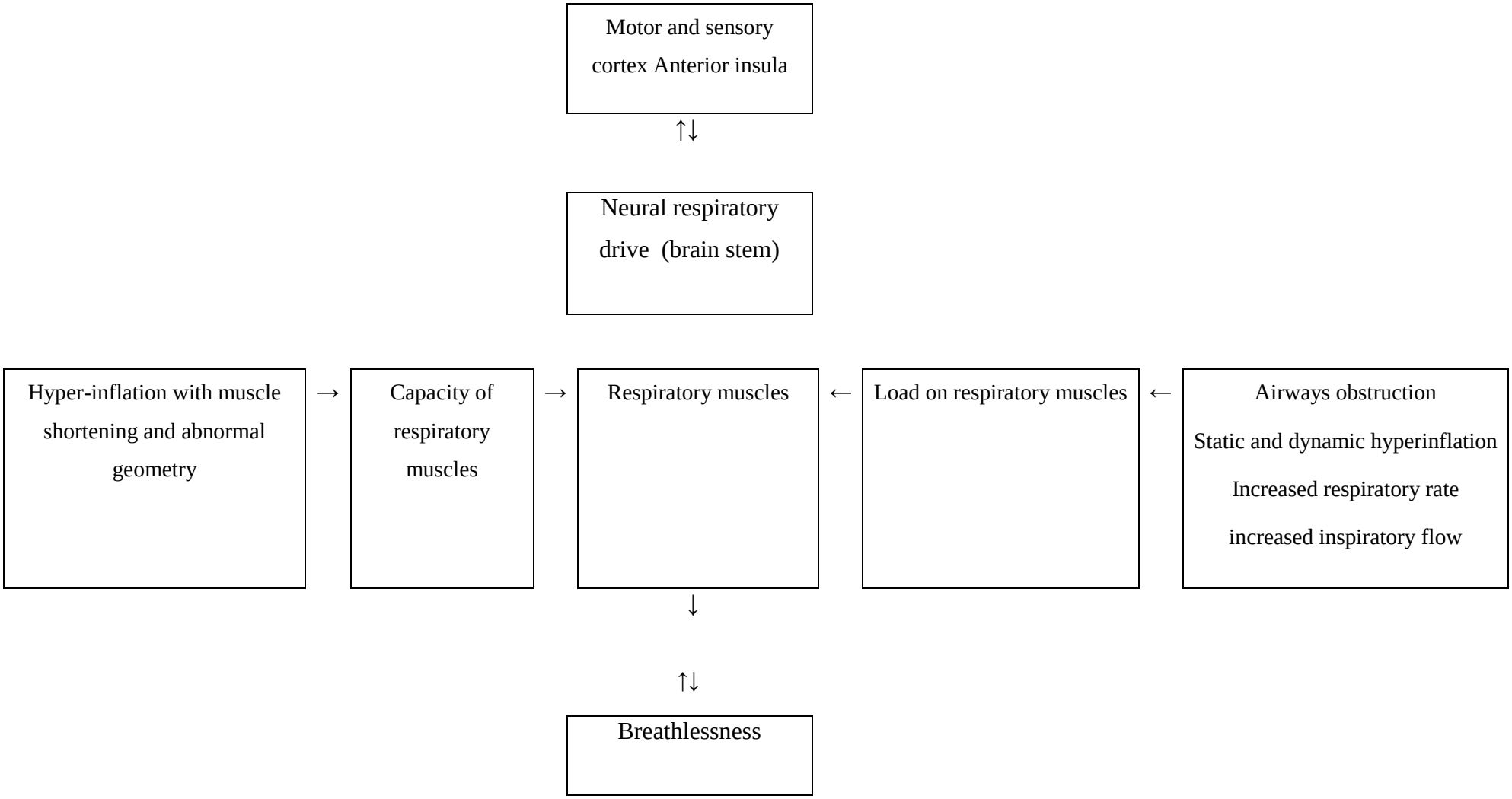


Figure 2 Respiratory muscle load-capacity imbalance modified from Jolley et al (68)

1.6 Descriptors of breathlessness

In the late eighties descriptors of breathlessness were investigated as a potential avenue that could help with the categorization and diagnosis of the cause breathlessness. The language used to describe the sensation was thought to accurately confirm the underlying physiological mechanisms and establish breathlessness differences between chronic disease groups. Therefore, this could have the potential to influence patient management and target the many interventions used for breathlessness in various chronic disease groups.

Three main descriptor clusters groups emerged from this exploration of language with the terms “air hunger”, “effort or work”, and “chest tightness” thought to be largely responsible for the different qualities of breathlessness sensation and relating to specific underlying neuro-physiological pathways (5). Systematic review of neurophysiological studies have since adopted these descriptive labels “air hunger”, “effort or work” and “chest tightness” in relation to the discussion about the potential afferent pathways and the corresponding sensations of breathlessness(5, 26).

1.6.1 Increased effort or work of breathing

The sensory quality of breathlessness known as the perceived “effort or work” of breathing is thought to be mediated by a combination of respiratory muscle afferents that project to the cerebral cortex, along with the voluntary cortical motor command or corollary discharge to respiratory muscles (69).This is similar to the mechanisms producing the sensation of work and effort when exercising limb muscles (26). The patient senses a feeling of fatigue, tiredness and discomfort while breathing and an inability to generate the muscle effort or strength necessary to breathe in and out faster. This is reported frequently in conditions like asthma, COPD, or diseases that decrease neuro-muscular strength and impair muscle performance such as Motor Neurone Disease (MND), or resulting from the processes of cachexia. The perception of breathing “effort or work” has been demonstrated in normal subjects by using external resistive or elastic loads (69, 70) or from inducing weakness of respiratory muscles, such as with the use of a partial neuromuscular blockade (71). These studies have consistently shown a substantially heightened perception of inspiratory force and effort resulting from the weakened respiratory muscles and the increased motor drive (69, 70).

1.6.2 Chest tightness

Research findings indicate that the perception of the sensory quality of breathlessness known as “chest tightness” is most likely to arise from the stimulation of airway receptors and pulmonary afferents. The sensation of “chest tightness” appears to be relatively specific to the experience of bronchoconstriction and is thought to occur predominantly at the onset of an asthmatic episode (72). Evidence from patients with asthma suggests that while various respiratory sensations are provoked during progressive airway narrowing, the specific feeling of “chest tightness” can be distinguished from other sensations. Study results demonstrate that while mechanical ventilation does not decrease the sensation of “chest tightness”, it does block the perception of “effort or work ”of breathing (73). Conversely, the constricted sensation resolves and responds more rapidly than the perceived “effort or work” of breathing when treated with nebulized salbuterol (74).

1.6.3 Air hunger

“Air hunger” is an unpleasant and distressing sensory quality of breathlessness that is experienced from the conscious perception of the urge to breathe (5). It has been described as being “starved for air” (75), a sensation that arises when the pulmonary ventilation rate is insufficient. The demand for ventilation in various respiratory diseases such as COPD often exceeds the compromised capacity of the patient, who perceives that they feel breathless and are unable to meet normal respiratory requirements to perform everyday activities (56). In basic terms, a load-capacity imbalance is perpetuated as the load on the respiratory muscles increases, while the capacity of the respiratory muscles decreases, or a combination of both factors heighten the neural respiratory drive to maintain homeostasis and adequate gas exchange (68). This proposed theory has been described by various terms including length-tension inappropriateness (76), neuro-mechanical uncoupling (77), neuromuscular dissociation (78) or efferent-afferent mismatch (79).

1.6.4 Limitations of breathlessness descriptors as diagnostic aids

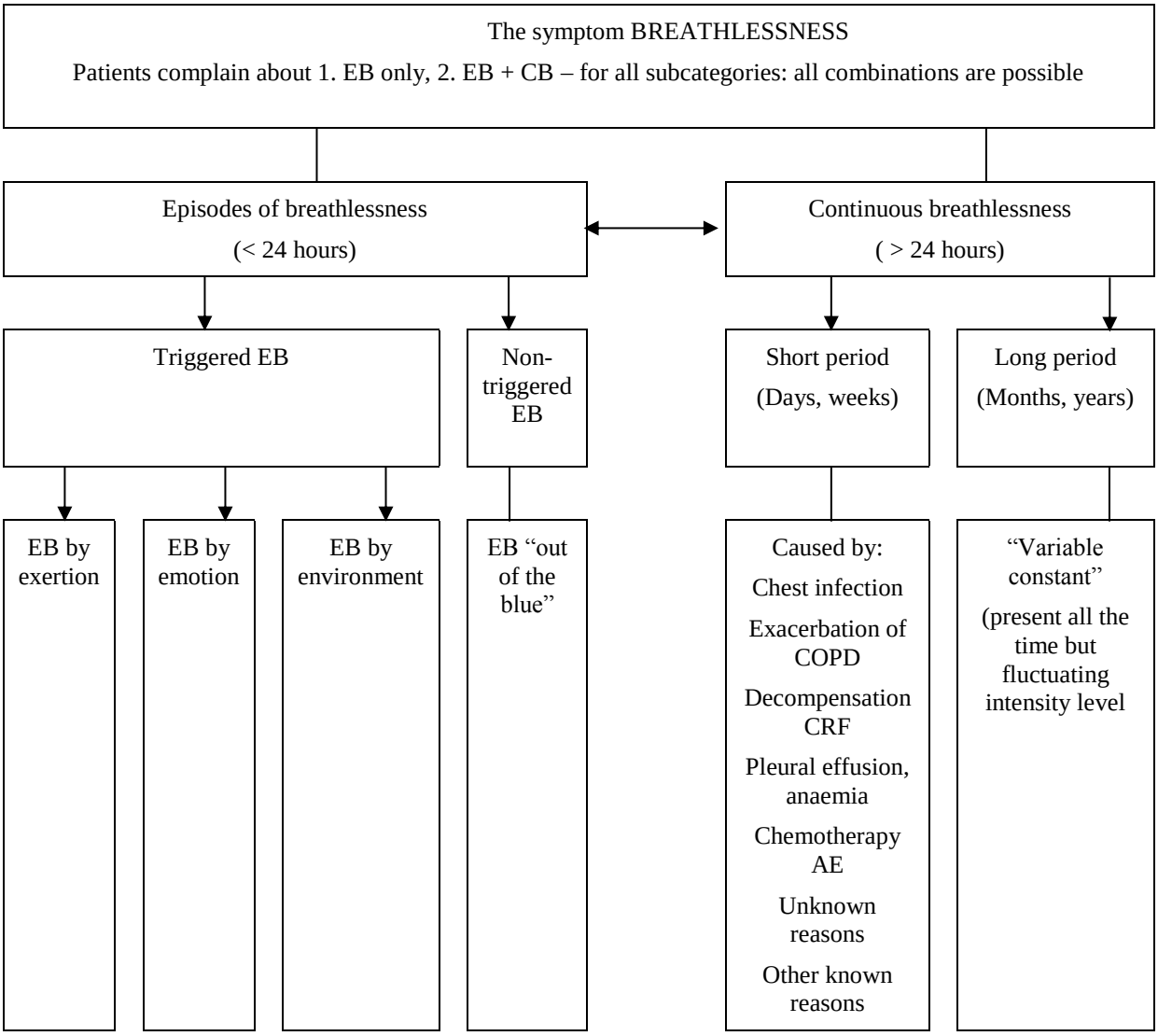
However, despite this promise, a major limitation of the descriptive work has now been identified in systematic review (80). The results of studies focus exclusively on the physical descriptors of the sensation, largely ignoring any affective element (80). This implies that the

patient's experience of breathlessness is not interpreted with any appropriate qualitative method that could help identify the variability of the language or descriptors used to suit time, place, character and social context. It suggests that there is limited useful application to manage the appropriate selection of different clinical interventions for breathlessness as the patient interpretation is confined to an endorsed list of terms, rather than their personal volunteered descriptions.

Nonetheless, descriptors do provide useful information in the evaluation of breathlessness and are incorporated in the multi-dimensional dyspnoea profile (MDP) (81). The MDP assesses the emotional response to breathlessness, as well as the breathing discomfort and sensory qualities during a specific time or activity and is designed to examine individual items that theoretically align with separate mechanisms (81). The MDP has been tested in the laboratory (82) and the clinical setting of emergency departments, where it offers clinician's a reliable and stable tool to measure multiple dimensions of breathlessness in patients during an acute visit (83, 84).

1.7 Categorization of breathlessness

The characteristics of breathlessness have also been described using qualitative methods. In-depth interviews that explored the descriptions of 51 patients with chronic heart failure, chronic obstructive pulmonary disease, lung cancer and motor neuron disease identified a possible new categorization for the symptom centred round the individual patient experience (85). Distinct patterns of breathlessness resembling the nature and qualities of acute, chronic or breakthrough episodes of pain were identified. The patterns of the breathlessness may vary therefore with the diagnosis, time, external or internal triggers, and the attributes of the patient's personality. The proposed new evidence-based categorization of breathlessness is displayed in Figure 3 and appears to be relevant to clinical management of a breathless patient. The characteristics and patterns may help to identify the most effective intervention and tailor the treatment for each individual. The two main categories identified were episodic and continuous breathlessness (85). Further subgroups were described based on whether episodes had known or unknown triggers, and whether the constant variable of breathlessness was experienced in the short or long term (85).



EB = Episodic breathlessness CB = Continuous breathlessness

Figure 3 Categorization of breathlessness by time and triggers based on patient experiences modified from Simon et al (85)

1.7.1 Continuous breathlessness

Continuous breathlessness was preliminary defined by patients as being constantly breathless or "present all the time "with very variable levels of fluctuating intensity, and was categorised by time, differentiated as being over 24 hours. Continuous breathlessness was reported as a total prevalence of 71% in the different disease groups, with COPD patients reporting the highest prevalence of 86% (85).

1.7.2 Episodic breathlessness

Episodic breathlessness has been differentiated by patients who describe an attack, crisis or incident of breathlessness. A systematic review of episodic breathlessness in advanced disease suggests that episodic breathlessness are characterised by high prevalence (81-85%), high frequency (daily), with severe peak intensity occurring in very short bursts of time (under 10 minutes' duration) . Known predictable triggers that may affect episodic breathlessness patterns include exertion, emotion or a change of environment. The most common predictable trigger is exertion with 98% experiencing this type of breathlessness from the diagnoses included (85). Breathlessness may also occur with no identifiable or known triggers and has been termed "out of the blue" with a reported total disease group prevalence of nearly 50%. A full list of the predictable triggers for episodic breathlessness identified are reproduced in Table 4.

Table 4 List of triggers for breathlessness modified from Simon et al (85)

Exertion	Emotion	Environment	Reasons for short period CB
Walking Climbing stairs Talking Slight exertion Stand up Carrying things Dressing/clothing Bending/leaning forward Housework, gardening Doing things in a rush Lifting things Eating/drinking Showering Stretching arms/lifting arms Standing in line Rolling over in bed at night Laughing, screaming Sex On the exercise bicycle	Panic Anger Excitement, upset Anxiety, fear Stress Impatience Argument Claustrophobia Annoyed, frustrated Worry about something Nervous Happy	Cold temperature (air, weather) Hot temperature Lie down flat Tiredness Perfumes, chemicals Dry air Wind Dust, humid air Mucus Pollen Stir fry (hot fat) Vinegar Powder Anaesthetic spray	Chest infection Acute exacerbation (COPD) Acute de-compensation (CRF) Chemotherapy Anaemia Pleural effusion

1.8 Effects on patients, carers and the NHS services

As breathlessness can be triggered by ordinary activities necessary for daily life, it can easily cause significant burden for the patient, family members or other informal carers and the health service. It may dominate with severe disturbance to all aspects of everyday life including physical, psychological, social and environmental problems.

1.8.1 Physical effect on patient

As discussed above, exertion is a known and common trigger of predictable breathlessness. Breathlessness is often precipitated on movement around the home and normal activities, performed by those in good health easily, may often be associated with heightened symptom intensity. Therefore, the patient may perceive a potential threat to their normal breathing pattern when walking around and their interpretation or the personal meaning that they attach to the unpleasant sensory experience could prevent them from exercising further or encourage avoidance of symptom associated physical activity. Exertion-induced breathlessness becomes counterproductive when it discourages the patient from persisting with exercise programmes because of its unpleasantness or believing it to be harmful (86). The resulting sedentary lifestyle compounds the patient's ability to perform normal movements further as global weakness of locomotor muscles and progressive deconditioning occurs (87). This in turn leads to a lowered aerobic capacity thereby hastening anaerobic processes that accumulate metabolic by-products in weakened muscles during exercise. Ultimately, this could increase the drive to breathe on less and less physical exertion, so that the patient experiences more breathlessness, leading to further self-imposed restriction in movements. The effect of limb muscle fatigue on the perception of respiratory effort has been studied in normal subjects. The results suggest the activation of ergoreceptors, afferents sensitive to skeletal muscle work that contribute to the perception of effort during breathlessness (88). This effect is also seen in ill-health, with the encouraging finding that partial reversal is possible with exercise (89).

A deconditioning spiral is aggravated in physical illness because of the compounding pathophysiological changes that occur with various cardio-respiratory diseases. For example, COPD patients have known peripheral muscle differences that result in limited aerobic function and consequential early onset of fatigue and lactic acidosis (45, 90), precipitating breathlessness during activities such as walking or climbing the stairs. Equally, the physical effects of breathlessness are more notable with upper limb work as any activity involving the use of the arms such as dressing or undressing increases the load on the respiratory system and reduces ventilatory reserve. The sensation of breathlessness was found to be higher in COPD patients when performing activities that involved mostly scapular musculature such as lifting objects or changing a light bulb (91) and a shallow, rapid, irregular respiratory pattern has been observed in COPD patients when combing their hair or tying shoes (92). This is partly to meet the higher metabolic demand from muscle work, but also because during upper

limb exercises these muscles are required to perform additional functions; stabilising posture, while generating the required movement and continuing to contribute sufficiently to respiration (68).

Therefore a profound disturbance to the normal activities of daily living is possible with increased dependency on others resulting from the interaction between the physical effects of breathlessness and the co-existing pathological disease processes. There is the potential for the patient to be restricted to sitting in a chair or they can become bed-bound due to a progressive deterioration in their exercise tolerance, with exacerbations of breathlessness becoming more easily precipitated by normal movement or even conversation.

Moreover, the restrictive nature of some interventions commonly used can also compound the functional difficulties arising from the breathlessness itself, such as the tubing and equipment necessary for home oxygen therapy (93). This has been described as "burdensome" by 65% of participants reporting on the acceptability of this intervention during a recent multi-centre randomised controlled trial (94). Many patients with breathlessness due to advanced disease may need a walking aid, and this in conjunction with oxygen tubing and other required equipment, may prove difficult for some to use safely when moving. Physical activity is therefore obstructed not only by the breathlessness itself, but also by the management of the symptom which may contribute and turn the home into an obstacle course with potential hazards for falls.

1.8.2 Psychological effect on patient

Breathlessness perception is influenced by the patient's own individual experience of past and current experience. Consequently the psychological effects and drivers of the symptom can be very high. The perception of breathlessness involves sensory recognition, interpretation and their meaning, and is therefore inherently subjective (26). The patient's perception and personal evaluation of the symptom will depend on their previous breathlessness experiences and the prevailing circumstances when an acute episode of breathlessness occurs.

A multi-dimensional model of breathlessness suggests that there is an affective component following the immediate unpleasant sensation of breathlessness and this stage is characterised

by predominantly emotional responses such as depression, anxiety, fear, frustration or anger (5). The impact of emotions on the sensory and affective components of perceived breathlessness has been examined in healthy volunteers. Participants are able to distinguish these two components and results suggest that the affective dimension that is most susceptible to emotional influence (40). This indicates that a patient's level of vulnerability to the emotional component of breathlessness may also be influenced by their pre-existing personality traits and it could mean that their breathlessness becomes a vicious spiralling symptom from their reaction to the symptom and the following interplay between the psychological and physical effects.

Similarly the underlying physiological mechanisms and pathways that convey the sensation of breathlessness to the patient may influence the affective state. Research suggests that certain types of breathlessness experience are more likely to induce a high level of emotional responses. Work with normal subjects exploring the affective dimension found that inducing the breathlessness sensation known as "air hunger" was far more unpleasant and associated with a strong emotional potency in comparison to the stimuli for the breathlessness sensation of "effort or work" (95).

A recent study that used The Memorial Symptom Assessment Scale-short form (MSAS-SF) to measure the frequency and distress of 32 highly prevalent symptoms found four psychological symptoms dominant in cancer and COPD; feeling sad, irritability, nervousness and worrying, the last being the most prevalent with over 65% suffering in both groups (18). It indicates that the majority of breathless patients who worry are at risk and susceptible to the development of anxiety-related problems. Excessive worrying is a known key feature associated with the diagnosis of Generalised Anxiety Disorders (96). Research strongly supports the role of anxiety as a key driver during the breathlessness experience. Anxiety alone was found to correlate significantly with the intensity of shortness of breath in cancer patients (21), and similarly work with other diagnoses such as asthma and COPD intrinsically link the symptoms of anxiety and breathlessness (42, 97). These findings concur with recent results from a cross-sectional study that examined the association within the general population finding a positive correlation between anxiety and breathlessness (98). Similarly the results of a prospective longitudinal population study investigating the change in breathlessness in relation to the symptoms of anxiety and depression over a 9 year time

period identifies more support for the psychological symptoms being the causal suspect and risk factor for the development of breathlessness (99).

Interpretation as to whether the breathlessness causes anxiety or the reverse scenario that anxiety causes the breathlessness is still open to debate. Discussion lends support to both theoretical viewpoints on the cause/effect relationship between a patient's psychological status and breathlessness symptoms (98, 99). However, indication from the general population studies with normal healthy subjects is that anxiety and depression can be a prime cause of breathlessness irrespective of the lung function or underlying disease processes (98). Therefore, anxiety symptoms may cause the initial misperception of physiological breathlessness intensity as unpleasant and worrying. The resulting emotional response may then escalate the breathlessness into severe intensity, beyond a normal physiological response to whatever triggered the breathlessness, with any underlying lung pathology heightening the process. It is also possible that not all anxious patients will be breathless and the causal pathway between breathlessness and anxiety will depend on the individual patient character as well.

1.8.3 Social effect on patient

The social environment can often have a significant impact on how people perceive their abilities and self-esteem (26). Frustration, loneliness, depression and loss of role may result, if the patient finds that their experience of the symptom limits their physical capabilities to the home (100-103).

The consequences of social isolation may contribute to a worsening of both the physical and psychological problems associated with breathlessness. A patient with low expectation and declining performance is unlikely to go out and socialise with friends or seek the medical support necessary to cope with their symptoms. There is an established connection between social relationships and physical health finding that in comparison to socially isolated individuals, well connected social people live for longer (104) and display an increased resistance to chronic diseases such as cancer and heart disease (105).

A review examining the neuro-physiological systems implicated in the connection between social experiences and physical or emotional health suggests that threats to social ties could

activate a neural “alarm system” (106), associated with adaptive responses to imminent danger or harm (107). A fundamental survival threat could be processed by the breathless patient experiencing social exclusion, resulting from the activation of the dACC and anterior insula (108, 109). Both the dACC and the anterior insula are well known for their roles in pain and threat-related mechanisms and also for the stimulation of autonomic and endocrine responses that could subsequently compromise and further compound the physical and emotional health problems of a patient. Furthermore, it is plausible that the effects of social isolation will become evident in the carer who becomes increasingly confined to the welfare of their patient and the duties around the home. Often carers may want to take care of a breathless family member, but feel they need adequate support to cope with the physical burden and effects of social isolation (110, 111). Social effects are potentially far reaching, not only for the patient, but also for the carer as it compromises their health, increasing the likelihood that they feel unable to cope with the patient’s breathlessness problems in the long term.

1.8.4 Effect on carers and family members

Carers can feel very frightened when their loved one is breathless (112) and uncertain how best to help. It could precipitate a situation where the carer is reluctant to leave the patient alone for fear of an unexpected, episodic breathless attack, increasing their isolation, or if an acute exacerbation occurs for example, while climbing the stairs, the carer may panic and call for emergency assistance.

This suggests that there are many processes that can dramatically alter the quality of life for the carer, not only in terms of the physical activity needed due to the demands inherent to a caring role, but there are also additional emotional or anxiety-related burdens to negotiate with breathlessness. A previous cross-sectional survey of lung cancer and heart failure (HF) caregivers data found considerable levels of burden with high scores for the Zarit caregiver questionnaire; mean 11.1 (SD 8.7); 95% CI 8.6–13.6, (n=47), and mean 9.6 (SD 9.0); 95% CI 7.0–12.2, (n=48) respectively (113). The interplay of the relationship between the carer and the patient may produce additional unseen problems. The patient may try to protect their carer or family member by choosing to deny or hide symptoms as they fear it will cause upset.

Qualitative interviews that examine the perceptions of carers suggest that they are the "invisible victims" of a patient's breathlessness experience (112), feeling powerless and helpless while witnessing an acute breathless attack (114).

It is possible that the symptom may distress the carer more than the patient, particularly if the carer has their own psychological problems, co-morbidities (115) or they lack the understanding of how to cope and use the interventions available to help with a breathless episode (116). The carer may have to contend with mixed emotions and can experience a host of difficulties arising from their caring role. These are displayed in Table 5.

Table 5 Carer emotions and possible reasons modified from Booth et al (117)

Frustration	How do they manage to do the things they enjoyed with the constraints imposed by the illness of their loved one.
Anger	The person they are caring for does not comply with the advice given, or from the confined existence they now share with their spouse after gradually losing touch with friends.
Exhaustion	They carry out everyday living tasks as well as those of their partner and the additional demands from the physical caring duties now needed.
Worry	They have their own illness and feel unable to give enough care or if they have family with problems that they are unable to devote adequate time too.
Bitterness	May be felt over what has happened or how they perceive the help they have received with their partner during breathless episodes.
Guilt	They feel they do not give enough care, or sometimes they wish they could escape the situation and think their partner would be better off if dead.
Distress	They watch their partner suffer, or from their feelings of exasperation or helplessness with the situation
Anxiety	They feel unable to influence their loved one's breathlessness or frightened about the future and what will happen if their partner stops breathing, dreading the thought of having to cope with the situation on their own
Depression	May arise from their feelings of worthlessness, guilty thoughts and social isolation.

These highlight the importance of assessment and management of carer's psychological needs in their own right, and not only as family members or relatives (114). These experiences are identified and targeted as key areas within the Cambridge Breathlessness Intervention Service (BIS), shown to improve distress due to breathlessness in a randomised controlled trial (8). The influence of breathlessness on carers is recognised in the complex intervention programme, and the extra support given may reduce carer exhaustion and

anxiety levels. This could potentially lead to a decrease in the number of emergency hospital admissions, while also improving the carer's health, mood, morale and quality of life and thus the ability to continue to provide support for the patients in their own home (8). The effect of breathlessness on carers, and the importance that they feel they have effective intervention to help is illustrated by a community-based study in West Australia. It was noted that patients are more likely to get oxygen if they have a carer, raising the question that the request may well have arisen due to a need in the carer rather than the patient (118). This indicates that the role of the carer is very important and needs to be taken seriously as they can influence the management of a breathless patient and ultimately affect the appropriateness of the medical interventions selected by clinicians.

1.8.5 Effect on National Health Services

The effect of breathlessness mismanagement may potentially be costly if episodes lead to inappropriate hospital admissions or increase the number of emergency ambulance responses. It is known that patients are more likely to re-attend the Emergency Department (ED) if breathlessness is a symptom (119), and breathlessness is a common symptom in people with palliative care needs who attend the ED (120, 121). Similarly, results from a cross-sectional study that analysed survey data from 986 emergency adult visits including COPD (n=239), asthma (n=395), CHF (n=320), chronic restrictive diseases (n=14) and mixed diagnoses (n=18) found breathlessness the most common reason for ED visits across all diagnoses (122). Moreover, breathlessness was associated with an approximate twofold increase in likelihood of admission for patients with COPD, odds ratio [OR] = 1.9, $p < 0.04$, and controlling for age in patients with CHF, OR = 1.7, $p < 0.035$ (122). In addition, the percentage of non-urgent visits that resulted in admission was notably higher for COPD (19%) and CHF (41%) in comparison to asthma (4%) or other general visits (6%) (122).

Although some ED visits may be entirely appropriate such as pulmonary oedema, chest infection, pulmonary embolus and not preventable through timely assessment and management in the community, patients may also attend unnecessarily if there is an exaggerated emotional response to breathlessness, or if they delay seeking medical attention, which in turn results in an uncontrolled episode of breathlessness or a sudden burst "out of

the blue". It is plausible that patients seeking medical attention in this way have not had their breathlessness addressed in an appropriate manner and inadequate consideration has been given to the affective dimension of the breathlessness experience. Potentially, the underlying sensory mechanisms of breathlessness could also impact on the likelihood that a patient will need ED support. A patient experiencing the breathlessness sensation termed "air hunger" may find it impossible to control their reaction as this type of sensory pathway is known to represent the sensory quality of "suffocating" or being "unable to get enough air in" (95). This is confirmed by a prior study that explored which dimensions of breathlessness prompted ED visits in 57 heart failure patients using respective interviews and breathlessness sensory descriptors (123). Results found high levels of breathlessness distress and intensity regardless of breathlessness duration with 46% of the sample describing their breathlessness as "choking", "smothering" or "couldn't get air" at the point of making the decision to visit the ED (123). Furthermore, recent studies that have evaluated the reliability and validity of the MDP tool in patients with chronic or acute cardiopulmonary conditions highlight the immediate perception and the emotional response as the main distinguishable domains recalled during the ED visit (83, 84).

Therefore, breathlessness as a clinical sign should trigger an investigation and diagnosis algorithm that pays particular attention to the affective component in both, a patient's ED visit or primary care presentation. It is possible that accurate assessment of the multiple dimensions of breathlessness, such as with the MDP tool, improves the formulation of a management plan for the patient symptom, rather than the clinical sign, which in consequence could help to prevent unnecessary admissions. This is particularly relevant given that breathlessness prevalence is predicted to rise from the aging population, implying a higher demand for health services and ultimately increasing the cost of service provision too. In the present economic climate with constricted health budgets and a rapidly growing population of service users with chronic refractory breathlessness, any intervention utilised to manage the symptom needs to be able to meet the demands of both the patient and the health services as a viable cost-effective option.

1.9 Summary of chapter one

In summary, breathlessness is a common, distressing and debilitating patient symptom that occurs in many advanced diseases, and has far-reaching and devastating consequences for the carer and family. The complexity of the symptom is highlighted in this chapter; many underlying causes exist with various potential sensory afferent input from both central and peripheral mechanisms of respiratory sensation. These combine to produce an individual breathlessness experience, widely recognised as multi-dimensional, resulting from the interaction of physiological, psychological, social and environmental factors. Therefore, the evaluation and management of the symptom is not straight forward, and problems exist with the clinical interpretation of breathlessness as a sign, rather than a symptom.

However, significant progress has also resulted from increased knowledge of the neurophysiological mechanisms, and the understanding that breathlessness has an important affective component similar to pain. The next chapter outlines the current management approaches to breathlessness, which are developing to reflect the multi-dimensional, complexity of the symptom, and uses interventions that are theoretically aligned to the different underlying mechanisms of respiratory sensation.

Chapter 2 Management of breathlessness

2.1 Background

Breathlessness is generated and perceived through complex and multiple mechanisms, as described in chapter one. This is particularly so for the person with chronic and advanced conditions. It is important to understand the underlying mechanisms of breathlessness as it affects clinical reasoning and decisions taken to provide the correct patient management. Diagnosis and optimal management of the main underlying clinical condition causing the breathlessness is critical followed by regular monitoring, and vigilance for additional reversible causes of breathlessness which should be effectively treated if possible and appropriate for the individual. For example, the presence of ascites or anaemia can both worsen breathlessness, and subsequently improved with drainage and transfusion respectively. However, despite the best care, it is often not possible to relieve all the symptoms and if chronic breathlessness persists in patients it is then described as refractory (14). Refractory breathlessness can be targeted with therapy in addition to ensuring the underlying condition is optimally treated. This chapter will discuss the non-pharmacological options for managing refractory breathlessness. A discussion of pharmacological therapies is beyond the scope of this thesis.

It is not surprising that relieving and maintaining the patient's sense of control over their experience of breathlessness can be at times complex and difficult. Many different mechanisms of perception are involved and it is possible that no two patients with the same diagnosis will feel breathless or experience it in the same way or at the same time. Data from qualitative interviews has categorised the different clinical types of breathlessness (85) demonstrating the necessity for employing both pharmacological and non-pharmacological techniques to adequately treat the demands of the symptom (124). Both the non-pharmacological and pharmacological approaches are able to modify and influence the central and peripheral pathways and likewise both the physiological and psychological elements that are involved in the perception of breathlessness.

2.2 Models of delivery

2.2.1 Breathlessness clinics

The clinical benefits of adopting a multi-faceted model of care for the management of breathlessness are now recognised (125). Research from the last decade resulted in the development of breathlessness clinics across the UK. A preliminary pilot study of 20 patients with advanced lung cancer who received "nursing interventions" at weekly sessions over 3-6 weeks from a nurse practitioner found that at 3 months in comparison to those who received usual care there were significant improvements in a range of outcomes (6). Results on a 0-10 numerical rating scale for breathlessness intensity at worst was intervention group; median 3.5 (range -1 to 7) versus control group median 0 (range -5 to 4); $p < 0.05$, distress due to breathlessness; intervention group median 5.3 (range 0 to 9) versus control group median -1.0 (range -4.5 to 3); $p < 0.01$, and functional capacity; intervention group; median 1.0 (range -0.5 to 2) versus control group median - 0.25 (range -1 to 1); $p < 0.02$ (6).

The subsequent multi-centre randomised controlled phase III study involving 119 patients with lung cancer demonstrated the benefits of using a similar nurse led intervention programme involving a range of strategies such as breathing control, distraction and relaxation which were tailored to individual patients. The results demonstrated improvements at 8 weeks in 5 of the 11 outcomes assessed. Significant median changes were found relative to baseline for Visual Analogue Score (VAS) breathlessness intensity at best: intervention group 1.3 (range -7.1 to 8), control group 7.0 (range -3.3 to 8); $p < 0.03$, World Health Organisation (WHO) performance status: intervention group 0 (range -3 to 3), control group 2.0 (range -1 to 3); $p < 0.02$, Hospital Anxiety and Depression Scale (HADS); depression: intervention group 0.5 (range -10 to 7), control group 6 (range -7 to 7); $p < 0.02$ and Rotterdam physical symptoms of distress: intervention group 2.5 (range -24 to 16), control group 14 (range -11 to 16); $p < 0.04$, although the statistical analysis did not account for the high attrition rate (7). These studies resulted in the development of breathlessness clinics at hospices and other service providers within the UK, thereby establishing the use of non-pharmacological interventions in clinical practice. High levels of satisfaction and significant

improvement in quality of life were subsequently reported in other evaluations conducted as part of the development, piloting and testing of breathlessness clinics (6, 7, 126, 127).

The Cambridge Breathlessness Intervention Service (BIS) has followed the Medical Research Council (MRC) Framework to develop a complex intervention model encompassing both pharmacological and non-pharmacological strategies for patients with chronic refractory breathlessness and advanced disease irrespective of cause (128). Results from the recently published phase III single blind mixed method RCT of BIS versus standard care with cancer patients (n=67), found the primary outcome, patient distress due to breathlessness significantly decreased, -1.29 (95% CI -2.57 to -0.005), P = 0.049; an outcome supported by the qualitative data as patients and carers also consistently confirmed specific aspects of the specialist breathlessness model and the accompanying interventions that had increased their confidence and knowledge to manage breathlessness (8). Likewise, the Breathlessness Support Service (BSS) in London has evaluated their service according to the MRC methodology and in their latest pragmatic, single blind RCT of BSS versus usual care (n=105), which included COPD and HF as well as cancer patients reported significant improvement in the mastery domain of breathlessness in the Chronic Respiratory Questionnaire (CRQ) at 6 weeks 0.08 (95% CI -0.38 to 0.52) P = 0.048 compared to control (9). This outcome resonates with the results from the Cambridge BIS as breathlessness mastery assesses patient's feelings of control over their breathlessness. Both of these service models offer the patient a mixture of home and clinic attendance with access to a multi-professional and interdisciplinary team comprising of physiotherapy, occupational therapy and palliative physicians, while the latter study has extended this to include respiratory physicians as part of the intervention team.

The National Institute for Health and Clinical Excellence (NICE) issued guidelines to recommend lung cancer patient access to non-pharmacological interventions based on psychosocial support, breathing control and coping strategies (129). Other NICE guidelines that extend to cover the needs of COPD patients do not detail the specific palliative services required for effective breathlessness management, instead access to pulmonary rehabilitation is recommended for all appropriate patients and includes those who have had a recent hospital admission for an acute exacerbation (130).

At present there are little data on the format or frequency of breathlessness programmes for cancer patients. Research with malignant disease is associated with a high drop-out rate due to deterioration and death. A previous study confirmed a 40 to 50% attrition rate in lung cancer patients after only 4 weeks of a nurse led intervention programme (7). A further cohort study of lung cancer patients seen by a physiotherapist in a breathlessness clinic reported an attrition rate of 33% over a period of 4 to 6 weeks and suggested that a shorter programme should be offered for malignant disease (126). Given the patient burden of regular training attendance especially in those with lung cancer where only approximately half of patients manage to attend for four weeks, it is important to understand the relationship between the amount of training needed and the optimal patient benefit. This hypothesis has been formally tested in an adequately powered phase III multi-centre study comparing one session of training with three (131). There was no evidence that three sessions offered additional benefit, including cost effectiveness in comparison to one. The authors concluded that a single session of breathlessness training was sufficient in this group of patients and minimised the risk of patient burden (132).

Furthermore, the intensity of service delivery is addressed by the phase III randomised controlled trial methodology for the Breathlessness Intervention Service (BIS) which operates two service models of breathlessness intervention due to different disease trajectory. One for malignant patients is delivered over 2 weeks while the other for non-malignant diseases such as COPD is delivered over 4 weeks (127). More importantly, irrespective of the length of breathlessness programme, attendance for the majority of patients particularly the elderly may depend on motivational behaviour (86). Exercise such as pulmonary rehabilitation or other activities are known to reduce the impact of breathlessness (133). But, inevitably the patient feels breathless when exercising and the unpleasantness of the symptom serves as a disincentive to continue with more activity.

2.2.2 Exercise and pulmonary rehabilitation

Exercise has an important role in managing breathlessness as it increases skeletal muscle bulk, quality and fitness (as described in chapter 1.5.1), (45-47). Exercise training is known in both research and clinical settings as a key component of a comprehensive care programme

for patients with chronic cardio-respiratory diseases. First described as pulmonary rehabilitation in the late 1960s by Petty (134) it is now defined as;

> "A comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behaviour change designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health enhancing behaviours" (135)

Pulmonary rehabilitation has since become an established and recommended standard of care for patients with chronic pulmonary diseases using exercise training of ambulatory muscles as a mandatory component (136). The American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) guidelines for pulmonary rehabilitation have been in place since the 1990s, with updates as the research evidence has amassed (135, 136). The latest update highlights the need to increase the applicability and accessibility of pulmonary rehabilitation in order to optimise behaviour change, maintain outcomes and refine the intervention so that it targets the individual needs of the complex patient (135).

A recently updated Cochrane review of pulmonary rehabilitation for COPD included 65 RCTs, involving 3822 participants for meta-analysis highlights the improvements in the health-related quality of life and strongly supports the inclusion of pulmonary rehabilitation as part of the management and treatment of patients with COPD (137). Results demonstrated statistically significant improvements for all of the included outcomes. In four domains of quality of life (QoL), Chronic Respiratory Questionnaire (CRQ) scores for dyspnoea, fatigue, emotional function and mastery, the effect was larger than the minimal clinical important difference (MCID) of 0.5 units; dyspnoea: MD 0.79, 95% confidence interval (CI) 0.56 to 1.03; n= 1283; studies = 19; fatigue: MD 0.68, 95% CI 0.45 to 0.92; n = 1291; studies = 19; emotional function: MD 0.56, 95% CI 0.34 to 0.78; n = 1291; studies = 19; mastery: MD 0.71, 95% CI 0.47 to 0.95; n = 1212; studies = 19 (137). Similarly statistically significant improvements were noted in all domains of the St. George's Respiratory Questionnaire (SGRQ) MD -6.89, 95% CI -9.26 to -4.52; n = 1146; studies = 19 (137). Other benefits have

also been identified such as increased exercise tolerance, amelioration of breathlessness during activity and a reduction in the number of hospitalisations (138-140).

However, despite the many positive benefits uncertainty exists as to the optimal duration for a pulmonary rehabilitation programme to achieve the maximal clinical efficacy (137, 141). Initial recommendations were based on Sports Medicine guidelines which proposed that a six week course was required to achieve an aerobic training effect in healthy individuals (142). The relevance of this recommendation for patients with chronic respiratory diseases has subsequently been the scrutiny of numerous studies that have investigated various parameters such as the length, timing, intensity and number of sessions delivered during a pulmonary rehabilitation programme (138, 143-145) particularly as completion rates from pulmonary rehabilitation are known to be poor with attendance as low as 50% (146) and drop-out rates that range from 23-31% (147, 148).

Furthermore, it remains unclear as to which components of pulmonary rehabilitation are essential and for which patients (149, 150). Rehabilitation programmes may differ in content and treatment combinations, but along with the standard exercise training it can include education, psychosocial support, breathing exercises and strategies to help promote self-management behaviour. The latest updated American Thoracic Society and European Respiratory Society (ATS/ERS) statement identifies health behaviour change as a key component in maintaining benefits from rehabilitation programmes in the longer term (135). A previous RCT of 43 COPD patients that investigated exercise training combined with a behavioural component that emphasized structured controlled breathing and strategies for coping with daily activities compared to exercise training and a lecture series adjunct found additional benefit for the comparatively older participants at 6 and 12 weeks with decreased breathlessness with activity $F:(2,26) = 3.43$, $p < 0.04$ (149). However, at 18 and 24 weeks, the other main primary points of analysis no significant differences were reported and a participant attrition rate of 43% at 24 weeks compromises the statistical power and relevance of the result (149).

The problem of maintaining the benefits from an exercise program has been identified in the general population, most of the improvements are short lived due to the problems of poor

longer term adherence (151). The results of a study that investigated motivation in 23 older adults using a walking exercise programme found that 14 (60%) did not adhere to the walking regime (86). The qualitative semi-structured follow up interviews of the elderly sample revealed that adherence to an exercise programme may be influenced by previous experience of exercise, beliefs about exercise, personality, and the unpleasant sensations associated with exercise (86).

Likewise, the initial gains from pulmonary rehabilitation are known to diminish over time. An RCT of 119 COPD patients found that the benefits of pulmonary rehabilitation were partially maintained for a year, but decreased after that time (139). A subsequent study with COPD patients which investigated the effect of an additional year of supervised support and contact after the initial exercise intervention suggested only modest benefits that were rapidly lost within 1 year thereafter (152). Further results from a RCT study that involved 123 COPD patients who had completed an 8 week pulmonary rehabilitation programme also failed to show significant difference between the standard care and the addition of a long-term maintenance program that included monthly supervised reinforcement, help to comply with home exercise and weekly telephone contact (153). Notably, the participants from both arms of the study who walked on most days or every day had significantly better quality of life $F:(1,121) = 6.21$, $p < 0.05$ from post-rehabilitation to 24 months compared to the irregular walkers (153). Moreover the results for the breathlessness measures indicated different rates of breathlessness change between non-walkers and walkers over time. A significant group time interaction was identified for both the University of California, San Diego Shortness of Breath Questionnaire UCSD (SOBQ), $F: (3,362) = 4.58$, $p < 0 .005$ and the CRQ Dyspnea scale $F: (3,356) = 3.46$, $p < 0.05$ (153). These findings suggest that regular exercise such as walking may protect some of the benefits gained from rehabilitation and slow the decline in health related quality of life.

However, the understanding of exercise behaviour and predicting the components needed for each individual patient to adhere to a regular maintenance exercise programme is still far from resolved. For many people, despite the positive benefits of exercise, breathlessness triggered by exertion frequently acts as a disincentive to undertake exercise (86). Often the breathlessness is interpreted as a negative experience and the patient may become less and

less active with breathlessness precipitated by any minimal exertion. The misinterpretation of breathlessness during exercise and attribution of the symptom to a sign of vulnerability or physical inadequacy, rather than a normal response to exercise may undermine the patient's self-efficacy beliefs (154). There is evidence from research in both the general population and in chronic medical conditions such as COPD and heart failure that self-efficacy plays an important part in improving exercise adherence (155-157).

2.2.3 Self-efficacy

Self-efficacy is defined as a person's belief of their ability to control, organise and perform actions that are necessary to accomplish a goal they believe to be important within a specific domain of functioning (158). The theory identifies how patients may acquire self-efficacy information from four primary sources. These are called enactive mastery, vicarious experience, verbal persuasion or social influence and physiological or affective states.

Enactive mastery experiences is regarded as the most potent source of information as it refers to the individuals own personal experiences and offers the highest assurance of information authenticity (158). The patient's experience of performance success or failure will likely validate or undermine their capabilities to cope with a given activity. Vicarious experience or modelling refers to another source of self-efficacy information derived through the observation and imitation of others. The patient may judge and compare performance and the consequences from another patient against their own capabilities. A third source of self-efficacy information is known as verbal persuasion or social influence. It involves the ability to convince patients that they have the ability to achieve their goals and uses the clinician's status or role to motivate action or provide feedback to promote continued effort (159, 160). Finally physiological or affective state describes a fourth source of self-efficacy information resulting from the physiological and psychological symptoms experienced during an activity. Pain, breathlessness, fatigue or emotional states such as anxiety may all effect the patient's self-efficacy beliefs and undermine their capability to perform a given task or maintain an exercise program long term. This is highlighted by the findings of a RCT of 102 COPD patients that investigated two domains of self-efficacy; one for managing breathlessness and the second for walking using three different intervention groups each designed to enhance the

four primary sources of self-efficacy information available to the patient (161), based on The Dyspnea Self-Management Program (162). The results found that although self-efficacy for walking was improved in all three groups from baseline; 7.2 (SD 2.5) to 8.0 (SD 2.1) post intervention with a mean change of 0.8 ($p < 0.0005$), there was no significant improvement in the self-efficacy for managing breathlessness amongst the groups when measured by the COPD self-efficacy scale (CSES) from baseline; 3.11 (SD 0.78) to 3.15 (SD 0.77) post intervention with a mean change of 0.04; ($p = 0.53$) (161). Furthermore the study reported that post intervention the breathlessness severity recorded after a six minute walk test (6MWT), Borg mean score 3.5 (SD 1.8) was not related to the CSES for managing breathlessness $r = 0.073$; ($p = 0.47$) (161). This may indicate that despite increased sources of enactive mastery and verbal persuasion from the inclusion of extra supervision and supported exercise sessions, self-efficacy and the patient's confidence to manage breathlessness could potentially be negated by the physiological and affective experience of breathlessness. Moreover, it is likely that self-efficacy levels and the ability to perform self-management tasks with a chronic disease such as COPD may be driven by gender, education, socioeconomic status or influenced by other co-morbidities such as depression.

A study of the self-management strategies used in 30 COPD patients found that women selected on average two more strategies for coping with breathlessness than the men (163) A further study of 79 COPD patients found significant differences between the sexes in the mean frequency of use for dressing and grooming strategies and changing eating habits (164). Identification of the main sources of self-efficacy information and understanding the individual's capability to manage breathlessness could provide direction for designing self-management strategies that help maintain exercise and ensure the most effective use of non-pharmacological interventions. A recent review that explored the factors that influenced an individual's ability to cope and adjust to living with COPD identified a conceptual model of 16 elements that include physical, psychological, social and existential determinants of self-management (165). Self-management and an active role in the symptom control for both the patient and the carer are recognised as important in a non-pharmacological approach (8, 166). The concept of symptom mastery and the ability to manage it efficiently on a daily basis to improve quality of life is a key objective with chronic refractory breathlessness patients, addressing the individual experience and mechanisms in an approach similar to chronic pain

management. Any improvement in symptom mastery and self-efficacy for breathlessness may help the patient feel more able to deal with a sudden acute episode of breathlessness. This approach forms part of the discussions which make up a pre-planned emergency routine or "ritual for crisis" at a breathlessness clinic appointment.

2.2.4 Emergency plans "ritual for crisis"

A "ritual for crisis" is defined as an action plan for managing anxious thoughts and unpleasant body symptoms (117). The most recent working party report from the ATS defines breathlessness crisis as;

> "sustained and severe resting breathing discomfort that…overwhelms the patient and caregivers' ability to achieve symptom relief" (167).

The patient's and family's reaction to breathlessness crisis can be a crucial element in understanding how they cope with the daily experience of breathlessness. Early implementation of an emergency plan and the use of practised self-management strategies may enable patients, carers and clinical staff to deal with any acute exacerbation of breathlessness quickly and effectively. These are key components of the breathlessness management model adopted by BIS and BSS (9, 117) and are recommended in the ATS guidelines for the clinical management of breathlessness crisis (167). The COMFORT mnemonic, (as displayed in Table 6) has been proposed to summarise the key therapeutic considerations during the development of an individualised care plan to manage breathlessness crisis between the patient, caregiver and healthcare services (167).

Table 6 COMFORT mnemonic (167)

C	Call for help, Calming voice and approach among patient and caregivers
O	Observe closely, assess breathlessness for ways to respond
M	Medications to be tried
F	Fan to face may decrease shortness of breath
O	Oxygen therapy as previously found useful
R	Reassure and use relaxation techniques
T	Timing interventions to reduce breathlessness – work together – reassess – repeat

2.2.5 Toolbox of interventions

Previous studies that investigated the preferred and perceived breathlessness self-management strategies in COPD found that all of the patients consistently selected 6-10 self-management strategies to effectively meet the demands of their breathless crises (163, 164). Therefore, the concept of a toolbox of interventions has been suggested to meet the multi-dimensional problems caused by chronic refractory breathlessness. The idea that the patient can access a range of previous successful strategies or interventions to manage their breathlessness helps to individualise an effective treatment plan. The toolbox can include both, pharmacological and non-pharmacological interventions enabling the patient to choose the most appropriate measure for every episode of breathlessness. Pharmacological interventions such as opioids, benzodiazepines, selective serotonin re-uptake inhibitors are commonly used and form the mainstay of the medical management for chronic refractory breathlessness, but a discussion of their use and evidence is not within the scope of this thesis.

2.3 Non-pharmacological toolbox of interventions

Non- pharmacological interventions are a first-line approach to breathlessness and are considered both as alternative options, or to complement the use of existing drug

interventions with chronic refractory breathlessness. The various interventions can be seen as modifying the mismatch in the drive to breathe through peripheral mechanisms (walking aids, exercise and the effect on skeletal muscle) or central drivers (anxiety management, relaxation therapy, facial airflow). Although individual interventions may often work through more than one action, three broad groupings are emerging for non-pharmacological interventions as those that affect breathing, thinking or functioning. These form the key components of the Breathing, Thinking, Functioning (BTF) model that explains how breathlessness is perpetuated and helps facilitate the correct rationale and focus for the patient's symptom management (168). Breathing is proposed as affecting the neuro-physiological pathways, central and peripheral involved in the genesis and perception of breathlessness. This category includes interventions such as breathing retraining exercises, the hand-held fan, acupuncture or acupressure. Thinking classifies a group of interventions that targets the central perception of breathlessness. Examples include listening, counselling, education, relaxation and cognitive behavioural therapy. The third category, functioning, involves the use of walking aids, neuro-muscular electrical stimulation (NMES), active exercise or techniques such as pacing that are designed to help patients achieve daily activities. However, the level of evidence available for some of the non-pharmacological interventions that focus on breathlessness as a primary outcome is at best variable or lacking due to the paucity of studies. This issue that was highlighted by a previous Cochrane Review (124) that assessed a range of alternative treatment modalities including both single and multi-component interventions. At the time the authors were only able to identify sufficient studies to conclude strong evidence of efficacy with NMES, chest wall vibration and moderate evidence for the use of breathing re-training exercises and walking aids, while other modalities such as auditory distraction or relaxation drew an inconclusive verdict simply because of the lack of research data available (124).

2.3.1 Neuro-muscular Electrical Stimulation (NMES)

Neuromuscular electrical stimulation (NMES) uses a lightweight battery powered stimulator unit to produce a controlled muscle contraction via self-adhesive skin electrodes (169). The intervention permits patients to safely exercise leg muscles at home without any formal supervision (170). Group based activities such as pulmonary rehabilitation may frequently

encounter problems such as timing, scheduling or travel which may not always be appropriate for patients who experience fatigue or breathlessness from minimal exertion (171, 172). Therefore, NMES may offer a particularly helpful alternative option to patients who are unable to attend hospital, but are willing to adhere to a NMES regime, or those who need a bridge at home before progressing to the demands of an aerobic based exercise programme at hospital (173). The usual programme involves 30-60 minutes of stimulation, typically the quadriceps with or without other lower limb muscle groups such as glutei or hamstrings, three to five times a week over a period of 4-8 weeks (169, 174).

A previous literature review that investigated studies of NMES in patients with cardio-respiratory diseases including COPD and chronic HF suggested that it appears to be a possible intervention to assist with the rehabilitation of patients showing positive effects on skeletal muscle and exercise capacity (174).These findings are consistent with a previous Cochrane review of NMES that examined 11 RCT studies involving a total of 218 participants that included COPD, chronic HF and thoracic cancer (175). Meta-analysis of 8 studies found a significant improvement in quadriceps muscle strength, the primary outcome following NMES compared to the control groups by a standardised mean difference (SMD) of 0.9 (95% Confidence Interval (CI) 0.33 to 1.46) (175).

Furthermore, a meta-analysis of exercise performance with 7 pooled studies found that the mean differences for NMES compared to control were 40 metres (95% CI -4 to 84, P = 0.08) for the six minute walk test (6MWT), 69m (95% CI 19 to 119, $p < 0.01$) for the incremental shuttle walk test (ISWT) and 160m (95% CI 34 to 287, $p = 0.01$) for the endurance shuttle walk test (ESWT) (175). These values only just fall short of the suggested minimal clinically important differences of 50m (95% CI 37 to 51) for the 6MWT (176) and 48m (95% CI 34 to 64) for the ISWT (177), but are relevant to clinical practice as the distance could be sufficient to make a noticeable difference to a patient's quality of life. For example, there is the possibility that a patient may be able to maintain their independence at home because they can reach the bathroom alone.

A recent update of the Cochrane review reached similar overall conclusions that NMES appeared to be more effective than the control conditions at improving thigh muscle strength

(178). However, it was still not conclusive if increases in skeletal muscle mass and strength changed the ability to exercise, or translated into clinically meaningful decreases in the perception of breathlessness during daily activity as few data focused on breathlessness measurement as an outcome (178). Two prior studies that used a quality of life questionnaire that contained "dyspnoea" or "dyspnoea in daily tasks" domains found significantly improved self-reported breathlessness values following a home NMES programme or a NMES programme combined with pulmonary rehabilitation compared to the pulmonary rehabilitation alone respectively (179, 180). An earlier study reported that the mean scores for CRQ "dyspnoea" after NMES were significantly improved compared with baseline (mean difference 1.4, 95% CI 0.5 to 2.3; $p<0.05$) and between groups (mean difference 1.2, 95% CI 0.4 to 2.0) after 6 weeks of NMES (179). The latter study found that after four weeks training there was a significant decrease in the score of the "dyspnoea in daily tasks" domain of the 28-item Maugeri Foundation Respiratory Failure questionnaire (MRF-28) in the NMES and rehabilitation group compared to the rehabilitation alone group -1.7 (1.0) vs 0.2 (1.2), respectively; $p = 0.05$ (180).

Interpretation of the results from studies that have examined the micro-structural muscle changes following NMES suggest that breathlessness might not be significantly influenced by the effects of the intervention, or benefit would be limited to certain sub-groups of patients. A prospective cross-over RCT of 17 patients with moderate COPD patients found that a high frequency 50Hz NMES programme for 6 weeks increased the muscle cross sectional Type II fibres, but decreased the Type I fibres, a result that became more pronounced in patients with diminished baseline muscle mass or strength (181). Moreover, a recent exploratory RCT study that investigated the physiological changes and mechanisms underlying NMES in 20 patients with severe COPD found the pattern of electrical stimulation as the key component that influenced improvement in the oxidative capacity of muscle fibres and any benefits seen in the cardio-respiratory responses (170). The results indicated the presence of 2 sub-groups; "responders" defined as patients who could sustain increases in the level of stimulation intensity and therefore achieve an aerobic training response, or "non-responders" defined as patients who were unable to tolerate any high level of stimulation and subsequently produced lower mean muscle contraction intensity (170). These finding are important as the structural muscle changes associated with advanced disease such as less

aerobic type I fibres (46), reduced oxidative enzymes (45) and early onset of lactic acidosis in COPD are known peripheral mechanisms that perpetuate breathlessness. (As described in chapter 1.5.1 skeletal muscle). It would suggest the need for an individual tailored approach to any patient programme of NMES that adjusts the level of stimulation and frequencies used in relation to the baseline status of the muscle being trained and accounts for other complicating issues that may affect outcome such as patient adherence (173).

In summary, when compared to the results from pulmonary rehabilitation research there is limited randomised controlled trial (RCT) level evidence to substantiate equivalent improvements in breathlessness perception, quality of life or reduced risk of re-admission from using NMES alone. However, it would also appear that NMES could be used as an effective adjunct to help prevent some of the inevitable progressive skeletal muscle changes and cachexia in certain sub-groups of patients with advanced disease. It is possible that it could be an effective stepping stone to more energetic activity for some patients, rather than a substitute for the aerobic training in a pulmonary rehabilitation programme. Moreover, it could have a potential role to produce incremental benefit when used in conjunction with a pulmonary rehabilitation programme (180), or it could be considered as more of an effective alternative than no exercise at all in patients who are unable or unwilling to undertake any form of pulmonary rehabilitation programme (175).

2.3.2 Chest Wall Vibration

Chest wall vibration (CWV) involves the application of electrical or manual high frequency oscillation to the chest wall. It has traditionally been used in clinical practice to assist the clearance of chest mucous in patients with neurological conditions such as multiple sclerosis (MS) or MND, although it may also help alleviate the breathlessness and distress caused as a consequence of the mucous retention, secondary to the weakened respiratory muscles that compromise the ability to initiate a cough. However, at present there are insufficient data available to support the potential effectiveness of CWV as an intervention to help with breathlessness in neurological patient groups. An earlier Cochrane review was only able to identify one RCT conducted with MS patients (124). The study reported significantly less

breathlessness in the patients randomised to receive the intervention at 12 weeks compared to baseline (182).

Results from other studies that tested the properties of CWV in COPD patients have also found significant reductions in breathlessness associated with in-phase CWV (183-186). In-phase CWV is defined as vibration of the inspiratory intercostal muscle during inspiration and the expiratory intercostal muscle during expiration (185). The in-phase CWV was thought to activate intercostal muscle spindles and cause modification of respiratory sensation (184). In contrast "out of phase" vibration involves the vibration of the non-contracting inspiratory intercostal muscle during expiration and the expiratory intercostal muscle during inspiration and is associated with increased breathlessness (183). However a major limitation is that all of the studies conducted with COPD patients were at a respiratory laboratory and do not address the implications or practicalities of how the intervention works in the clinical or home setting. This makes it difficult to establish if the intervention is acceptable to patients and it is not clear if a patient could successfully use the intervention alone.

It has also been postulated that the effect of CWV is specific to the type of breathlessness experienced (187). It is known that breathlessness encompasses several distinct sensations such as work and effort, air hunger and chest tightness that are mediated by various afferent sources (5). Therefore, it is possible that CWV only effects certain respiratory sensations; a hypothesis that was formally tested in healthy adults using two experimental conditions to induce air hunger from breath holds and through mechanical ventilation at constant hypercapnia (187). The results demonstrated that CWV at the 2nd and 3rd intercostal spaces during either inspiration or expiration did not relieve the sensation of air hunger and led the authors to propose that the beneficial effects of CWV were limited to circumstances where work and effort were the dominant breathlessness sensations experienced (187). This would suggest that the intervention may only be effective for certain episodes of breathlessness and it could limit the number of patients who find the intervention useful.

In summary, the role of CWV is still far from understood and the practicalities of using the intervention outside of a respiratory laboratory are not known. In addition the limited number

of studies indicates that further research is required to fully assess potential patient groups or individuals who may benefit (or not) from intervention use.

2.3.3 Breathing re-training exercises

Controlled breathing is a term used to embrace a range of breathing retraining exercises (188). The techniques or exercises most commonly employed are known as pursed-lip breathing (PLB) and diaphragmatic breathing (DB). These breathing techniques usually form a core component of any routine breathlessness patient management and are often added to pulmonary rehabilitation programmes as part of the self-management strategy primarily devised for COPD patients (189, 190). The aim is to ameliorate adverse pathophysiological effects of disease processes by improving the strength and endurance of the respiratory muscles, optimizing the pattern of thoracic-abdominal movement and decreasing the dynamic hyperinflation of the diaphragm (191). Any reduction in the diaphragmatic hyperinflation and improved muscular fibre length could help decrease the respiratory muscle load and stimulation of pulmonary C-fibres (J receptors) that drive the load-capacity imbalance and resulting breathlessness (68).

The evidence level for this type of non-pharmacological intervention is regarded as moderate and most of the studies undertaken have exclusively focused on COPD patients (124). Previous systematic reviews of the various breathing techniques offer inconclusive and conflicting views as to the efficacy of each method and the role with different sub-groups of COPD patients (189, 192, 193). Most of the controversy seems to relate to the questionable efficacy and problems reported with DB. This method has been described as predominantly breathing with the diaphragm while minimising the activity of the accessory muscles that may aid inspiration (192). It is proposed that correct DB improves chest wall movement and the distribution of ventilation, while lowering the energy expenditure involved in breathing and potentially the accompanying breathlessness (191). But three prior reviews have refuted the efficacy for breathlessness intensity (188, 189, 193), and only one suggests possible relevance for a particular COPD sub-group, or adaptation of the patient posture to increase the intra-abdominal pressure and counteract the possible negative effect of a paradoxical breathing pattern (192).

A paradoxical and asynchronous breathing pattern is described as the simultaneous inward movement of the abdomen and the outward movement of the upper chest during inspiration that consequently compromises the efficiency of breathing and increases breathlessness (194). However, a more recent study that sought to identify the predictors for the efficacy of DB with COPD patients suggests that those most likely to benefit have intact respiratory muscle strength, diaphragmatic mobility and are still able to increase tidal volume during DB, while conversely patients with marked hyperinflation of the lungs, limited diaphragmatic excursion and tidal volume change may signal a poor responder who is likely to breathe in a paradoxical manner (190).

Past reviews of the evidence available for PLB have drawn mixed conclusions about the efficacy of the technique and it would appear only beneficial in certain sub-groups of COPD patients (188, 189, 193), yet PLB is commonly cited as a breathing technique instinctively used, or the easiest to learn (195). It is described as slow exhalation for 4-6 seconds through the lips when held in a whistling or kissing position (195) and is often accompanied by the patient instruction "blow as you go". Prior studies report that PLB reduces respiratory rate, breathlessness and improves tidal volume and oxygen saturation at rest (196-199). The mechanism thought to responsible for the effect of PLB is the prolonged expiration that decreases airway collapse and limits the hyperinflation from the loss of elastic recoil pressure in the lungs (188). However the benefits of PLB seem to be inconclusive and efficacy limited to certain COPD sub-groups that have substantial physiological change or loss of lung elastic recoil pressure (188).

In summary, all of the past reviews of DB and PLB have been unable to clearly answer the question of whether the breathing re-training exercises significantly effects the patient's perception of breathlessness. This in part may relate to the study selection as reviews include trial designs other than RCTs or offer conclusions based on the physiological outcomes that correlate inconsistently with symptoms (200). The most recent Cochrane review of PLB and DB for COPD patients highlights the lack of quality evidence and research studies that have focused on the primary outcome of breathlessness. Only 2 RCTs are identified as using the primary outcome of breathlessness for each of the techniques; PLB (201, 202) and DB (203, 204) respectively, while methodological shortfalls across all of the included studies (200).

The Cochrane review concludes improved functional capacity measured on a 6MWT; mean difference 50 metres for PLB studies involving 60 participants and mean difference 35 metres for DB studies involving 30 participants, but inconsistent benefits with breathlessness and health related quality of life measures (200). This raises the issue as to whether breathlessness intensity is the most appropriate outcome to record improvement as it is possible that a patient could utilise either PLB or DB to walk further before reaching their maximal breathlessness intensity, but they may still feel no change to their breathlessness as the maximal intensity is still the same at the end of the distance walked.

However, the Cochrane review conclusions do concur with other prior mixed method studies that have investigated the perceived effectiveness of breathlessness self-management strategies in COPD participants. The results from one survey found that PLB was rated the least effective among the 11 topmost breathlessness self-management strategies identified from a sample of 30 patients (163), while another survey of 79 patients also reported that breathing exercises were the least helpful of the available techniques, unless the participant had prior experience of pulmonary rehabilitation in which case a significant difference in benefit was noted (164). Therefore it would appear similar to NMES, that an individualised approach should be adopted when teaching breathing retraining exercises to all patients with respiratory diseases as it is not clear from the current evidence available who will respond to which technique or who could potentially experience incremental benefit with breathlessness. Furthermore, the majority of studies are limited to the findings from COPD patients and it is possible that other sub-groups could find benefit but insufficient research data is available to conclude this issue.

2.3.4 Walking aids

There are various walking aids available to assist patients with mobility and exercise capacity, although only the wheeled walking frames such as the 3 or 4 wheeled rollators are suitable for respiratory patients with breathlessness problems as repeated upper arm elevation, such as that required to lift and move a un-wheeled walking frame, demands extra metabolic and ventilatory response (205). These findings concurred with a subsequent study that examined the effect of different walking aids in 27 COPD patients during 4 days of

consecutive testing with random ordered 6MWTs; the authors observed decreased distance walked, mean 165m (SEM 13) with an un-wheeled walker (Zimmer frame), in comparison to the wheeled walker (rollator frame), mean 212 (SEM 17) (206). Similarly, other studies that have examined the patient benefits from wheeled rollator use during the 6MWT have consistently shown significant reduced breathlessness and increased walking distances (207-210).

The mechanisms of action are thought to relate to the effects of the forward lean posture and the shoulder girdle support which helps respiratory muscles to increase maximal force generating capacity (211). Earlier study with four normal subjects found significantly increased ventilatory capacity when their elbows were firmly braced on a table for four minutes, a change attributed to the improved function of the accessory muscles that expand the ribcage (211). The authors speculated that this effect assumes greater importance in COPD as these patients depend more on the inspiratory muscles due to pathophysiological disease changes that result in a flattened and ineffective diaphragm (211). This is confirmed by the results of a study with COPD patients which assessed the mechanisms of improvement in exercise capacity from rollator use (209). Results demonstrated significantly increased maximal voluntary ventilation (litres/min) with arm support, median 60 (IQR 36 -65), in comparison to no arm support, median 55 (IQR 36 -65), $p = 0.001$, and significantly higher tidal volume (litres) at the end of the 6MWT with the rollator, median 0.98 (IQR 0.92 -1.43) versus no rollator, median 0.92 (IQR 0.81 -1.37), $p = 0.03$ (209). Simultaneously, the patients also significantly improved their walking distance (metres) with the rollator, median 462 (IQR 424 -477) compared to without the rollator, median 416 (IQR 396 – 435), $p = 0.04$, and experienced less breathlessness with the rollator, Borg breathlessness score, median 5 (IQR 4 -7) versus without the rollator, median 6 (IQR 4 -7), $p= 0.10$ (209).

Likewise, other prior studies that have examined relief of breathlessness from the forward lean posture in COPD have proposed increased ventilatory capacity or higher maximal inspiratory pressure thought to be associated with improved length-tension relationship of the diaphragm (141, 212, 213). These findings underline the importance of the forward lean posture in relation to potential patient benefit from rollator use. Theoretically, it also suggests that a rollator could be used, not only to assist mobility, but as a static device in an outdoor

situation that provides the patient with postural and upper limb support during episodes of exertion induced breathlessness, thereby speeding recovery.

However, although research studies have demonstrated benefits such as decreased breathlessness and increased walking distance from rollator use during exercise testing (207-210), these results do not seem to translate into significant improvements in the patients quality of life or functional capacity when a rollator is used long-term at home (214). The results of a RCT designed to assess the effect of rollator use on quality of life in 31 patients with COPD identified no between group differences after 1 or 2 months in any of the domains of the CRQ (214). For example, the CRQ breathlessness change at 2 months was 0.13 (95% CI -0.57 to 0.84) in the rollator group versus no rollator group 0.036 (95% CI -0.13 to 0.20), $p = 0.1$ (214). Furthermore, the authors identified a sub-group of patients, 8 out of 18, who were infrequent users utilising the device less than 3 times a week, despite indicating their preference for walking with the rollator (214). The lack of adherence to the rollator suggests that there may be other unknown drivers that influences the patient's use of the device and could reduce the potential benefit to functional capacity. For example, the patient may feel embarrassed and self-conscious of what others may think when using a walking aid in public, a likely problem given that Gupta et al identified that most outside activities (81%) were associated with rollator use (214).

In summary, despite the promising results shown by rollator use in COPD patients during acute exercise testing these effects do not seem to equate to meaningful changes in everyday quality of life. Moreover, it appears that there are other psychological and social issues at play which could influence patient adherence to a rollator thereby potentially reducing possible benefits. Finally, the rollators proposed mechanisms of effect align to the pathophysiological changes that occur in COPD patients, such that the forward lean posture improves the function of a flattened diaphragm and assists the accessory muscles in the biomechanical efficiency of breathing. It is not known if the rollator would work in a similar way in diagnoses such as cancer or HF, although it is very likely that benefit would result from the maintenance of skeletal muscle bulk, which is important in the genesis of breathlessness and from improvements to the biomechanical efficiency of walking. However,

at present there appears to be no research that has evaluated the benefit in these groups therefore the evaluation is limited to COPD patients.

2.3.5 Distractive Auditory Stimuli

Attentional distraction, such as distractive auditory stimuli therapy (DAS) is an intervention that primarily tries to influence the patient's perception of their breathlessness during exercise or at rest, usually by listening to music. It involves directing the focus of the conscious state away from one task or sensation (e.g. breathlessness) toward another stimulus (e.g. auditory), which causes decreased cognitive processing of the former task or sensation (e.g. reduced perception of breathlessness). Information concerning the modulation of breathlessness by attentional processes are limited (215), although a more recent study that investigated the effects of DAS measured two distinct dimensions of breathlessness; the sensory perception or intensity and the affective perception or unpleasantness, in addition to the perceived global level of breathlessness and the patient's positive or negative affective state (216). Results from the study, a crossover RCT of 20 COPD patients demonstrated that the DAS group had a significantly decreased unpleasantness of breathlessness VAS during a 6MWT, mean 0.3mm (SD 2.1) in comparison to the non-distraction group mean 1.8mm (SD 2.7), $p<0.05$, but no such differences were found in the intensity of breathlessness VAS mean 0.1mm (SD 3.8) and 0.0mm (SD 3.3) respectively (216). Furthermore, the results for positive affectivity were significantly higher in the DAS group mean 31.5 (SD 7.9) compared to the non-distraction group mean 29.5 (SD 8.2), $p < 0.05$ (216). These findings suggest that DAS specifically effects the patient's affective state, therefore it could benefit those who feel anxious about breathlessness symptoms experienced during exercise. Theoretically, it may also help a patient to increase training intensity or duration as well as improve the likelihood of adherence to a pulmonary rehabilitation programme. A view endorsed by a recently published systematic review which examined the effects of DAS on exercise capacity, symptoms and health related quality of life in patients with COPD and included 13 studies, (12 controlled or crossover RCTs and 1 cohort study) with a total of 415 participants (217). Meta-analysis of 2 pooled studies (n=65) found increased exercise capacity when DAS was used for at least 2 months weighted mean difference 98m, (95% CI 47-150) (217), although inconsistent benefits were reported when DAS was used as a short-term strategy during

exercise testing or at rest (217). This indicates that DAS benefits seems to relate to regular, long-term use with exercise and may reflect that desensitization to exertion induced breathlessness occurs gradually with DAS until it becomes part of a learnt patient strategy after time. However, given that the systematic review findings are limited by the small number of studies and the high level of heterogeneity in the training programmes (217), the evidence available does not provide a comprehensive or clear assessment of the role of DAS with chronic refractory breathlessness. Moreover as the research is limited to COPD patients it is not possible to evaluate if DAS would be effective with breathlessness problems in other diagnoses such as cancer, HF or MND.

In summary, although accurate evaluation of DAS as an intervention to alleviate breathlessness is limited by the low volume of research and the lack of study in patient groups other than COPD, it would seem that as an adjunct to pulmonary rehabilitation the strategy of listening to a favourite piece of music during exercise could be a worthy distraction that helps to enhance patient performance and improve adherence to the intensity of the training programme

2.3.6 Hand-held fan

The hand-held fan is a small, lightweight non-pharmacological intervention that can be easily and safely used by patients in most circumstances (See Figure 4).

Figure 4 Hand-held fan

2.3.7 Rationale for the hand-held fan

There are no clinical guidelines to assist the decision making or procedure available to identify which patients to select to use the hand-held fan and there is still a limited evidence base with only three published studies to date (218-220). The evidence for the hand-held fan has only been analysed once through a Cochrane review in 2008 and at the time a lack of sufficient evidence meant that the systematic review was unable to conclude if there were any benefits from this non-pharmacological intervention (124). Two studies were identified by the review; one a cross-over RCT (218) and the other a submitted conference abstract (221). Baltzan found a transient, but significant reduction in breathlessness from a fan blowing onto the face in addition to the flow of oxygen from a nasal cannula on day one during 3 subsequent days of exercise tests in 17 COPD patients (221). The following first adequately powered cross-over RCT that recruited 50 participants with any advanced disease diagnosis found a significant difference in VAS with a decrease of 7.0mm, (95% CI 2.5-11.7mm), p = 0.003 after the hand-held fan was directed to the face compared to the leg. But the authors also identified an inadequate wash-out period of 10 minutes that limited conclusive analysis of the breathlessness improvement, although any error would have been in the direction of an underestimate of benefit. Sub-group analysis indicated that the timing and length of beneficial response to airflow may vary among individuals (218). These studies suggest that airflow in the short-term could be effective at relieving breathlessness both at rest and at the start of exercise when the flow of air from a fan is directed to the face.

However, the results of a subsequent longitudinal RCT study that involved 70 patients published shortly after the crossover RCT failed to show similar benefits of air flow when the hand-held fan was used longer term. The primary outcome was the use of the hand-held fan or wristband after 2 months and although approximately half of those allocated to the hand-held fan arm were still using the intervention at two months and only 20% of the comparator arm were using a wrist band, this did not reach statistical significance. However, this was a phase II trial and thus not designed to test efficacy. A subgroup of hand-held fan users commented very favourably with regard to overall opinion, and it may be that their appraisal took more than breathlessness intensity into consideration (219). Furthermore assessment of breathlessness intensity was framed in terms of "on average over the past 24 hours" rather

than in relation to “breathlessness now” immediately before and after hand-held fan use. The conflicting studies do not provide conclusive or sufficient evidence of the effectiveness of airflow and the data suggests that certain patients groups may find more benefit from the hand-held fan than others (219). It could also be possible that some patients find that the airflow from a simple object like a hand-held fan a less believable or plausible treatment when compared to the medical equipment that accompany the delivery of oxygen or medication such as beta agonists.

2.3.8 The potential role of the hand-held fan

The passage of cool air over the nasal mucosa receptors and facial skin innervated by the lower branches of the trigeminal nerve are two possible afferent sources of respiratory sensation and offer plausible mechanisms to relieve breathlessness that merit further investigation (26, 222-225). Previous studies with animals demonstrate a decrease in ventilation following cooling of the upper airway (226), while research with normal volunteers found that cold airflow directed at the cheek significantly reduced breathlessness associated with an inspiratory resistive load and hypercapnia (227). The cooling may provide the patient with an alternative comfortable sensation that could operate as a distraction from the other unpleasant respiratory sensations of breathlessness. A prior study that assessed the preferred and perceived effectiveness of breathlessness self-management strategies in 30 COPD patients found that getting fresh air was ranked in the top three along with medication and oxygen to help ameliorate episodes of breathlessness (163).

In addition the results from a preliminary study that explored the feasibility of using magnetoencephalography (MEG) scanning for patients with chronic refractory breathlessness found that the pattern of alpha wave activity in the parietal–temporal regions changed and decreased when airflow was used during recovery from exercise (228). These findings suggests that the sensation of cool airflow is potentially an afferent signal that could modulate the mismatch in the central perception of breathlessness and lead to decreased neural respiratory drive.

Moreover, two other prior studies have demonstrated the possibility of increased exercise tolerance with the use of cold air in patients with respiratory disease. Marchetti et al reported improved performance of a leg ergometer test with a large fan directed to the face in comparison to the leg, but no difference in the breathlessness intensity experienced in 4 COPD patients using a randomised cross-over design (229). A further RCT of 19 COPD patients who exercised on a cycle ergometer had increased peak exercise tolerance in cold air (-13 °C) when compared to breathing room air (230).

2.3.9 The potential role of airflow

These findings also indicate another role for cool airflow, to help improve the chances of patient adherence to exercise. Exercise is known to be important to help manage breathlessness and strong evidence of the benefits has amassed (as described earlier in chapter 2.2.2 Exercise and pulmonary rehabilitation). However the physiological and affective sensations that accompany breathlessness induced by exertion may discourage the patient from persisting with the activity. It is possible that the breathlessness sensations experienced could influence the patient's self-efficacy and capability to cope with any exercise, potentially negating any positive interpretation of exercise achievement. Therefore the use of non-pharmacological interventions such as the hand-held fan may help provide the solution to decreasing the unpleasant sensations associated with exercise and could help encourage patient compliance with pulmonary rehabilitation or adhere in the longer term to a maintenance programme. However, it is not often perceived that patients could use cool airflow as an effective solution to relieve exercise induced episodes of breathlessness.

Likewise, airflow is not usually considered an important clinical option for the relief of acute, or acute exacerbation of chronic refractory breathlessness, Oxygen is firmly entrenched in the minds of most people as the normal option to help with breathlessness as the element is fundamental to life and survival. Therefore, it follows that this intervention is likely to be favoured particularly in settings where it is often initiated by paramedics, emergency services, or by the ward staff "out of hours", irrespective of oxygen saturation levels.

Oxygen is commonly prescribed for the palliation of chronic refractory breathlessness, with one survey demonstrating that 70% of responding clinicians would prescribe oxygen irrespective of oxygen saturation and a further 35% that would prescribe solely on patient request (231). Moreover, it is not only the patients who can influence the clinical rationale for oxygen therapy as the findings from a large consecutive cohort study suggested that the carer may also exert an important role. Results demonstrated that patients were more likely to be prescribed oxygen if they lived with their carer than if they lived alone (118). The qualitative data clearly indicates that there may be other motives that operate and undermine the therapeutic reasons for considering oxygen treatment.

Nonetheless, the accumulation of evidence from both RCT studies and systematic reviews that have examined the efficacy of oxygen therapy compared to medical air for the relief of breathlessness in a variety of patient groups (cancer, chronic heart failure, kyphoscoliosis and COPD) with mild or normo-hypoxaemia have consistently failed to show any additional benefit from oxygen therapy in comparison to medical air for the relief of breathlessness (94, 232-235), although one Cochrane review of COPD describes modest benefit (93). More importantly, the results from a large, adequately powered, international, multi-centre trial that randomised 239 participants (COPD 63%, cancer 16%) to receive at least 15 hours a day of oxygen or medical air delivered via home concentrator for seven days suggest that the medical air used in the placebo arm may not be an inert comparator as previously thought (94). The primary outcome was breathlessness intensity measured twice daily, morning and evening using a 0 to10 NRS. Significantly the results reported that both the medical air and oxygen improved breathlessness; the mean morning and evening scores decreased by -0.8 (95% CI -0.5 to -1.1) and -0.4 (95% CI -0.1 to 0.7), respectively ($p<0.001$) irrespective of the study arm (94). These findings indicate the likelihood that medical air delivered via nasal cannula is a meaningful active intervention. This view is echoed by a recent paper that assesses the current evidence base for oxygen. The review indicates that neither the mild hypoxemia nor the partial pressure of inhaled oxygen appear to be the key mechanisms in the perception and amelioration of chronic refractory breathlessness (225). The results from Abernethy et al are the most generalizable to date and suggest the possibility that airflow could have a role with a wide target population. Airflow provided by the hand-held fan may prove a much less burdensome portable patient option and there are considerable costs

implications for healthcare services when compared to the instigation of oxygen therapy and the associated equipment such as cylinders or a home concentrator for the gas delivery. However, qualitative data that examine the patient's perception of airflow is scarce to date. It is not known whether a patient or carer would consider airflow from a hand-held fan an acceptable option in comparison to oxygen given the evidence of the social and cultural beliefs that may influence the use of this therapy.

2.4 Calming Hand

The Calming Hand is a tool designed to help patients cope better with episodes of breathlessness. Similar, to the hand-held fan it can be easily utilised in any circumstances due to its simplicity (See Figure 5). It was initially used by Dorothy House Hospice Care as a component of their "Breathlessness Management Toolbox"(236). This booklet is composed of various non-pharmacological techniques that are usually applied in the physiotherapy management of palliative patients with refractory breathlessness.

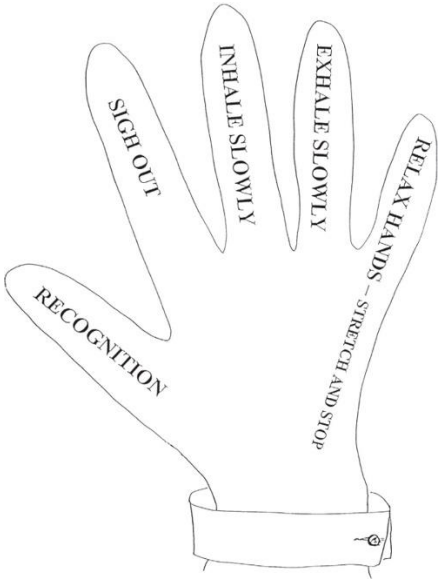


Figure 5 Diagram of Calming Hand (237)

The Calming Hand has only recently been formally identified in practice as a coping tool regularly used by palliative care physiotherapists in breathlessness treatment (238). It has

been used clinically for nearly a decade, yet there is very little, if any, published evidence of the effectiveness, physiological mechanisms of action or patient benefits from use of the Calming Hand. The only evidence found was from unpublished MSc thesis results presented at conference (238). Burnett studied this tool using mixed methods with a survey of physiotherapists, sampled from non NHS palliative care institutions (hospices) through electronically administered questionnaires. The response rate was 61% of the sample population. Of those who responded, 88% of physiotherapists stated that they used the Calming Hand regularly or frequently with patients (238). These results suggest that the Calming Hand tool is commonly practised as an intervention for breathlessness with patients by physiotherapy clinicians across hospice establishments. However a limitation of the work is that the survey has investigated the Calming Hand in the context of an acupressure technique only. This does not allow for an accurate interpretation of the survey findings as it is not clarified whether the technique is effective from the acupressure perspective alone, or if it is a combination of various components that may provide perceived benefit with patients.

2.4.1 The potential role of the Calming Hand

The emerging prevalence of this intervention in breathlessness management programmes suggests clinicians feel that the Calming Hand is potentially a valuable and appropriate measure to effectively address episodes of breathlessness. Interestingly, the questionnaire results from the MSc thesis identify that the Calming Hand was perceived by clinicians to be the most effective compared with the other acupressure techniques incorporated in the "Breathlessness Management Toolbox" (238). However, at present this finding is solely the proxy judgement of the physiotherapist's surveyed and the study did not measure patient reported outcomes.

It is not known if there are any clinical trials or other grey literature that report the clinical effectiveness of this coping technique in relieving breathlessness in palliative patients, or if alternative sources investigate the most appropriate use in breathlessness management. At present it would appear to be a technique that is applied generally to patients experiencing chronic refractory breathlessness without regard to their diagnosis, or evaluation of the

breathlessness sensations and personality traits. It may be of value to certain sub groups and not to others.

2.4.2 Rationale for the Calming Hand

The performance of the Calming Hand could affect the patient's perception of breathlessness and even augment benefit if there are any potential underlying physiological or psychological mechanisms. A preliminary examination of the Calming Hand instructions suggests the possibility of three plausible mechanisms; sighing, breathing control and relaxation.

Sighing is a long deep breath that occurs spontaneously several times an hour in a healthy person or can be produced voluntarily. Sighing prevents atelectasis of the lung alveoli, restores lung compliance and improves the efficiency of gas exchange (239-242). More recently, a study that investigated spontaneous breathing in 42 healthy subjects during 20 minutes of quiet sitting found that the respiratory dynamics before and after a sigh were different (243). Preceding a sigh total variability of minute ventilation gradually increased, which suggested greater randomness in the respiratory pattern. Following a sigh there was significantly higher respiratory variability compared to before the sigh (243). The authors concluded that a sigh acts to re-set structured respiratory variability and adds information to the respiratory system (243). Therefore, the initiation of a sigh at the start of the Calming Hand strategy may help reduce the sensation of breathlessness by restoring a more regular pattern of breathing.

It is also possible that a sigh may influence the affective component of breathlessness. A prior study that examined the sigh rate during 10 minutes of quiet sitting in 75 female participants who scored high or low for trait negative affectivity found different patterns in respiratory variability in response to sighing between the two groups (244). This led the authors to suggest that sighing might have different functions according to the affective state and may be determined by the individual's psychological expression of emotions such as sadness, relief or frustration rather than physiological characteristics (244). However, although spontaneous sighing is linked to the subjective relief of negative emotional states (245, 246), is not clear how easy or practical it is for patients to perform an instructed sigh during an

episode of breathlessness or if the effects are similar to a spontaneous sigh. This problem is highlighted by a prior study that investigated the changes in respiratory variability and muscle tension following a spontaneous sigh in comparison to an instructed sigh after a mental stress test in 43 healthy participants (247). The results found that a spontaneous sigh was followed by decreases in muscle tension and a re-setting of respiratory variability, while in contrast an instructed sigh seemed to inhibit recovery of both muscle tension and respiratory variability (247). Nonetheless, as the research are restricted to a laboratory setting with healthy young participants it is not possible to deduce what the implications would be for patients or if the effects are the same in other environments.

A second plausible mechanism of action relates to the performance of a long slow exhalation followed by gentle inhalation during the Calming Hand strategy. This may produce similar effects to breathing control or breathing re-training exercises, such as DB or PLB as outlined earlier in chapter 2.3.3 The correct performance of DB is thought to improve ventilation and chest wall movement, thereby reducing the effort of breathing and potentially alleviating breathlessness (191). Likewise, PLB which focuses the patient's attention on prolonged exhalation is proposed to decrease airway collapse and limit hyperinflation from the loss of elastic recoil pressure in the lungs (188), which helps alleviate breathlessness and improve oxygen saturation at rest (196-199).

Finally, it is also possible to speculate that the Calming Hand could promote relaxation through an amalgamation of motor and sensory input from the hands. The holding and stretching of the fingers are techniques associated with Mitchell's relaxation (248). This type of physiological relaxation method is based on reciprocal muscle inhibition and is described as a series of ordered isotonic contractions that are performed in conjunction with DB to assist postural realignment (248). However, apart from one RCT of 24 healthy subjects that found a significant reduction in respiratory rate, mean 19.37 (SE1.30) versus mean 14.63 (SE0.67), $p < 0.01$ following two sessions of Mitchell's relaxation (249), other research that examines the physiological effects or benefits of this technique with breathless patients are scarce. Gift et al tested the effectiveness of a pre-recorded progressive muscle relaxation message designed to release tension in 16 muscle groups at four weekly sessions and included home practice with 26 COPD patients (250). The results showed no significant

differences between the two groups in breathlessness and anxiety VAS measurements taken after the fourth session, although breathlessness ratings decreased to a greater extent in the relaxation group compared to the control (250). Similarly, a study that tested progressive muscle relaxation in 59 HF patients with two training sessions and used a pre-recorded message for home practice found a non-significant trend towards a greater improvement in symptom status (breathlessness and fatigue) and psychological distress (251).

These studies do not provide sufficient evidence to conclude whether progressive muscle relaxation can help with breathlessness symptoms, or aid interpretation of the relaxation technique used in the Calming Hand strategy. It would seem more probable that any potential benefit from the Calming Hand results from using all of the components (sighing, breathing control and muscle relaxation) together rather than individually, or possibly the patient could feel more confident and re-assured that they have an extra tool to try in the event of a crisis episode of breathlessness.

2.5 Summary of chapter two

There are many non-pharmacological interventions available to help with breathlessness management. Some interventions such as NMES, and walking aids have at least some evidence to support their use for breathlessness. When this thesis was planned, a preliminary search identified limited research in support of the hand-held fan (124), but there were several oxygen RCTs, where potentially useful data could be found in the medical air comparator arms. Initial database searches for the Calming Hand failed to show any published work regarding this tool, although it is in common clinical practice. Since the Cochrane review (124), there have been two phase III RCTs published which confirm benefit for the complex breathlessness interventions delivered at home or in a breathlessness clinic by a multi-professional team (8, 9).

The hand-held fan and the Calming Hand promote breathlessness self-management and both can be used as part of an emergency plan for dealing with an acute exacerbation of breathlessness. The patient's hand represents a simple tool that is immediately accessible, constantly available, does not get lost as is the risk with information leaflets, ensuring quick

initiation of the strategy. It can be administered independently by the patient or the carer and has the potential to prevent escalation of anxiety into panic from the sudden onset of breathlessness, thereby possibly avoiding a crisis hospital admission. Likewise, the portable lightweight hand-held fan can fit in the pocket or handbag and may serve not only as a source of airflow, but as a prop object with the patient secure that there is a device to try if the need arises. These non-pharmacological interventions represent simple measures that could be cost-effective requiring little clinician input or funding.

In view of the of the available evidence for the hand-held fan and Calming Hand and the issues highlighted so far, in chapter three studies with data from published studies of either the hand-held fan, or medical air comparator groups of oxygen RCTs will be included in a preliminary evaluation of airflow for the relief of breathlessness.

Chapter 3 Preliminary systematic review of airflow

3.1 Background

The first two chapters have described possible mechanisms whereby cool airflow over the lower face and nasal mucosa may alleviate the sensation of breathlessness, and the evidence base for the hand-held battery operated fan has been summarised, highlighting that this offers a simple practical way of providing airflow for patients in everyday clinical practice. This chapter presents a systematic review and exploratory analysis of the evidence relevant to the hypothesis that non-oxygen enriched cool airflow to the face reduces the sensation of breathlessness.

3.2 Research question

Is airflow effective at relieving chronic refractory breathlessness in adult patients with mild hypoxaemia or normoxaemia in advanced stages of any malignant or non-malignant disease?

3.3 Rationale

Previous oxygen studies have used medical air delivery as a placebo in case any benefit was perceived in response to the presence of the medical equipment. A placebo is described as a dummy treatment administered to the control arm in a RCT in order that the specific and nonspecific effects of the experimental treatment can be distinguished (252). However, as Abernethy et al noted, breathlessness intensity improved in both arms indicating that, as the sham oxygen concentrator was intended to counter any possible nonspecific effects, the medical airflow may be an active comparator and not part of a placebo response (94).

3.3.1 The secondary analysis of comparator arm measures as observational cohort data: a novel approach for preliminary assessment of effect

The results from the non-oxygen enriched air control arm of many oxygen studies may therefore be useful as a source of preliminary information about airflow as the results relate

directly to the passage of medical air delivered via face mask, mouth-piece or nasal cannula. Studies with baseline and post treatment measures of breathlessness intensity would give "before and after" data regarding the effect of non-oxygen enriched airflow. By treating these control arm measures as cohort observational data, it might be possible to gain useful preliminary data to see if there is any indication that airflow could be beneficial, and thus worth testing in further RCTs and to examine the variability around the reported change in measures to inform the design of such a study.

The most robust approach to identifying the effect of an intervention is to conduct a systematic literature review to identify relevant RCTs of the intervention under study and a comparator, and if possible, to perform meta-analyses. The Cochrane Methods Group exemplifies the framework with formal, transparent and explicitly agreed methodology that is most familiar to clinicians and academics (253).

However, the Cochrane Methods group also discusses the use of data from other study designs and supports the inclusion of non-randomised studies as a justifiable approach if the question or area of interest may not be appropriately answered from RCTs (254). In this case, as there are limited RCT data on airflow with only two experimental trials of the hand-held fan published at the time of this review, different study designs have been considered as an alternative source of airflow data.

Moreover, as the results from Abernethy et al (94) indicated the possibility that the medical air delivery was an active intervention there are further unanswered questions and added rationale to examine the published data available from the placebo arm of oxygen studies in relation to this hypothesis. Therefore, the review includes the active intervention arm data from any RCT of the hand-held fan as well as two sources of non-randomised data; the data drawn from the comparator placebo arms from the RCTs of oxygen which are assessed as if it were data from a cohort observational design study and the results extracted from studies with an *a priori* cohort observational design that were identified through the SR methods. In this SR, the Cochrane group recommendations for SR of non-randomised studies were followed and it is acknowledged that there is increased risk of bias from an approach that uses single arm data for both the hand-held fan and oxygen studies.

3.3.2 Limitations for this approach

Although the review has strictly adhered to the recommended Cochrane guidance for minimising reporting bias from the inclusion of non-randomised studies (254), with an explicitly stated *a priori* protocol of the patient population, the airflow intervention delivery, and the outcome measures, any conclusions drawn are limited by the methodological approach. It is acknowledged that the findings are based on "before and after" values which potentially have a higher likelihood of known bias, particularly those resulting from selection bias. Therefore the meta-analyses are to be interpreted with caution as confounding biases may shift the estimate of the intervention effect, increase the variability of the observed effects and introduce more heterogeneity among studies (255). However, this approach represents an acceptable way of providing a preliminary review of existing prospective cohort data (254) and moreover it may be possible to glean important insights about airflow that could inform the choice of research questions and design for the proposed PhD study.

3.4 Objectives

The primary objective of this review was to determine preliminary data regarding the effect of non-oxygen enriched facial or nasal airflow for the relief of chronic refractory breathlessness in adult patients with mild hypo- or normoxaemia.

3.5 Inclusion and exclusion criteria

In order to find the relevant papers from which to extract the data from the comparator arm, the following criteria were used.

3.5.1 Study design

Randomised Controlled Trials (RCTs), controlled clinical trials (quasi-randomised experimental trials with or without blinding) and observational cohort studies were included.

3.5.2 Participants

Adult patients with chronic refractory breathlessness from any advanced disease aetiology were included. The inclusion criteria were as follows in the individual diseases:

- Malignancy: advanced primary and metastatic cancer patients, who have undergone disease treatments like chemotherapy, radiotherapy or surgical interventions.
- Chronic Obstructive Pulmonary Disease (COPD) with forced expiratory volume in 1 second (FEV^1) of less than 50% predicted value
- Interstitial lung disease or pulmonary fibrosis where breathlessness is present
- Chronic heart failure: New York Heart Association (NYHA) stage III-IV
- Motor Neurone disease and other neurological disease where breathlessness is present or forced vital capacity (FVC) less than 80%
- Kyphoscoliosis: a moderate - severe sideways and forwards curvature of the spine Cobb Angle > 50° and FEV^1 of less than 50% predicted value

These criteria were adapted from the Cochrane review of non-pharmacological interventions for breathlessness (124). The cut-off point was at least 50% of the study population were classified in advanced, palliative or later stages of disease as defined above. Participants in studies with any condition not regarded as progressive, refractory to treatment and advanced such as asthma were not included in the review.

3.5.3 Exposure

Studies were included if airflow was;

- Delivered from either a fan (hand-held or table) or non-oxygen enriched compressed air (using the control arm results only from oxygen/helium studies);
- Directed at the nasal mucosae, orally or at the facial skin innervated by the lower two branches of the trigeminal nerve.

- Using a non-invasive ventilatory method (nasal cannula, mask or mouthpiece), but not Non Invasive Partial Pressure Ventilation (NIPPV)

Administered:

- single dose *during ambulation*, or *at rest* taken as needed (PRN *pro re nata*) (93)
- Short-Burst Oxygen Therapy (SBOT) intermittent use *before* exercise or *after* exercise for recovery (256)
- continuously over 15hr a day as Long-Term Oxygen Therapy (LTOT) studies or during the night as Nocturnal Oxygen Therapy (NOT studies) (257)

Airflow directly administered to the trachea, or at sub-zero temperatures was excluded

3.5.4 Primary outcome measures

Studies were included where breathlessness was measured as the primary or secondary outcome. The following subjective measures of breathlessness were included:

Breathlessness severity, intensity, unpleasantness or distress measured on a uni-dimensional scale such as:

- Modified Borg Score, a categorical scale with ratio properties
- Visual Analogue Scale (VAS), 0 - 100mm anchored 0 = no shortness of breath and 100mm = shortness of breath as bad as can be
- Numerical Rating Scales (NRS), 0-10 numbered scale anchored 0 = Not breathless at all and 10 the worst imaginable breathlessness
- Likert scales with verbal responses such as “a bit better”, “much better” or “no difference” or any other validated uni-dimensional scale for measuring breathlessness.

Studies were only included if they reported the breathlessness outcome measures for at baseline and post-treatment or “before and after” measures of breathlessness.

3.5.5 Secondary outcomes

The following secondary outcome measures from studies were also considered for possible meta-analyses:

- Quality of Life: disease specific questionnaires e.g. chronic respiratory questionnaire (CRQ), St Georges Respiratory Questionnaire (SGRQ), generic measures e.g. short form 36 (SF-36),
- Depression or Anxiety Specific Measurements: Hospital Anxiety and Depression score (HADS)
- Ambulation and activity limitation: Incremental Shuttle Walk Test (ISWT) or 6 minute Walk Test (6MWT)
- Self-efficacy: general self-efficacy scale (GSES)
- Participant preference and satisfaction with the treatment
- Participant withdrawal and drop-out from the studies
- Adverse effects recorded

3.6 Search methods for study identification

3.6.1 Electronic searches

A preliminary search of the electronic databases were made through the library electronic resources at the University of York and University of Hull during March 2012 and these were up-dated during Feb 2015.

- CINAHL (1980 – 2015)
- MEDLINE (1946 – 2015)
- AMED (Allied and Complementary Medicine) (1985 – 2015)
- PHYSIOTHERAPY (1980 – 2015)
- The Cochrane Central Register of controlled trials (CENTRAL) 2015
- Cochrane Database of Systematic Reviews (CDSR) 2015
- Cochrane Pain, Palliative and Supportive Care Trials Register 2015

All titles and abstracts from the search results were reviewed against the inclusion criteria by Flavia Swan (Hull York Medical School, University of Hull) and Alison Newey (University of Manchester), with recourse to Miriam Johnson, Principal Supervisor, (Hull York Medical School, University of Hull) as a third reviewer in case of disagreement. The same process was followed for the retrieval of full papers and study inclusion was decided through agreement by consensus. The results are presented in Figure 6, Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA statement (258) flow diagram of study retrieval and selection. The reasons for study exclusion are presented in the Appendix 1, Characteristics of excluded studies and the references to the excluded studies are listed in Appendix 2.

3.6.2 Searching other resources

The reference lists of all the relevant studies and systematic reviews were checked and hand-searches were made for any further studies. The search included published conference abstracts and proceedings. E-mail contact was made to known experts to try and identify any other sources of unpublished data or grey literature. Furthermore searches were made of www.care.search.com.au and www.controlled-trials.com.

3.6.3 Language

The study selection was restricted to those in the English language due to the resource constraints of the PhD studentship.

3.6.4 Search Terms

The following search terms and combinations were used:

Population: Chronic AND obstructive AND pulmonary AND disease; COPD, heart AND failure OR congestive; motor neurone disease OR amyotrophic lateral sclerosis; interstitial lung disease; neoplasm; kyphoscoliosis; pulmonary fibrosis.

Exposure: Hand-held fan OR fan; air flow; medical air; oxygen inhalation therapy OR oxygen treatment; facial OR nasal AND cold OR cooling.

Outcome: Difficult AND breath; short AND breath; dyspnea OR dyspnoea; exercise; activities of daily living

The MeSH terms and truncations from the full search strategy are displayed in Appendix 3.

3.6.5 Data collection

For each of the included studies one researcher, Flavia Swan, extracted the study parameters using a *pro forma* to record the evidence relevant to the review topic systematically, summarising the study design, patients, interventions, comparators and outcomes. The studies were sub-divided and categorised into groups according to the characteristics of the airflow delivery as shown in Tables 8, 9, and 10.

3.6.6 Risk of bias in included studies

Two independent review authors, Flavia Swan and Alison Newey, judged the quality of reporting and internal validity for each of the included studies. The RCTs were assessed with the Cochrane Risk of bias tool (259). Bias was assessed in the following domains: randomisation (sequence generation and allocation concealment), blinding (of participants and assessors), withdrawals/dropouts and incomplete outcome data. The cohort study was evaluated according to the Cochrane guidelines for assessing bias in a non-randomised study (254). See Table 11 and 12 methodological quality of included studies.

3.6.7 Statistical Analysis Plan

The data extracted from the included studies were assessed for potential suitable primary and secondary outcomes that could be appropriately combined for meta-analyses. The results of outcomes from studies that were not comparable and could not be included in any possible meta-analyses were described narratively. Studies that were judged as sufficiently clinically homogeneous were divided into sub-groups and pooled together for meta-analyses.

The preliminary data calculations of the mean difference and SD were conducted using STATA Version 12.1. The outcome measurements recorded for breathlessness were analysed as continuous outcomes. In the case of a cross-over RCT the meta-analysis was calculated with the data from all of the participants using the baseline and after measurements as for a cohort observational design, which meant that a paired analysis was not necessary. For studies that recorded median values, the mean were calculated from the extracted study data using the formulae of Hozo, (2005) (260), from the median *m*, the range *a* to *b*, and sample size *n*:

$$\text{Mean} = (a + 2m + b)/4 + (a - 2m + b)/4n$$

$$\text{Var} = (a^2 + b^2 + m^2 + (n-3)\,((a + m)^2 + (m+b)^2)/8 - n \times \text{mean}^2)/(n-1)$$

Heterogeneity was tested using a Chi squared test of homogeneity (Chi^2) to check for the difference between the individual study effect and the pooled effect of the studies. The I^2 statistic was also used to quantify the inconsistency across studies and approximate the proportion of total variation in study effects that was due to heterogeneity for each meta-analysis. A random or fixed effects model was selected according to level of statistical heterogeneity observed using the Cochrane Statistical Methods group guide (261); 0% to 40%: was considered to represent low heterogeneity, 30% to 60% moderate and 50% to 90% substantial. All meta-analyses were performed with the computer software Comprehensive Meta-Analysis Version 2.2048.

A sensitivity analysis was attempted for any study that was identified as including a sub-group of participants that did not fit the review criteria of mild hypo- or normoxaemia. This was to check that results were stable and to assess for any significant difference in the breathlessness outcome between the hypoxic and non-hypoxic participants.

3.6.8 Selection of studies

Selection of studies

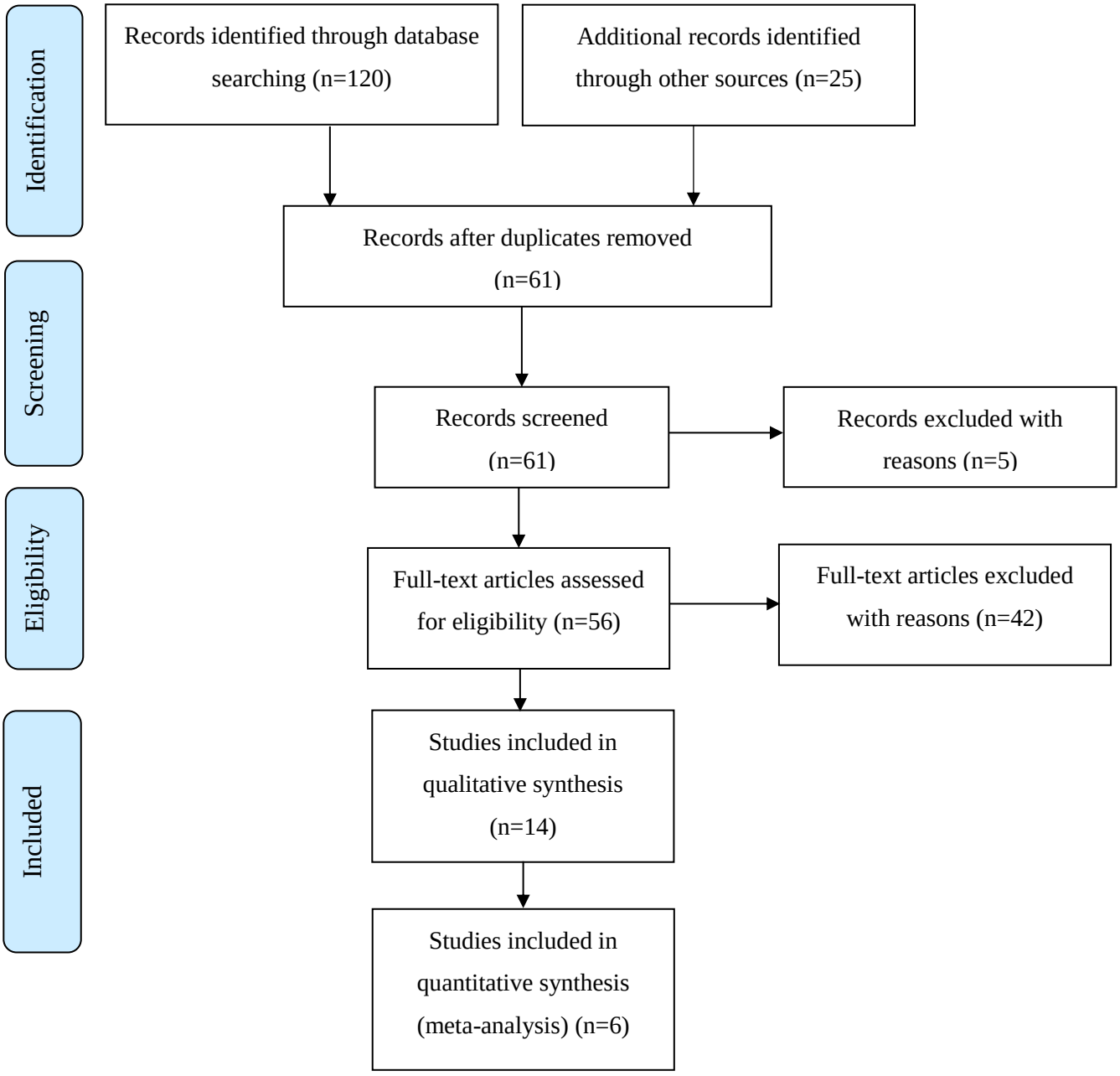


Figure 6 PRISMA 2009 Flow-diagram of study selection and retrieval adapted from The PRISMA statement (258)

3.7 Results

A total of 14 studies met the inclusion criteria for this preliminary review regarding the effect of non-oxygen enriched facial or nasal airflow for the relief of chronic refractory breathlessness in adult patients with mild hypo- or normoxaemia (94, 218-220, 223, 262-270). See Table 7 references to included studies.

Table 7 References to the included studies

Reference number	Authors	Title	Journal	Year	Volume	Issue	Pages
94	Abernethy A, McDonald C, Frith 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		784-93
218	Galbraith S, Fagan P, Perkins P, et al	Galbraith S, Fagan P, Perkins P, et al Booth S, et al The use of a hand-held fan to manage breathlessness – A feasibility study Does the use of a hand-held fan improve chronic dyspnea? A randomised controlled, crossover trial	Journal of Pain and Symptom management	2010	39	5	831-838
219	Bausewein C, Booth S, Gysels M, et al.	Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial	BMC palliative medicine	2010	9	22	
220	Booth S, Galbraith S, Ryan R, Parker R, & Johnson, M	The use of a hand-held fan to manage breathlessness – A feasibility study	Palliative Medicine	2016	30	5	504-509
223	Booth S, Kelly MJ, Cox NP, Adams L, Guz A	Does oxygen help dyspnea in patients with cancer?	American Journal of Respiratory and Critical Care Medicine	1996	153		1515–8

Table 7 References to the included studies

Reference number	Authors	Title	Journal	Year	Volume	Issue	Pages
262	Eaton T, Fergusson W, Kolbe J, Lewis CA, West T	Short-burst oxygen therapy for COPD patients: a 6-month randomised, controlled trial	European Respiratory Journal	2006	27	4	697–704
263	Eves ND, Petersen SR, Haykowsky MJ, Wong EY, Jones RL	Helium-hyperoxia, exercise, and respiratory mechanics in chronic obstructive pulmonary disease	American Journal of Respiratory and Critical Care Medicine	2006	174	7	763–71
264	Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gene RJ	Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia.	Chest	2001	120		437–43
265	Marciniuk D, Butcher S, Reid J et al	The effects of Helium-Hyperoxia on 6 minute walking distance in COPD – A randomised, controlled trial	Chest	2007	131	6	1659-1665
266	McDonald CF, Blyth DM, Lazarus MD, Marschner I, Barter CE	Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia.	American Journal of Respiratory and Critical Care Medicine	1995	152		1616–9
267	Moore R, Berlowitz D, Denehy L, et al	A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia	Thorax	2011	66		32-37

Table 7 References to the included studies

Reference number	Authors	Title	Journal	Year	Volume	Issue	Pages
268	Philip J, Gold M, Milner A, et al	A randomised, double-blind crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer	Journal of pain and symptom management	2006	32	6	541-550
269	Scorsone D, Bartolini S, Saporiti R, et al.	Does a low-density gas mixture or oxygen supplementation improve exercise training in COPD?	Chest	2010	138	5	1133-1139
270	Wadell K, Henriksson-Larsen K, Lundgren R	Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxemia.	Journal of Rehabilitation Medicine	2001	33	5	200–5

These studies were divided into three main sub-groups based on whether the airflow was delivered, i) at rest (218, 220, 223, 268), ii) over days or weeks (either intermittently or as periods of continuous flow) whilst the participant continued with usual general activities (94, 219, 262, 267), or iii) during specific episodes of exertion induced breathlessness (263-266, 269, 270). See Tables 8, 9 and 10 for the sub-grouping details.

Table 8 Characteristics of included studies sub-group: i) at rest

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure(s)	Timing of measurement	Results	Improvement with air Yes/No
Booth et al (1996)	Single-blind cross-over RCT	N = 38 Males: 22 Age Median: 71 Range: 54-90yrs Diagnosis: Lung Cancer 20, COPD 13, Cardiac 4 Baseline dyspnoea score: VAS 59mm	Oxygen	Cylinder air	4l/minute for 15 minutes via nasal cannula	VAS (mm) Modified Borg Scale	After 15 minutes of breathing oxygen or air at rest.	VAS = -11mm change after air 48mm, p<0.001	Yes
Booth et al (2016)	Feasibility observational cohort	N = 31 Males: 20 Age mean: 74.8 SD 11.49 Diagnosis: Mixed population, non-malignant cardiorespiratory disease: 8 (26%) Baseline dyspnoea score: Mean VAS 48mm SD 27.4	Hand-held fan to face	No comparator group	Airflow from hand-held fan to face for 5 minutes	VAS (mm), NRS	After 5 minutes at rest	VAS = Mean 35mm SD 25.7 after 5min air Mean change = 12mm SD 21.2	Yes

Table 8 Characteristics of included studies sub-group: i) at rest

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure(s)	Timing of measurement	Results	Improvement with air Yes/No
Galbraith et al (2010)	Cross-over RCT	N = 50 Males: 23 Age mean: 71.3, range 33-90yrs Diagnosis: Mixed population; COPD = 26, lung cancer = 11, heart disease = 15 Baseline dyspnoea score: VAS Fan/face 1st group = 31mm (12-61mm)	Hand-held fan to face	Hand-held fan to leg	Airflow from hand-held fan to face for 5 minutes	VAS (mm)	After 5 minutes at rest and after 10 minute washout	VAS = -7.0mm Median change after 5 minutes Fan/face 1st group (IRQ 1.5 - 14.5) VAS = -10.0mm Median change incl 10 minute washout Fan/face 1st group (IRQ 3.5 – 17), P=0.003	Yes
Philip et al (2006)	Double-blind cross-over RCT	N = 51 Males: 31 Age median: 65 Range: 33-82yrs Diagnosis: NSCLC = 22, Small cell lung cancer = 6, Breast = 8, Colorectal = 4 Others = 11 Baseline dyspnoea score: VAS Median Air 1st = 52mm (range 23-92) VAS Median Air 2nd = 42mm (range 10-70)	Oxygen	Medical Air	4l/minute for 15 minutes via nasal cannula	VAS (mm)	Before and after 15 minutes of gas	VAS median After air 1st = -3mm change (range -19 to 7) VAS median After air 2nd = -11.5mm change (range -20 to 45) VAS Mean change = -13.4mm	Yes

Table 9 Characteristics of included studies sub-group: ii) general activity

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure	Timing of measurement	Results	Improvement with air Yes/No
Abernethy et al (2010)	Double-blind RCT	N = 239 Males: 63% Air =119 Age mean: Air = 74yrs (SD 10) Diagnosis: Mixed COPD = 152, Primary lung cancer = 33 Baseline dyspnoea score: Am air = 4.6 (SD 2.4) Pm air = 4.7 (SD 2.3)	Oxygen	Room air via concentrator	2l/min via nasal cannula for at least 15hrs a day (LTOT)	NRS 1-10	Am and pm each day, within 30 minutes of waking and bedtime for 7 days	Am = -0.7 NRS point change Pm = -0.5 NRS point change, (p = 0.5)	Yes
Bausewein et al (2010)	Feasibility longitudinal phase II RCT	N = 70 Males: 36 Age mean: 65.6yrs (8.80) Diagnosis: COPD = 45, cancer = 25 Baseline dyspnoea score: 3.7 (1.83)	Hand-held fan to face	Wristband	Airflow from hand-held fan	Modified Borg score	Monthly over 6 months	Handheld fan: Mean Borg score change over 2 months = 0.6 (SD 2.1), p = 0.90	No, but phase II so not powered to test

Table 9 Characteristics of included studies sub-group: ii) general activity

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure	Timing of measurement	Results	Improvement with air Yes/No
Eaton et al (2006)	Double-blind parallel RCT	N = 78 Males: 36 Age mean: 77.3yrs (7.06) Diagnosis: Moderate/ severe COPD Baseline CRQ score: Air = 17.5 (4.2)	Oxygen	Cylinder air	2l/minute via nasal cannula over 6 months (SBOT)	CRQ	Monthly over 6 months	CRQ = Average change over 6 months: air group = -3.6	No
Moore et al (2011)	Double-blind RCT	N = 143 Males: 99 Age mean: 71.8yrs (SD 9.8) Range: 43-78 Diagnosis: Stable COPD Baseline dyspnoea score: Air = 17.5 (SD 4.9	Oxygen	Cylinder air	6l/minute via nasal cannula at home for 12 weeks with activity (SBOT)	CRQ	At 4 weeks and 12 weeks	Air: 4 weeks = 18.4 (SD5.8) 12 weeks = 18.4 (SD 5.8) Air: CRQ = Mean change at 4 and 12 weeks = 0.9	Yes

Table 10 Characteristics of included studies sub-group: iii) Exertion –induced breathlessness

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure	Timing of measurement	Results	Improvement with air Yes/No
Jolly et al (2001)	Double-blind RCT	N = 20 Males: 19 Age mean: 68.5yrs (SEM 2.5) Diagnosis: Stable COPD Baseline dyspnoea score: Borg mean score Desat group Baseline 6MWT = 5.82 (SEM 0.46) Non-desat group Baseline 6MWT = 4.22 (SEM 0.46)	Oxygen	Cylinder air	3l/minute via nasal cannula	Modified Borg score	Before and after 3 x 6 MWTs with at least 45minutes washout between walks	Borg mean score: Desat group Air 6MWT = 5.82 (SEM 0.42) No change Non-desat group Air 6MWT = 4.44 (SEM 0.73) No change	No
Marciniuk et al (2007)	Double-blind crossover RCT	N = 16 Males: 7 Age mean: 67 (SD 8) Diagnosis: Moderate to severe COPD Baseline dyspnoea score: Borg mean score Baseline 6MWT = 5 (SD 2)	100% Oxygen or Helium-hyperoxia (70% HE: 30% O^2)	Cylinder air	15l/minute via face mask 8l/minute via nasal cannula	Modified Borg score	Before and after each 6 MWTs on visit 1,2 and 3 with 60 minutes washout between walks	Borg Mean score After 6MWT Air = 3.5 Mean Borg score change = -1.5 decrease	Yes

Table 10 Characteristics of included studies sub-group: iii) Exertion –induced breathlessness

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure	Timing of measurement	Results	Improvement with air Yes/No
McDonald et al (1995)	Double-blind crossover RCT	N = 26 Males: 24 Age mean: 73 (SD 6) Diagnosis: Stable severe COPD Baseline dyspnoea score 6MWT: Air group = 3.8 (SD 1.4) CRQ = 14 (SD 5)	Oxygen	Cylinder air	4l/minute via nasal cannula	Modified Borg score CRQ	After 6 and 12 weeks of home cylinder air using 6MWT exercise test with 20 minute washout between walks	Borg Mean score Home air: 6MWT with cylinder air = 3.8 (SD 1.5) No change CRQ score Home air = 17 (SD 6) CRQ = 3 point change	No with 6MWT Yes with CRQ
Scorsone et al (2010)	Double-blind RCT	N = 30 Males: 23 Air: 10 Age mean: 67.3yrs (SD 8.3) Diagnosis: Moderate to severe COPD Baseline dyspnoea score: Before training incremental load exercise Borg: Air = 7 (SD 3) Before training constant load exercise Borg: Air = 8 (SD 3)	40% Oxygen or Helium - hyperoxia (60% HE: 40% O^2)	Humidified room air	Mouthpiece from a Douglas bag	Modified Borg score	During exercise before and after a 2 month pulmonary rehabilitation programme, 3 times a week for 20 minutes on cycle ergometer	After training incremental load exercise Borg: Air = 4 (SD 2) After training constant load exercise Borg = 5 (SD 3) Borg change = -3 point decrease both exercise tests	Yes

Table 10 Characteristics of included studies sub-group: iii) Exertion –induced breathlessness

Study author	Study Design	Population	Intervention	Comparator	Mode of gas delivery	Outcome measure	Timing of measurement	Results	Improvement with air Yes/No
Wadell et al (2001)	Single-blind crossover RCT	N = 20 Males: 10 Age mean: 67yrs Range: 52-73 Diagnosis: Stable COPD Baseline dyspnoea median score: Test A (Air) At rest; Pre-training Borg: Air group = 1.5 (0-3) Test A (Air) After 6MWT, Pre-training Borg: Air group = 6.5 (4-9)	Oxygen	Air	5l/minute via nasal cannula	Modified Borg score	During exercise using 2 x 6MWT (air/O^2 or O^2/air) with 1hour washout before and after a 2 month pulmonary rehabilitation programme, 3 times a week for 30 minutes on a treadmill	Test A (Air) At rest; Post-training Borg: Air group = 1 (0-3) Test A (Air) After 6MWT, Post-training Borg: Air group = 6 (1-7) Borg change = -0.5 point at rest and after exercise test	Yes

3.7.1 Description of the hand-held fan studies (N=3)

3.7.1.1 Design and population

Three studies (n=151) used the hand-held fan as an intervention; a feasibility phase II longitudinal RCT (n=70), (219), a feasibility cohort study (n=31), (220) and a phase III cross-over RCT (n=50), (218). All three recruited a mixed population of people with breathlessness due to a variety of advanced conditions including COPD (n=78), cancer (n=48), heart failure (n=17) and other causes (n=8).

3.7.1.2 Mode of delivery

Two of the hand-held fan studies used the intervention for 5 minutes to direct airflow to the face or cheek of participants while at rest (218, 220) and the third study assessed the acceptability of the hand-held fan when used with general activity over 6 months (219).

3.7.1.3 Comparator

The two hand-held fan RCT studies used different comparators; a wristband was worn over 6 months in one study (219) and the hand-held fan was directed to the leg for 5 minutes in the second study (218). The third study, a cohort design, did not include a comparator group (220).

3.7.1.4 Outcome measures

The primary outcome measures used were the VAS (0-100 mm) in two studies (218, 220), with the NRS (0-10) in addition to the VAS in one study (220). The designated primary endpoint was the use of the hand-held fan at two months as a binary yes/no measure while the Modified Borg Scale of breathlessness severity was a secondary outcome measure in one study (219).

3.7.2 Description of the medical air studies (N=11)

3.7.2.1 Design

There were eleven RCT studies (n=699) that used oxygen, helium hyperoxia or both gases for the active intervention arms compared with non-oxygen enriched medical air as a placebo arm (94, 223, 262-270). There was a wide range of study size from 16 to 239 participants (94, 265).

Four were cross-over studies (223, 265, 266, 268) and the remaining seven used a parallel group design (94, 262-264, 267, 269, 270). Nine studies were double blind (94, 262-269) and two studies were single blind (223, 270).

3.7.2.2 Population

The eleven studies represent 536 participants with COPD, 104 with cancer and 14 with cardiac disease.

Eight of the eleven studies had inclusion criteria requiring moderate to severe COPD for study entry (262-267, 269, 270) of which, five also required the patients to have stable disease. (263, 264, 266, 267, 270).

Two studies recruited mixed populations that included participants with COPD, cancer and cardiac disease (94, 223) and one study selected participants only with a diagnosis of advanced cancer (268).

3.7.2.3 Mode of delivery and source of airflow

The source of airflow in seven studies was from an oxygen cylinder (223, 262-267). In the other four studies one used a sham concentrator (94), the second a Douglas bag (269) and the remaining two studies did not state the airflow source used (268, 270). Medical air or compressed air was delivered through nasal cannulae in eight studies (94, 223, 262, 264, 266-268, 270). Of the remaining three studies one used both a face-mask and a nasal cannula (265), the second used a non-rebreathing face-mask (263) and the third study required subjects to wear a nose-clip and breathe humidified air via a mouthpiece (269).

3.7.2.4 Flow rates

The flow rates varied widely in the studies. Two studies used 2l/minute (94, 262) and three studies used 4l/minute (223, 266, 268). A further four studies singularly administered flow rates of 3l/minute (264), 5l/minute (270), 6l/minute (267) and 8l/minute via nasal cannula or 15l/minute with face mask (265). The remaining two studies that also investigated Helium-hyperoxia did not report the flow rates used during the exercise tests (263, 269).

3.7.2.5 Flow duration and timing

Two of the eleven studies provided medical or compressed air for 15 minutes to the participants at rest (223, 268). A further two studies assessed the effects of Short Burst Oxygen Therapy (SBOT), used by the participants as they felt needed for daily activity which triggered breathlessness over 3 and 6 months respectively (262, 267) and one study examined the effect of using Long Term Oxygen Therapy (LTOT), aiming for 15 hours a day over one week (94). The remaining six studies were all designed to assess the effect of oxygen enriched air on exertion-induced breathlessness. These studies selected a wide range of parameters in the exercise programmes and timing of the participant tests. Three of the studies focused on the use of supplemental airflow during a pulmonary rehabilitation programme. One study lasted 6 weeks with the participants inhaling the assigned gas while on a cycle ergometer for 3 times a week for 30 minutes during pulmonary rehabilitation (263). A second study used a two month rehabilitation programme and administered medical gas to participants while on a cycle ergometer for 3 times a week for 20 minutes (269). The third study used a two month rehabilitation protocol that involved the participants inhaling medical gas during a treadmill exercise programme of 3 times a week for 30 minutes (270). The other three studies examined breathlessness induced by an ambulatory test that was measured on a level walking course. All of the studies selected the standard 30m corridor 6MWT, but the timing and number of 6MWTs varied between them (264-266). One study conducted all three walking tests on the same day; the participants inhaled room air for the basal walk and compressed air on the subsequent walks with at least 45 minutes washout between the three walks (264). In the second study the participants performed the walking tests over the course of 3 visits with 60 minutes washout between the walks, although the timing of the three visits was not stated. On the first visit the participants inhaled room air during a practice walk test, while on the subsequent second and third visits the participants

performed two 6MWTs each visit, inhaling the room air gas mixture for 5 minutes before and during the walk test (265). The third study examined the effect of using airflow during a 6MWT that was conducted at baseline, and again at 6 and 12 weeks with the additional provision of SBOT used by the participants as they felt needed for daily activity which triggered breathlessness at home for the duration of the study period (266).

3.7.2.6 Outcomes

Out of the 11 studies, five were focused on the primary outcome of breathlessness intensity (94, 223, 262, 267, 268). Of the five studies, two selected the VAS (223, 268), two reported the CRQ dyspnoea (262) and one study measured the NRS for breathlessness (94). The remaining six studies were equally focused on both breathlessness sensation and function (262, 264-266, 269, 270). Five studies identified the modified Borg breathlessness score as one of the main outcome measurements (264-266, 269, 270), with one of these selecting the CRQ in addition to the modified Borg score (266), and one study assessed the Borg breathlessness score as a secondary outcome (263).

Four of the six studies used the 6MWT as an outcome measurement (264-266, 270). This was measured on the standard corridor walk in three studies at varying times and visits (as described above) (264-266), and measured twice on a non-motorised treadmill; both before and after rehabilitation with a 1 hour rest in between the tests in one study (270). The remaining two studies measured the participant's isotime responses (defined as the end of exercise) to an incremental and constant load cycle test while breathing air at baseline and following the rehabilitation programmes (263, 269).

3.8 Risk of bias in included studies

3.8.1 Randomisation

All of the fourteen included studies, apart from one, a feasibility cohort design (220), were described as RCTs. However, it was only possible to verify the randomisation process (adequate sequence generation and allocation concealment) in seven of the studies (94, 218, 219, 223, 262, 263, 267). Judgement was not possible in the remaining six RCT studies as insufficient detail of the randomisation methods were reported (264-266, 268-270).

3.8.2 Blinding

As it is not possible to provide a realistic placebo comparator for cool airflow, participants and researchers were not blinded in the three hand-held fan studies (218-220). Although two of the studies did attempt to blind the assessors (218, 219), this was judged as likely to have been broken. In addition, one study did not tell participants which of the interventions (the hand-held fan to face or the hand-held fan to leg) was being tested as the active intervention (218). The incomplete or lack of blinding was thought likely to influence the outcome measurements reported for breathlessness, therefore they were all judged as high risk of bias. Two of the studies were feasibility phase II trials and thus were not designed to test for effectiveness (219, 220) and although there was an inadequate washout period in the third study, this was adjusted for in the analysis (218).

Blinding was undertaken in all eleven of the oxygen RCTs. Nine studies were described as double blind (94, 262-269). Of these, eight were judged low risk of bias (94, 262, 263, 265-267, 269) and one had an unclear risk of bias due to the lack of study details (268). The remaining two studies were single blind with the participant masked to the gases delivered, but not the researcher (223, 270). One study adequately described the blinding of the participants using indistinguishable cylinders and was judged as low risk of bias (223). The second study stated that participants were unaware if they were breathing oxygen or air, but there was inadequate description to permit judgement, therefore it was regarded as unclear risk of bias (270).

3.8.3 Withdrawals, incomplete data

Of the fourteen studies included in the review, twelve adequately addressed participant withdrawals and incomplete outcome data; these were considered to be low risk of bias (94, 218, 220, 223, 263-270). The remaining two studies were considered to have an uncertain risk of bias (219, 262). In one study the proportion of attrition in both arms were considerable, however this was a feasibility, phase II design and it is unclear what influence this has on the statistical analysis (219). The second study reported the flow of participant numbers and attrition with reasons, but did not provide any description of how the statistical analysis managed the imbalance of missing outcome data across the three study arms at the end of the six month trial (262).

3.8.4 Selective outcome reporting

There was no evidence of selective outcome reporting; all fourteen of the studies reported the pre-specified primary and secondary outcomes, therefore all of the studies included in the review were judged as low risk of bias (94, 218-220, 223, 262-270). The study protocols were also available for seven of the studies (94, 218-220, 263, 267, 268).

3.8.5 Free of other issues of bias

Ten of the studies appeared to be free from potential sources of bias such as considerable baseline imbalance or bias related to the specific study design, therefore they were judged to be low risk of bias (94, 218, 219, 262, 263, 265, 267-270). Of the remaining studies, three reported insufficient information to adequately assess the other risk of bias (223, 264, 266), and one was judged high risk due to the increased risk of bias resulting from the before and after non-randomised, cohort design with no comparator group (220). See Table 11, Risk of bias summary of included RCT studies and Table 12, Methodological quality of non-randomised, cohort study.

Table 11 Risk of bias summary of included RCT studies

Study reference number	Study author	Sequence generation	Allocation concealment	Blinding	Withdrawals, incomplete data	Selective outcome reporting	Free of other issues or bias
94	Abernethy (2010)	+	+	+	+	+	+
218	Galbraith (2010)	+	+	-	+	+	+
219	Bausewein (2010)	+	+	-	?	+	+
223	Booth (1996)	+	+	+	+	+	?
262	Eaton (2006)	+	+	+	?	+	+
263	Eves (2009)	+	+	+	+	+	+
264	Jolly (2001)	?	?	+	+	+	?
265	Marciniuk (2007)	?	?	+	+	+	+
266	McDonald (1995)	?	?	+	+	+	?
267	Moore (2011)	+	+	+	+	+	+
268	Philip (2006)	?	?	?	+	+	+
269	Scorsone (2010)	?	?	+	+	+	+
270	Wadell (2001)	?	?	?	+	+	+

Table 12 Methodological quality of non-randomised cohort study

Study reference number	Study author	Study design	Blinding	Withdrawals, incomplete data	Selective outcome reporting	Free of other issues or bias
220	Booth (2016)	Feasibility Cohort	-	+	+	-

Codes:

+ = Low risk of bias

? = Unclear risk of bias

- = High risk of bias

3.9 Quantitative results by sub-group

3.9.1 Breathlessness at rest (N=4)

All of four studies demonstrated improvement with airflow delivered at rest from the hand-held fan (218, 220), or from cylinder medical air via nasal cannula (223, 268). Results from Galbraith (2010) estimated a -7mm VAS improvement in the intensity of breathlessness (95% CI 2.5-11.7mm) from using the hand-held fan to the face for 5 minutes, after accounting for an inadequate washout period in a crossover design RCT (218). Preliminary data from the hand-held fan cohort study showed a mean -12mm VAS improvement in intensity of breathlessness (95% CI -19.3 to -4.4) following 5 minutes use of the hand-held fan to the face (220). The results from the two studies using airflow delivered from cylinder medical air via nasal cannula at rest for 15minutes demonstrated a mean -11mm VAS improvement in breathlessness intensity (95% CI -5.0 to 17.0), (223) and a mean -13mm VAS improvement in breathlessness intensity (95% CI -6.3 to 20.5), (268). These four studies were sub-divided into two groups and included in meta-analyses (See Table 14, Hand-held fan for people breathlessness at rest and Table 16, Cylinder medical air for people breathlessness at rest.)

3.9.2 Breathlessness on everyday general activity (N = 4)

The results for the CRQ breathlessness scores from three studies of the use of cylinder medical air at home for everyday general activity were mixed (262, 266, 267). Eaton (2006) reported a -3.6 point decrease after 6 months (262) and McDonald (1995) the opposite with a 3 point increase after 12 weeks (266), while Moore (2011) only found a small change of 0.9 points at 12 weeks (267). The other two studies measured breathlessness outcome using a uni-dimensional scale; Abernethy (2010) found a -0.7point NRS breathlessness reduction in the morning and a -0.5 NRS breathlessness decrease in the evening after 1 week of using medical air delivered from a concentrator for at least 15 hours a day (94), while Bausewein (2010) reported a limited modified Borg score change of -0.6 (SD 2.1) after 2 months use of the hand-held fan (219). It was not possible to combine any of the studies for meta-analysis due to the diversity of the study design and the various parameters of airflow delivery over different periods of time.

3.9.3 Exertion-induced breathlessness (N =6)

Two studies found no change in mean Borg breathlessness scores after using airflow from cylinder medical air during a 6MWT repeated on the same day (264), or repeated at 12 weeks (266). In contrast, Marcinuik (2007) found a -1.5 mean Borg breathlessness score reduction after using airflow from cylinder medical air for a 6MWT repeated on 3 separate visits, although the time period between the visits were not stated (265).

Airflow delivered as medical air used during a pulmonary rehabilitation programme in three studies demonstrated variable improvement in mean Borg breathlessness scores (263, 269, 270). After the training the results from a constant load exercise test using medical air delivery on a cycle ergometer found a reduction of -1.8 points (263), and -3 point mean Borg breathlessness score improvement (269). A smaller decrease of -0.5 point Borg breathlessness score was recorded after pulmonary rehabilitation programme for a 6MWT conducted on a treadmill using medical air delivery (270).

Two of these studies were suitable to include in a meta-analysis (263, 269), (See Table 18, Cylinder medical air for people with exertion-induced breathlessness). It was not possible to include the third study, (270) as the study data reported on treadmill exercise and not the results from a cycle ergometer. Moreover, the study did not report the results necessary to incorporate in a meta-analysis for a continuous variable (270).

3.10 Meta-analyses

Six studies were sufficiently homogeneous to include in meta-analyses. These studies were divided into three sub-groups based on whether the airflow was delivered:

- From the hand-held fan for people breathlessness at rest with mixed diagnoses (218, 220)
- From cylinder medical air for people breathlessness at rest with an advanced cancer diagnosis (223, 268)
- From cylinder medical air for people with exertion induced breathlessness during pulmonary rehabilitation and a diagnosis of COPD (263, 269)

3.10.1 The hand-held fan for people breathlessness at rest

The data extracted from the two hand-held fan studies that provided airflow at rest representing 81 participants with mixed diagnoses including COPD, cancer and cardiac disease were included in a meta-analysis with the primary outcome of breathlessness on a VAS (100mm), (218, 220), (Table 13).

Table 13 Extracted data: Hand-held fan for people breathlessness at rest

	Mean change	SD	n
Galbraith (2010)	-7.0	16.0	50
Booth (2016)	-11.87	21.24	31

For Galbraith (2010), (218), a crossover design the meta-analysis was calculated using the authors estimated difference which was adjusted for the inadequate washout period and the data from all 50 participants who received the hand-held fan to face were used.

Table 14 Meta-analysis: Hand-held fan for people breathlessness at rest

Study name	Mean	SE	Var	95% CI	z value	P
Galbraith (2010)	-7.0	2.3	5.2	-11.5 to -2.5	-3.1	0.002
Booth (2016)	-11.9	3.8	14.5	-19.3 to -4.4	-3.1	0.002
Random	-8.5	2.2	5.0	-12.9 to -4.1	-3.8	<0.0001

Airflow delivered by the hand-held fan at rest improved breathlessness using a "before and after" cohort design in a mixed population of patients with mild or normoxaemia with a significant benefit SMD -8.5, 95% CI -12.9 to -4.1, p<0.0001 (Table 14).

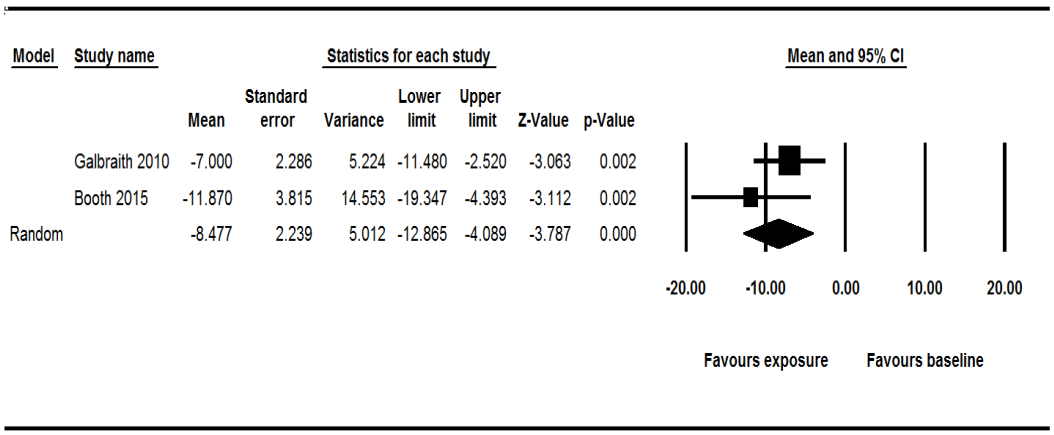


Figure 7 Forest plot: Hand-held fan for people breathlessness at rest

A random effects model was chosen in the meta-analysis to account for the variation in study design, although no significant heterogeneity were observed in the studies, Chi^2 P value = 0.3, (I^2 =17%), (Figure 7).

3.10.2 Cylinder medical air for people breathlessness at rest

A further meta-analysis were conducted with the data extracted from the two studies that provided medical airflow at rest representing 89 patients with advanced cancer using the primary outcome of breathlessness on a VAS (100mm) (223, 268), (Table 15).

Table 15 Extracted data: Cylinder medical air for people breathlessness at rest

	Mean change	SD	n
Booth (1996)	-11	19	38
Philip (2006)	-13.4	25.7	51

For Philip (2006), (268), a crossover design the meta-analysis was calculated with the data from all 51 participants, but in each case the before and after measurements were compared. Mean values were calculated using the formula of Hozo (2005) (260).

Table 16 Meta-analysis: Cylinder medical air for people breathlessness at rest

Study name	Mean	SE	Var	95% CI	z value	P
Booth (1996)	-11	3.1	9.5	-5.0 to 17.0	-3.6	0.0004
Philip (2006)	-13.4	3.6	13.0	-6.3 to 20.5	-3.7	0.0002
Fixed	-12.0	2.3	5.5	-7.4 to 16.6	-5.1	<0.0001

Airflow delivered as cylinder medical air at rest improved breathlessness in patients with advanced cancer and mild or normoxaemic using a “before and after” cohort design with a significant benefit standardised mean difference (SMD) -12.0, 95% CI -7.4 to -16.6, P<0.0001 (Table 16).

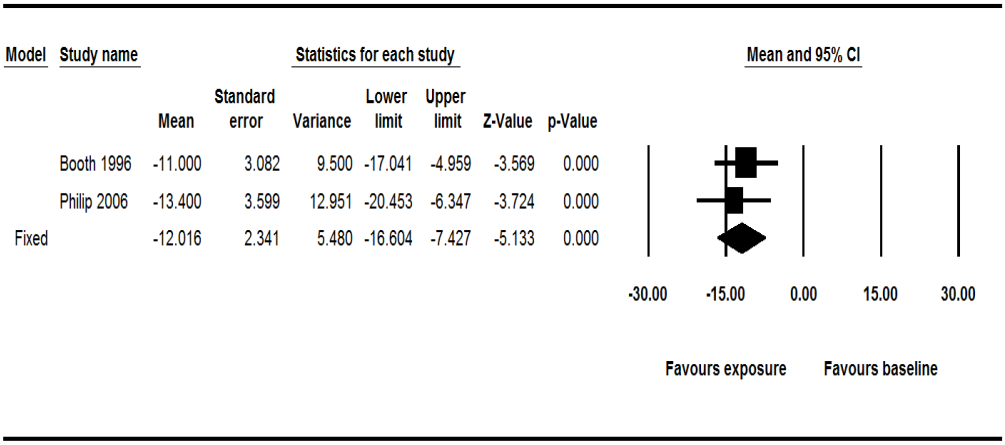


Figure 8 Forest plot: Cylinder medical air for people breathlessness at rest

A fixed effects model was used in the meta-analysis as there was no evidence of heterogeneity observed in the studies, Chi^2 P value = 0.6, (I^2 =0%) (Figure 8).

3.10.3 Sensitivity analysis

A sensitivity analysis was attempted to exclude the data from the sub-group of hypoxic patients in both studies (223, 268). But it was not possible to extract any of the values required for a sensitivity analysis due to the limited results data reported in both studies. However, given that the hypoxic sub-group represents 23 participants from the total of 89 sampled in the two studies it is assumed that 25% amounts to a minority of the data and one would expect the authors to have reported the sub-group results had there been a significant difference in the outcome between the hypoxic and non-hypoxic participants.

3.10.4 Cylinder medical air for people with exertion induced breathlessness

The data extracted from two studies, representing 29 participants that used the primary outcome of breathlessness on a modified Borg score which was induced by a cycle ergometer constant load exercise test were included in a meta-analysis (263, 269) (Table 17).

Table 17 Extracted data: Cylinder medical air for people with exertion-induced breathlessness

Study name	Mean change	SD	n
Eves (2009)	−2.9	0.7	19
Scorsone (2010)	−3	0.7	10

For Eves (2009), (263), SD was calculated from 95% confidence interval, and for Scorsone (2010), (269) it was assumed to be the same as Eves (2009) (263).

Table 18 Meta-analysis: Cylinder medical air for people with exertion-induced breathlessness

Study name	Mean	SE	Var	95% CI	z value	P
Eves (2009)	−2.9	0.16	0.0258	−3.2 to −2.6	−18.1	<0.0001
Scorsone (2010)	−3	0.22	0.049	−3.4 to −2.6	−13.6	<0.0001
Fixed	−2.9	0.13	0.017	−3.2 to −2.7	−22.6	<0.0001

Airflow delivered as medical air during a constant load exercise test after pulmonary rehabilitation programme significantly improved breathlessness using a “before and after” cohort design with a SMD -2.9, 95% CI -3.2 to -2.7, P<0.0001 (Table 18).

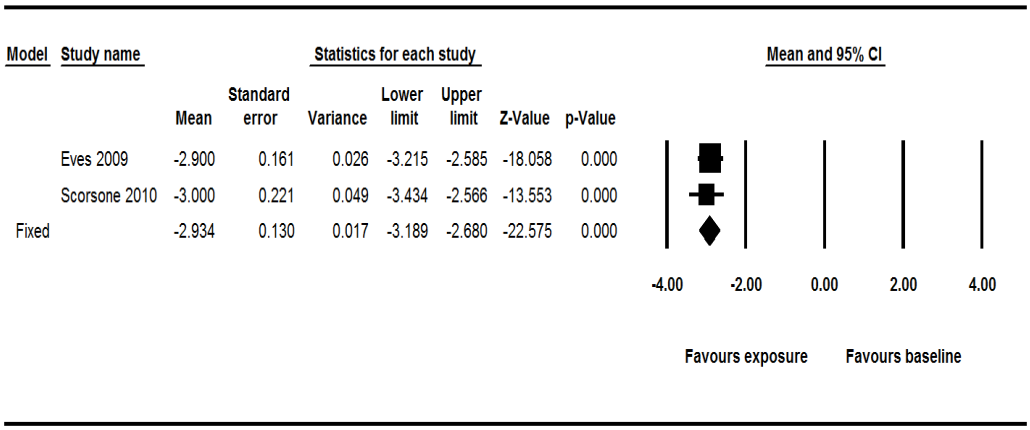


Figure 9 Forest plot: Cylinder medical air for people with exertion-induced breathlessness

A fixed effects model was used in the meta-analysis as no evidence of heterogeneity were observed in the studies, Chi² P value = 0.7, (I^2 =0%), (Figure 9).

3.11 Discussion

3.11.1 At rest (N=4)

Improvement was noted both for the nasal delivery of non-oxygen enriched air and for the facial delivery of airflow from a hand-held fan at rest. These results are in keeping with the previous findings of a Cochrane review that found no difference in the benefit of oxygen over and above that of medical air in patients with advanced cancer or cardiac disease (234). Moreover, the results from the meta-analyses; -8.5mm VAS (95% CI -12.9 to -4.1) hand-held fan and -12mm VAS (95% CI -7.4 to -16.6) cylinder medical air are both comparable with the suggested Minimal Clinically Important Difference (MCID) for breathlessness in a variety of conditions. A small effect size is known as -5.5mm and -9mm VAS score was identified as representing a significant enough change for the patient to consider one treatment more favourable than another (4, 271). Therefore, airflow delivered from either a hand-held fan or from cylinder non-oxygen enriched medical air represent interventions that are able to offer cancer patients clinically relevant relief to breathlessness experienced at rest.

However, although three of the four studies have mixed populations (218, 220, 223), most of the included patients had a diagnosis of cancer. Therefore, it is not known if improvement would be representative among other sub-groups such as COPD or chronic HF. In a previous Cochrane review for the symptomatic benefit of oxygen for normoxemic COPD participants, a sub-group meta-analysis of 4 studies that delivered oxygen as SBOT failed to show improvement of oxygen over medical air, Standardised Mean Difference, SMD 0.01 (95% CI -0.26 to 0.28), p=0.95 (93). These figures are consistent with this preliminary review data and could suggest that in COPD patients with mild or normoxaemia at rest the short term delivery of airflow offered as cylinder medical air or from a hand-held fan is the equivalent to the benefit derived from oxygen therapy. However, a further study would be required to test the hypothesis and quantify the benefit of gas delivery at rest for COPD and chronic HF participants at rest.

3.11.2 Breathlessness on everyday general activity

The review was only able to identify one study that reported repeated airflow measurements and analysed a LTOT delivery protocol with everyday general activity, in that patients (n=239) were assigned to receive at least 15 hours a day of oxygen or medical air via a concentrator for seven days. Results demonstrated improved breathlessness scores with the mode of medical air delivery; -0.7 NRS point in the morning and -0.5 NRS point in the evening; p = 0.5 (94). In relation to the MCID these values only just fall short of a moderate change estimated as a 1 point NRS difference in breathless patients with a variety of conditions (4). However, a -0.5 NRS point change does equate to a small effect size and should not be dismissed as indiscernible difference for the patient.

These findings are in contrast to the results of a previous Cochrane meta-analysis of 14 COPD studies that found oxygen delivered in a continuous mode during exertion or as LTOT was significantly better than medical air, SMD -0.46 (95%CI -0.59 to -0.33), p<0.00001 (93). Only two of the 14 studies analysed in the Cochrane review (264, 266) were included in this airflow review due to the requirement for repeated measurements. Both studies evaluated different protocols of medical air delivery using airflow with everyday general activity (266), or during an exertion induced breathlessness test (264), while neither utilised a LTOT procedure of over 15 hours a day. Moreover, at the time of the previous Cochrane review the data from the Abernethy study which included 63% COPD participants was not published

and the authors noted that there were many small studies, coupled with significant heterogeneity in the meta-analysis (93). Therefore, it may be that the magnitude of benefit shown by oxygen over medical air could diminish once the Cochrane review is updated to include the Abernethy results, as well as the more recent data from a further study included in this preliminary airflow review which also conferred no additional benefit from ambulatory oxygen over medical air when used with general activity in 143 COPD patients for 12 weeks (267).

The other three everyday general activity studies (262, 266, 267) that examined a SBOT procedure of medical air delivery did not consistently identify the same benefit. The CRQ breathlessness scores varied widely from -3.6 points after 6 months (262), to 0.9 point (267), or 3 points (266) at 12 weeks respectively. Therefore, the results from two studies (266, 267) align with the MCID for the CRQ represented by a mean score change of 0.5 per item (272), but the third study suggests no gain from using cylinder medical air for breathlessness during everyday general activity (262).

The differences in CRQ results may in part relate to the study parameters used such as the length of the study and the time points for evaluation. It is also possible that as an outcome measurement alone the breathlessness domain of the CRQ may not appropriately reflect any improvement in breathlessness with everyday general activity an issue highlighted by a previous paper. Breathlessness scores may remain static or worsen after the initial introduction of an intervention to alleviate symptoms because patients are able to exert themselves to the same level of breathlessness without realising that their exercise tolerance has changed, or if they do identify improvement this has not previously been measured within the study protocols (273). It is likely that any improvement in exercise tolerance will only occur gradually over time. Therefore, monitoring exercise and activity outcome measurements could help to quantify the benefits of airflow delivery over time.

Moreover, the far-reaching and complex effects of breathlessness means that it is not possible to select a single tool that can accurately measure all the dimensions (274). In addition the progressive nature of a life limiting disease makes it inherently difficult for researchers to identify the most appropriate measurement to demonstrate positive patient benefits with activity over time. This challenge may reflect the limited breathlessness improvement that was found in the only study, which examined the use of the hand-held fan with everyday

general activity over two months (219). The authors reported a small Borg score change -0.6 (SD 2.1) at 2 months (219), although it is noted that as a phase II feasibility study it was not designed with sufficient power to test the effectiveness of airflow from a hand-held fan. Nonetheless, a sub-group of hand-held fan users commented very favourably about the intervention (219), but the average breathlessness over the past 24 hours is only likely to reflect the daily change in breathlessness severity, whereas measuring specific time points in the recovery from the intensity of breathlessness after general activity may accurately reflect the improvement in breathlessness related to exercise tolerance change over time. Furthermore, the recently published results from two studies that investigated an integrated specialist breathlessness service for patients with advanced disease and refractory breathlessness demonstrated significant improvements in symptom mastery and coping with the distress due to breathlessness (8, 9) This indicates that symptom mastery and the level of distress related to breathlessness may be more suitable outcomes measurements to appropriately reflect what improvement the patient feels is important and should be incorporated into the design of a future feasibility study that assesses the effect of airflow delivered from the hand-held fan in relation to everyday general activity.

In summary, the nature of the preliminary evidence means that it is not possible to conclude that the hand-held fan or cylinder medical air delivery offers meaningful breathlessness improvement with everyday general activity. However, these findings do suggest that cool facial airflow provides benefit. This would require further assessment and indicates some of the potential key future research questions. A further feasibility study is recommended to explore the variability around different outcome measurements used with breathlessness to try and identify which are the most appropriate to use to assess the effect of airflow from a hand-held fan during or after general activity.

3.11.3 Exertion induced breathlessness

The modified Borg score was also used to measure breathlessness in three of the studies that investigated exertion-induced breathlessness. The results seem to mirror the CRQ findings from the everyday general activity studies, with inconsistent changes reported in the mean Borg breathlessness scores. Two studies reported no change after using airflow from cylinder medical air for a 6MWT repeated on the same day (264), or repeated after 12 weeks (266), while the third study identified -1.5 point improvement after using airflow from cylinder

medical air during a 6MWT repeated on 3 separate visits (265). These results do not help clarify whether or not airflow is helpful with exertion-induced breathlessness. It is plausible that the patients experience the same level of breathlessness during the walking tests without noticing if their exercise tolerance has improved. In this case it would be expected that the 6MWT distances would increase or the number of patients stopping the test would decrease, but none of the results demonstrated significant improvements that would represent the MCID for the 6MWT which is known as 25 metres for COPD patients (275). Jolly (2001) reported 4 metres increase in 6MWT distance in patients who do not de-saturate on exertion and a 50 metres decrease in patients who do de-saturate with exertion (264). The other two studies found little change with only small increases in 6MWT distance of 3 metres (265) and 12 metres (266) respectively. It is possible that these results reflect the use of the 6MWT, a sub-maximal exercise test that allows the patient to dictate their walking speed and rest if needed. Therefore the distance walked and the breathlessness intensity experienced after the 6MWT could reflect the patient's ability to pace their walking or manage their breathlessness level to a known past experience, rather than relate to the effects of airflow delivered during exercise.

The length of time to recover from exertion induced breathlessness would be recommended as a potential outcome measurement to assess in a future feasibility study. Previous evaluation of breathlessness recovery times in thoracic cancer patients after a progressive exercise test demonstrated that breathlessness scores decline rapidly to baseline after 4 minutes with a range of 1-7 minutes (276). Therefore, the effectiveness of airflow from the hand-held fan or cylinder medical air could be assessed using a point-in-time measure of breathlessness intensity when administered during the recovery time from exertion induced breathlessness. This would permit the evaluation of a study design that assesses an exercise test and possible improvement to lower limb muscle over time, in addition to testing the effectiveness of the hand-held fan or cylinder medical air for the relief of exertion induced breathlessness after the exercise test.

In contrast, the three studies that measured the mean Borg breathlessness scores in relation to airflow delivered during a pulmonary rehabilitation programme all found differing levels of improvement in breathlessness intensity. This was measured at a time point defined as exercise isotime in two studies (263, 269), and both during and after a non-motorized treadmill 6MWT in the third study (270). Results demonstrate significant Borg breathlessness

score changes in two of the studies -1.8 point (263) and -3 point (269), which are comparable with the MCID in COPD (271), while a smaller effect size of -0.5 point was found in the third study (270). These results could reflect the type of exercise protocol that was used in the study design to induce breathlessness and test exercise capacity. The constant load exercise test on a cycle ergometer delivers a consistent pace during the exercise test that is programmed and controlled by the researcher (263, 269), whereas the non-motorised treadmill 6MWT was driven by the patient's own walking speed making it possible for them to decide on their pace (270), thereby exerting control over the level of breathlessness experienced.

It is possible that the benefits in part may relate to the completion of a formal pulmonary rehabilitation programme, a recommended standard of care for patients with COPD, known to improve exercise tolerance, muscle strength and significantly decrease breathlessness (136). However, the improvement in Borg breathlessness scores may also indicate that airflow could have a potential role to help improve exertion induced breathlessness experienced during pulmonary rehabilitation. The data from two studies (263, 269) that were combined in a meta-analysis demonstrated significantly improved breathlessness with a SMD -2.9, 95% CI -3.2 to -2.7, $P<0.0001$. These figures represent a clinically relevant difference that may be of value to patients trying to comply with an exercise regime. The MCID for patients with chronic breathlessness from a variety of conditions is known as a 1 point improvement in the Borg score (4, 271). But as the meta-analysis used limited participant data (n=29), it is not possible to know if the benefit found would be representative.

A previous Cochrane review of oxygen supplementation during exercise training for people with COPD and mild or normoxemia found little support for the use of oxygen over medical air, but conclusions were also limited by the lack of evidence available (277). The authors found that only the constant power exercise end of test Borg breathlessness score significantly favoured oxygen over medical air with an effect size of -1.2 (95% CI -2.4 to -0.6), while the results for the functional and maximal exercise end of test Borg breathlessness scores did not confer any additional benefit of the oxygen over medical air (277). This evidence supports the findings of this review that airflow is a beneficial intervention to help with exertional breathlessness in patients with COPD and mild or normoxemia during exercise training. However, this would require further testing in a future RCT which excludes COPD patients who qualify for LTOT.

Furthermore, the review is unable to answer whether airflow has a role with COPD patients who are mild or normoxemia at rest, but de-saturate on exertion. A previous Cochrane review of COPD patients with mild or normoxemia included a sub-group analysis of 15 studies where exertional desaturation was an inclusion criteria. The authors found that oxygen was beneficial for breathlessness in comparison to medical air with a SMD -0.33, (95%CI 0.46 to 0.20), P<0.00001 (93). This suggests that airflow may only be appropriate with certain sub-groups of COPD patients and early desaturation could indicate a patient who is more likely to gain benefit from oxygen during activity (278). Moreover, the review is unable to assess if there is any benefit from medical air delivery during everyday general activity or exercise in patient groups other than COPD as none of the included studies examined the effect of airflow in cancer, chronic HF or other sub-group populations.

3.12 Limitations

In this review the data used were analysed as cohort "before and after" design, although much were collected in the context of RCTs. The analyses do not include a comparator or control group so it is not possible to know if any change is truly caused by the airflow delivery or due to some other factor. The review meta-analyses provide a preliminary indication of the pooled effect estimate of airflow only. No adjustments were made to the calculated effect estimates to control for confounding bias present in non-randomised cohort data, therefore, data should be interpreted with caution and with a view to informing further work using a randomised control trial. The number of studies that fulfilled the review criteria was restricted by the need for baseline breathlessness measures. Some studies (223, 268) that did report repeated measurement and were thus included, did not report data in a format suitable for meta-analysis necessitating the use of statistical assumptions. Therefore, for these studies the formulae from Hozo (2005), (260) was used to calculate the SD and SE required for the meta-analysis. Moreover, it was only possible to include two studies in each of the meta-analyses, therefore the results pertain to a small number of participants and it is not conclusive if the benefits found are representative.

3.13 Summary of chapter three

This chapter provides preliminary evidence that airflow delivered at rest from a hand-held fan and from cylinder medical air via nasal cannula can provide a clinically important discernible reduction in breathlessness intensity experienced in cancer patients.

There was inconsistent signal from the available evidence that airflow helps with breathlessness experienced during everyday general activity, or with exertion induced breathlessness in people with advanced cardio-respiratory diseases, although preliminary data suggests that airflow may help with pulmonary rehabilitation in COPD patients.

The review identified limitation from using the 6MWT to record change in breathlessness intensity during everyday general activities. Therefore, the selection of an appropriate exercise test will be a key challenge for a future study design.

Finally, none of the studies included in this review assessed the effect of airflow from the hand-held fan in relation to the carer experience. Carers often suffer considerable distress from living with a breathless patient (112, 117), as highlighted in chapter one, thus in addition it would be useful to investigate if the hand-held fan helps relieve carer burden and improves their management of a breathless person in any subsequent work.

In view of the findings from chapter three, a systematic review and meta-analyses of airflow and the available evidence highlighted so far, in chapter two for the hand-held fan and Calming Hand, in chapter four the proposed study aims, objectives and research questions are outlined.

Chapter 4 Aims and objectives of thesis

4.1 Overarching aim of this thesis

The overarching aim of this thesis is to investigate the effectiveness of two non-pharmacological interventions which are currently used in clinical practice (cool facial airflow from the hand-held fan, and the Calming Hand) with regard to breathlessness management in people with chronic breathlessness and implications for clinical practice and future research. The rationale for the choice of these two interventions was discussed in chapter two, in the context of what is known about non-pharmacological interventions for breathlessness management, and the potential role of airflow from the hand-held fan was examined in chapter three, a systematic review and meta-analyses of airflow.

4.2 Overarching Research Question

What is the effectiveness of two non-pharmacological interventions which are currently used in clinical practice (cool facial airflow, and the Calming Hand) with regard to exertion-induced breathlessness management in people with chronic breathlessness and implications for clinical practice and future research?

4.2.1 Specific Research questions

Specific questions identified from chapter two and three are summarised below:

1. Does airflow from a hand-held fan or use of the Calming Hand provide benefit for breathlessness when used for exertion-induced breathlessness?
2. Does airflow from a hand-held fan or use of the Calming Hand help patients' functional abilities?
3. Does the use of a hand-held fan or the Calming Hand influence the carer level of burden or ability to cope with the patient's breathlessness problems?
4. What are the most important outcome measures to the patient and what will appropriately reflect any patient benefit from using the hand-held fan or Calming Hand?

In order to answer these questions, an adequately powered RCT would be required. However, before this can be done, the feasibility and uncertainties relating to a proposed phase III trial would need to be addressed, therefore a further specific feasibility research question is outlined below;

5. Is a phase III RCT to test the effectiveness of the hand-held fan and or the Calming Hand for breathlessness in people with chronic breathlessness feasible?

4.3 Feasibility study aim

The aim is to test the feasibility of a phase III RCT to investigate the effect of two non-pharmacological interventions (hand-held fan and Calming Hand) for chronic refractory breathlessness in the context of exercise and advice.

4.4 Feasibility study objectives

The specific objectives of the feasibility plan were to test main uncertainties in relation to:

- The recruitment and retention of participants in order to assess for a future sample size calculation for a subsequent phase III study
- The acceptability of the study protocol in terms of the quality, amount and missing data
- The views and experience of participants and carers with regard to the use of the interventions and the most useful outcomes
- The assessment of the variability around the outcome measures to inform choice of the most appropriate outcome measure and primary endpoint

4.5 Summary of chapter four

This chapter has presented the main aim, objectives and research questions in relation to the proposed feasibility study. The next chapter discusses the methodology for a mixed method feasibility design.

Chapter 5 Methods and Methodology

5.1 Introduction

In the last chapter, the aim, objectives and research questions were identified. In this chapter, the study designs chosen in order to address the questions are described and justified, followed by a summary of the methodological approach used. Finally, a description of and rationale for the mixed-methods approach is given.

5.2 Feasibility study

The term 'feasibility' is an overarching term for preliminary studies and the term 'pilot' refers to a specific type of study which resembles the intended trial in aspects such as, having a control group and randomisation (279). The NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) define feasibility studies as studies used to estimate important parameters that are needed to design the main study, e.g., standard deviation of the outcome measure, willingness of patients to be randomised, willingness of clinicians to recruit participants, number of people eligible, follow-up rates, response rates and adherence/compliance rates. Feasibility studies may have no plan for further work and their aim is to assess whether it is possible to perform a full-scale study (280). In contrast a pilot study is distinguished as a version of the main study run in miniature to determine whether the components of the main study can all work together and focuses on the processes of running the main study, i.e., to ensure the mechanisms of recruitment, randomisation, treatment and follow-up assessments. The aim of the pilot is to provide training and experience in the running of the trial and to highlight any problems so they may be corrected before the planned main study begins (280).

In relation to this mixed method study design, feasibility was appropriate to understand the possibility of conducting a full scale trial and to target the key uncertainties associated with the interventions (281). It is also particularly important in palliative care to test recruitment, retention and data completion as these may be important sources of bias and barriers to the effective conduct of a study. Palliative care has long been associated with gatekeeping and recruitment difficulties (282, 283), and achieving an adequate, representative and unbiased sample is often cited as one of the most common and complex methodological challenges

(282). Therefore the important issues to address in the feasibility study were the recruitment and retention rate of participants, as well as understanding the feasibility of the sampling strategy and assessing the most appropriate study design, procedure and outcome measures for a future trial.

5.3 Rationale for quantitative design and methods

The quantitative component chosen was a RCT, a well-known and established design that is suited to the evaluation of the effectiveness of an intervention and moreover is considered the most appropriate design and method to use with complex interventions (281, 284). The piloting of the hand-held fan and the Calming Hand required a randomised method to reduce the potential sources of bias. If a cohort or other non-randomised method were selected as a pilot then the increased risk of bias could potentially provide misleading results that limits the confidence for a future definitive trial design in terms of the predicted recruitment, sample size calculations and outcome measurements.

5.3.1 Pragmatic design

A pragmatic RCT design was chosen to answer the research questions and produce a realistic clinical test as to whether or not the interventions worked, for whom and when. Therefore, it was not appropriate to consider a placebo comparator as the objective was to estimate the effectiveness of the interventions and not to explain or establish the underlying biological or physiological mechanisms of how or why the interventions worked or not. A previous feasibility study of the hand-held fan also found that the plausibility and acceptability of the placebo intervention was limited (219). Moreover if a placebo were considered such as another device to hold in the hand then this could negate the opportunity to capture the real-life effects of the hand-held fan, itself and potentially important data could be missed about how patients use the intervention. Furthermore, if there is positive benefit from the clinician's input and how the intervention is delivered then this is a worthwhile effect to have as it replicates the usual clinical practice and improves the generalizability of the results, thereby maximising the external validity of the trial. Therefore, the trial was designed so that all of the participants received the usual routine breathlessness care management. This was a breathlessness advice leaflet adapted from the Cambridge Breathlessness Intervention Service (BIS) model, which has demonstrated reduced distress due to breathlessness (8, 117). In line

with the pragmatic design, a wide eligibility criteria was chosen for the study population which sought to maximise the possible recruitment opportunities and increase the generalisability of the results to patients with chronic refractory breathlessness, irrespective of the underlying diagnoses.

5.3.2 Factorial 2x2

A factorial 2x2 design was chosen to permit the evaluation of the two different complex interventions within the same feasibility trial. This design has some important advantages as it maximises the data possible from one trial, which is particularly relevant in the context of palliative care where patient burden from study participation is often cited as an issue (282, 285), and it provides a viable economic method to test the effectiveness of two different interventions in one trial reducing both the financial and trial burden price.

More importantly, since the hand-held fan and the Calming Hand are usually applied as part of a multifactorial breathlessness management programme, a future phase III factorial 2x2 RCT would be able to separately test for incremental benefit or harm. Sample size calculations from the feasibility design will inform the most appropriate outcome measures for a phase III factorial 2x2 trial that will be able to "tease" out the different effects of the two interventions and assess if there is significant incremental benefit that is discernible to the patient.

A future fully powered phase III factorial four arm RCT will permit the assessment of any potential positive interactions between the two interventions in terms of increased benefit in the presence of each other, or the possibility of a negative interaction whereby one intervention counters the benefit of the other intervention when used together as opposed to alone. Equally, the design will identify if there is a "ceiling limit" to the amount of benefit possible from the cumulative use of interventions for breathlessness management. This effect has been identified in a previous study where the addition of further different strategies to augment the optimal level of palliative care provision did not produce any further increases in patient benefit (286).

5.3.3 Probability Sampling

In conjunction with the factorial pragmatic RCT design, a probability block of four randomisation schedule generated by a web-based random number sequence generator using a 1:1:1:1 ratio: Hand-held fan and usual breathlessness care, versus Calming Hand and usual breathlessness care, versus both hand-held fan and Calming Hand and usual breathlessness care, versus the usual breathlessness care only was chosen as the most appropriate to ensure even and sufficient participant numbers in all four arms of the study. In addition, although no formal calculation of sample size was required for the feasibility design, it was thought that ten participants in each of the four study arms would generate adequate data to indicate if there were any variability of the change around the outcome measurements and was an appropriate, achievable target in terms of the known difficulties of recruitment and attrition in palliative care, therefore the study aimed to recruit 40 participants in total.

5.3.4 Outcome measurements

The outcome measures were chosen to reflect the multidimensional effects of chronic refractory breathlessness. The selection was further informed by the findings from the systematic review of airflow (Chapter three), and previous research recommendations for breathlessness measurement in advanced disease (274, 287). All of the outcome measures are reproduced in the Appendix 4, Case Report Form.

5.3.4.1 Numerical Rating Scale

A unidimensional scale, the numerical rating scale (NRS) was deemed appropriate to measure the sensation of breathlessness in terms of intensity, distress and unpleasantness scored as an “average over the last 24 hours” or “at worst over the last 24 hours” at the start and end of the study period. The NRS intensity and distress of breathlessness were also rated as “right now” after an exercise test at maximal breathlessness from exertion and again every minute during the recovery period at the start and end of the study. Prior study confirms that breathlessness “right now” and “average” are different constructs (288). The NRS 1-10 scale also correlates highly with Visual Analogue Scale (VAS) ratings in people with COPD (288). The NRS is also more repeatable than the VAS and therefore requires a smaller sample sizes to detect any change in breathlessness (289), matching the feasibility design chosen. In

addition, the NRS correlates strongly with the four-level categorical Verbal Descriptor Scale (VDS), a practical tool that can be used to monitor severe breathlessness intensity if assessment by the full NRS is not appropriate (290). More importantly, recently published data from a feasibility observational study indicates that the NRS is more precise than VAS at identifying duration of breathlessness response to cool airflow with a median duration of breathlessness response, NRS = 35 minutes, (95% CI: 20.7-49.3) versus VAS = 75 minutes, (95% CI: 2.8-147.2) and is recommended for point in time measurement of breathlessness severity (220). Therefore, the NRS was judged as the most suitable of all the validated unidimensional measures available to use with the hand-held fan.

5.3.4.2 Life-Space questionnaire

The Life-Space questionnaire was selected to assess the physical and psychological restriction imposed on a patient's everyday movements and activity. This questionnaire was designed by Stalvey et al to assess the full spatial extent of mobility in community-dwelling older adults. The patient's life space is conceptually divided into five zones according to the level of movement the patient is able to make away from home and whether or not assistance and/or equipment are needed (291). This conceptual model is reproduced in Figure 10 showing life-space levels as a series of concentric areas radiating from the room where a person sleeps (291).

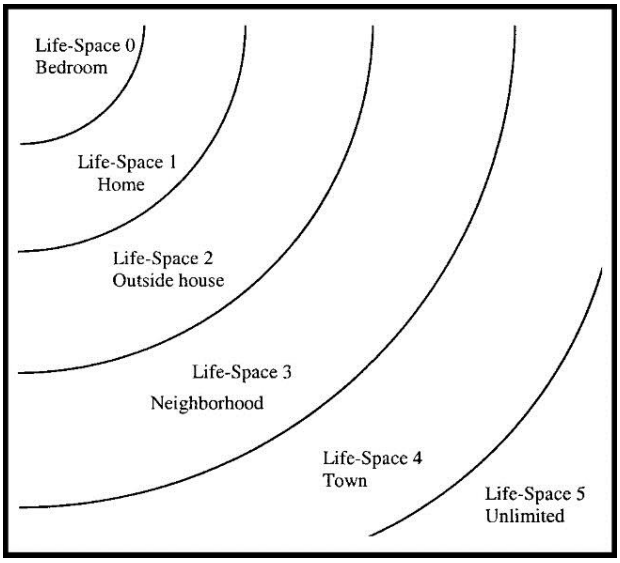


Figure 10 Conceptual model of life-space levels (291)

The Life-Space assessment was found to have good construct and criterion validity with an elderly population (292), in addition it has established test-retest reliability (intra-class correlation coefficient = 0.96) (293). More importantly, the questionnaire recognises that the domains of ambulation and physical functioning can be affected by other factors such as health, emotion and cognitive states (291), therefore it is ideally suited to assess how chronic refractory breathlessness influences the patient's magnitude of movement around and away from home, while also evaluating if the hand-held fan and/or the Calming Hand can affect their life-space limits.

5.3.4.3 Incremental Shuttle Walk Test

Exercise and general activity were identified from the systematic review of airflow (Chapter three) as key areas to address in the design of a future feasibility study. In addition, the length of time to recover from exertion induced breathlessness was reported as an important outcome measurement that required further detailed evaluation. Therefore, the study protocol needed to include an exercise test so that the effectiveness of the interventions could be assessed by using a point-in-time measure of breathlessness intensity that was administered during the recovery time. The inclusion of a walking test also meant that it was possible to assess the patient's exercise capacity and possible improvement to lower limb muscle with general activity over time, in addition to testing the effectiveness of the interventions during the recovery from exertion induced breathlessness. The Incremental Shuttle Walk Test (ISWT) was considered the most appropriate exercise test to induce maximal exertional breathlessness and was also used as an outcome measure at the start and end of the study period. This selection was based on the findings of the airflow SR and previous study which found that patients exercised maximally (294) because the walking speed of the test is externally controlled by the investigator and does not permit the patient to rest or pace themselves and influence the outcome measurement of exertional breathlessness. Therefore, a standardised walking pace with incremental speed increases achieves maximal breathlessness from exertion in all participants and the distance walked appropriately reflects any changes in functional capacity over the study period, in contrast to the subjective problems that are associated with the self-paced 2, 6 or 12 MWT (295, 296). Constant workload tests that use a cycle ergometer or a treadmill were also considered as an option, however it was not possible to utilise these tests due to the lack of equipment available in the Clinical Trials Unit. This in

combination with the restricted working space limited the choice for the protocol to the selection of a walking test.

The ISWT was first developed for use in patients with COPD (297), and was subsequently validated in comparison to a treadmill exercise test (298). It is a well-known, safe, reproducible and effective method for the assessment of functional capacity in patients with pacemakers, chronic HF, advanced cancer or those attending pulmonary rehabilitation (294, 299-301). Therefore, the objectivity of the walking test combined with the suitability and validity in many advanced disease diagnoses made this the most appropriate research tool to use in the study protocol for the measurement of exertion induced breathlessness and exercise capacity over time.

5.3.4.4 General Self Efficacy Scale (GSES)

Self-efficacy is known as a person's belief of their ability to control, organise and perform actions that are necessary to accomplish a goal they believe to be important within a specific domain of functioning (158). This was identified in chapter 2.2.3 as a key construct that could influence the patient's ability to cope with sudden acute on chronic episodes of breathlessness, as well as their confidence to manage everyday exertional breathlessness from general activities (302). Therefore, the General Perceived Self Efficacy Scale (GSES) was selected to try and understand the individual's capability to manage breathlessness, and further evaluate if the interventions could influence the patient's competence and self-efficacy status. The GSES measures a person's beliefs about their capability to handle new or difficult tasks and was originally developed by Schwarzer et al, consisting of 10 items that are rated on a 4-point scale with the anchors, "not at all true" and "exactly true"(303). A previous review of the research using the GSES reported the internal consistency coefficients for a variety of samples and countries that ranged from 0.75 to 0.91 (304). This indicates that some of the values, below 0.80, fall outside the acceptable range for research (305, 306). However, more recent evaluation with Item Response Theory, a model-based approach to understand the nonlinear relationships between item characteristics and individuals' response patterns suggests that the criticisms of the General Self-Efficacy measures were overstated and the psychometric evidence to date supports the construct validity of the GSES (307). In relation to the study the problems identified with the General Self-Efficacy measures were not thought to be a major concern because the aim of the protocol was to explore the

feasibility and acceptability of the outcome measure to the patient and the carer, rather than analyse the factor structure underlying the responses to the items.

5.3.4.5 Zarit Burden Interview

The Zarit Burden Interview (ZBI) Short Form were used to explore potential carer burden from living with a person suffering from chronic refractory breathlessness. The ZBI Short form questionnaire was developed from the longer revised 22 item version (308) to provide researcher's with a tool to assess the level of carer burden from living with cognitively impaired adults that was easier to administrate (309). The ZBI short form has subsequently been validated in advanced conditions (310), and the 4 item ZBI which was designed as a screening version of the original ZBI was found to correlate with the full version and have comparable validity (309). Therefore, the quick and simple 4 item version ZBI was selected as the most appropriate and user friendly outcome measure to provide preliminary data about carer burden. This information was then used to guide the questions in the follow-up interview and help contextualise the carer's experience of living with a breathless person.

In summary, all of the outcome measures chosen were designed to respect the burdens and needs of the different participants. Shortened assessment tools were used whenever possible such as the GSES rather than the lengthy chronic pulmonary obstructive disease (COPD) Self-efficacy Scale and the abbreviated ZBI 4 item questionnaire instead of the longer 22 item version. Similarly, the Demographic Report Form was also kept intentionally brief and the NRS was administered by the study investigator on the telephone on Day 14 to help ease of completion.

5.3.5 Study procedure

The study procedure was designed to test the hand-held fan and Calming Hand in the context of an exercise test at the start and end of the study period and when used at home with everyday general activity that induces breathlessness over 28 days. The study duration was set at 28 days. This was assumed to be sufficient time for any potential increases in lower limb strength, exercise tolerance and was guided by a recent mixed method study of the fan with exercise advice which used a 4 week protocol (311). Participants received the usual care breathlessness management and the interventions during one visit. This was informed by

previous research that identifies equivalent benefit from one training session in comparison to three (131), and aimed to minimise possible patient burden from study attendance to and from the hospital.

5.3.6 Limitation of quantitative design and methods

Although the main risks from selection and subversion bias were addressed by the choice of a RCT design that used a computer generated randomisation process, the block of four sequence order did mean that it was possible to predict what intervention arm the last participant would be assigned too. Theoretically, therefore there was a limited opportunity for selection bias, but given the difficulty with recruiting sufficient numbers to the study it is highly unlikely that any bias influenced the selection of the last participant. Nonetheless, the pragmatic approach did introduce the chance of other sources of bias that could have undermined the validity of the trial. For example, the study investigator and the participants were not blinded to the interventions under investigation. This meant that ascertainment bias was possible from my beliefs as a physiotherapist and pre-conceptions about the interventions in terms of perceived benefit (or not) which in consequence could have also influenced the delivery of the hand-held fan and the Calming Hand to the patients. However, if ascertainment bias occurred it will have been consistent across all the participant's data since I was the sole investigator collecting and reporting all of the outcomes.

In relation to the participants the non-blinded approach meant that bias was possible if the patients "saw" benefits where there was none or over-estimated the effect of the interventions in an attempt to please the investigator or report what they thought the study results should be. Furthermore, patient preferences may have influenced the choice to try the hand-held fan or Calming Hand before the end of the study resulting in dilution bias, or resentful demoralisation may have occurred if a patient were randomised to usual care when they were hoping to be assigned to one of the intervention arms, thereby influencing their level of compliance and the way they reported the outcomes at the end of the study. However, the key objectives of this feasibility trial were to assess the suitability of the protocol and to look at the variability around the outcome measures in order to estimate a sample size calculation for a phase III trial as opposed to measuring the effectiveness of the interventions. Therefore the assessment of these potential sources of bias could benefit a future definitive study design

and it is possible that the qualitative follow-up interviews may illuminate both known and unknown problems of bias that result from the pragmatic approach.

5.4 Rationale for qualitative design and methods

A qualitative method was used to complement and add value to the RCT results as this provides an in-depth understanding of the patients and carers experience of the feasibility study in terms of the interventions, the design, the outcome measurements and any other benefits or harm not otherwise captured in the quantitative data. The qualitative component aimed to explore the context in which the interventions were effective (or not) as well as the nature of their effectiveness. In addition, the qualitative method can help to improve the understanding of known issues in palliative care such as recruitment and retention, as well as identify other pertinent problems with the trial protocol such as non-compliance, missing data or possible concerns about the randomisation process.

5.4.1 Semi-structured Interviews

Semi-structured, individual interviews were deemed the most appropriate qualitative method to match the research questions and investigate what the perceptions, beliefs and experience of patients and their carer (if consented by the patient) were held in relation to the interventions and the feasibility protocol. The semi-structured interview is a widely used research method which can give insight into perceptions and behaviours (312). More importantly, the analysis of a large dataset of 104 qualitative interviews examining the acceptability of an open-ended interview for research in palliative care patients and carers found that the method did not cause distress and was a highly acceptable, empowering and therapeutic process (313, 314).

Qualitative methods such as participant observation were not considered applicable due to the practicalities of observing participants in their own homes, nor was this a possibility within the constraints of the PhD study. Furthermore, this type of method would not have achieved an understanding of the participant's thoughts and beliefs towards the trial protocol or the acceptability of the outcome measures selected. Likewise, if a focus group were used this method would not have automatically allowed for all the participants to equally express their views or disclose thoughts that they felt self-conscious about because the structure and

content of the discussion may vary considerably given the unique dynamics of the specific group interaction (315).

5.4.2 Interview Design

Linked interviews were conducted with both patients and their carers due to the nature and complexity of the interventions used in the study. The MRC Complex Interventions guidance recommends that a multi-perspective approach should guide the evaluation of a complex intervention as it is important to understand the range of possible effects, how they may vary among participants, as well as whether the interventions work in everyday practice (281). The addition of the carer's perspective enriches the understanding of the trial experience and can help to explore complex complementary or contradictory perspectives which is of particular value in palliative care where carers and family members often play a vital role in helping to manage symptoms (316).

Linked interviews can be conducted separately or as a patient and carer dyad and both methods would obtain a different account to the other (313, 316). If a joint method were chosen then it is possible that the presence of the patient during an interview with their carer could influence the potential disclosure of feelings such as burden or distress. Previous qualitative work that examined the acceptability of interviews found separate interviews with carers nearly always evoked emotional reactions and led to tears (313). There is also the opportunity for the interaction between the carer and the patient to influence the discussion process, in that the carer dominates the conversation and answers questions for the patient, or there is the possibility of stirring up antagonism between them. The interaction and dynamics of the relationship between the patient and carer were not the focus of the interview as the main aim were to obtain everyone's individual perspective in relation to the acceptability of the study protocol and their assessment of the interventions effectiveness (or not). Therefore the decision was made to conduct the interviews alone to allow the full expression of all views as opposed to using a joint method that could constrain the potential open discussion of sensitive or embarrassing issues.

A topic guide was considered most appropriate to ensure that the structure and content of the interviews aligned with the research questions, as well as guiding my role as a qualitative researcher. The topic guide was informed by the research questions, yet it was sufficiently

flexible to allow the opening of another avenue of questioning if an unexpected answer were given.

5.4.3 Purposive Sampling

A purposive sample was selected to capture the maximum variation of the participant's experience of the study and included the carer's opinion too (if consented by the patient). This sampling strategy was chosen so that participants were drawn from all four arms of the feasibility RCT and permitted the inclusion of characteristics gender and whether the patient had a formal carer or not (as displayed in Tables 19 and 20; Sampling framework for patient and carer interviews).

Table 19 Sampling framework for patient interviews

		Usual care	Hand-held fan + usual care	Calming Hand + usual care	Hand-held fan + Calming Hand + usual care
Male	Carer	+	+	+	+
	No carer	-	+	-	+ +
Female	Carer	+	+	-	-
	No carer	-	-	+	+

+ = interview, - = no interview

Table 20 Sampling framework for carer interviews

	Usual care	Hand-held fan + usual care	Calming Hand + usual care	Hand-held fan + Calming Hand + usual care
Male	-	+	-	-
Female	+	+ +	-	+

+ = interview, - = no interview

It could be argued that the choice to sample purposively means that findings are not generalizable to the study population. Therefore, another option would have been to consider the use of a probability sampling strategy where a random sample of participants were

interviewed to provide a representative view. However, this approach was not adopted as the objective were to gain a full and complete understanding of the participant's experience in each of the four arms of the trial, thereby enriching the quantitative data and providing information relevant to the research questions and the design of a future study.

5.4.4 Philosophy

The theoretical approach of Grounded Theory (317) was considered appropriate to reflect the chosen contextualist position that all knowledge is local, provisional and situation dependent (318), and as such the interpretation of results will differ according to the context in which the data were collected and analysed. Four dimensions have been identified as influencing the production of knowledge;

1. Participant's own understanding
2. Researcher's interpretations
3. Cultural meaning systems which inform both the participant's and researcher's interpretations, and
4. Acts of judging particular interpretations as valid by scientific communities (318).

Therefore, the contextual analysis of the interview data acknowledges the subjective nature of the findings and the influence my analytical style as the researcher, along with the level of inference required to understand the linguistic meaning of the interview data.

Grounded Theory can be applied within a realist or a contextualist framework as the approach depends on which version is selected and how the meaning of the language is viewed by the researcher (319). Early articulation of the theory implies a realist perspective in that the findings exist and are discovered within the data (317), while later versions suggest that the findings are the result of the construction of inter-subjective meanings, aligning with a contextual approach (320). Therefore, the latter perspective of Strauss and Corbin (320), was chosen as this appropriately reflects the contextualist position and assumptions of myself as the researcher. A modified Grounded Theory method was deemed necessary as the data were approached with a set of specific research questions and the aim was to develop categories and themes to illuminate the data collected, generating new insight into the participant's and carer's experience of the interventions and the study protocol. The method involved a

systematic coding of the interviews, in which categories were developed and saturated with appropriate examples to demonstrate relevance to the research questions, as opposed to a realist approach that forces the textual material into known categories (319). In accordance with a contextual philosophy the goal of triangulation of the data was to achieve completeness and provide a complementary picture of the participant's and carer's experiences of the study.

5.4.5 Analysis approach

Thematic analysis was selected as the method of choice to analyse for themes within the data that related to the research questions. This method was first described by Boyatzis (321) and later expanded on by Braun and Clarke (322). It is identified as a foundation method for novice researchers that is flexible to meet the demands of a wide range of epistemological approaches and can result in a rich and detailed account of the data (322). Moreover, the thematic method was chosen to give maximum variation of views from the sampling of the four arms of the study, whereas other methods of analysis such as Interpretative Phenomenological Analysis (323) would not have been appropriate as this is attached to a phenomenological approach. A qualitative approach that considers the individual's experience of reality in great detail and requires an observational method to study a small homogenous sample in relation to the phenomenon under investigation.

5.4.6 Limitations of qualitative design and methods

The semi-structured interview is a social interaction between the researcher and the participant that relies on the researcher-led agenda, yet equally relies on what was said in answer by the participant (312, 324). It is known as a subjective method that is open to bias from both the researcher and the participant. The interview data represents the participant's experience of the interventions during the context of the feasibility trial which was not a prolonged exposure and did not provide the opportunity to observe the participant's behaviour directly with the interventions outside of the clinical setting. Therefore, the findings relate to the timeframe of 28 days which may not fully reflect the "true" patient behaviours and interaction with the interventions or how they were used at home during the study. It is also possible that participants may try to portray what they think the researcher wants to hear about the interventions in an attempt to please or answer in a socially

acceptable manner, especially in light of myself, the researcher also being the therapist who provided the study intervention and data collection. More importantly, the interview itself could be interpreted as a therapeutic intervention for breathlessness (325); a limitation that was minimised as all interviews were conducted at follow up after completion of the four week trial.

The interviews are based on the participant's memory and their ability to accurately reconstruct events. As the feasibility study design sampled a palliative population there is the possibility that age, co-morbidities and medication could all influence the participant's recall of their breathlessness experiences during the study. The retrospective interpretation of how the interventions operated during episodes of exertion induced breathlessness could be distorted by the patient's emotional status thus increasing the saliency of some memories over others (326). However, although the subjective component of breathlessness may change recollection and influence how the patient's perceives their ability to cope or manage everyday activity, the qualitative data gained in this respect can be compared and contrasted to the results from the quantitative design. Therefore, the synthesis of these data sets together may provide valuable insight into the relationship between the patients perception of intervention benefit (or not) and the variability around the outcome measurement data (or not), thereby appropriately informing a future definitive study design.

5.5 Rationale for mixed methods approach

A mixed methods approach was chosen to address the variety of research questions formulated from the preliminary exploration of the evidence available for the Calming Hand, (Chapter two), and the systematic review of airflow and the hand-held fan, (Chapter three). This approach combines the elements of both quantitative and qualitative philosophies that have historically been applied as individual and mutually exclusive methodologies in health-care research. Quantitative methodology is based on positivism and is associated with the observation of a single external reality. Key attributes include the objectivity of the researcher, the deduction of fact through hypotheses testing and the production of data associated with either high internal validity from laboratory controlled conditions or high external validity from clinical trials that are generalizable to the population under study. In contrast, qualitative research has its foundation based on the constructionist epistemological paradigm. Its main association is with research conducted in the field of social sciences, in

particular the study of human beings, where results are reported as the experience of individuals within specific contexts and knowledge is seen as being subjectively constructed through a process of interaction with others (324).

The two paradigms have traditionally been viewed as incompatible particularly when the differences are expressed from a conceptual perspective in terms of the nature of knowledge and how it is generated. But when the emphasis is on the differences in the strengths of the research methods that are derived from the paradigms, then the differences can be viewed as compatible because the strengths of one method can be used to enhance the other. Therefore in this context the mixing of methods may be justified as the results produce a greater understanding of the subject under study than would be gained by using either method alone (324).

5.5.1 Pragmatism

Pragmatism has been suggested as a mixed methods approach that opposes the conventional alignment with either positivism or constructionism paradigms and advocates the research questions as the central tenet, matching the most appropriate method to the questions being studied (327, 328). It is based on the philosophy that methodologies cannot be true or false, only more or less appropriate (329). Therefore the emphasis is to employ both quantitative and qualitative strands in a complementary manner to enrich the data, thereby producing a more complete and comprehensive picture (330, 331). In addition, the mixing of the quantitative and qualitative methods not only deepens and broadens the purpose of the study, it provides the opportunity for potential triangulation of the findings (331). Triangulation refers to the process whereby the data from using the different methods are compared and contrasted in relation the measurement of the same phenomenon to reach consistent or convergent conclusions (332).

5.5.2 Concurrent triangulation

In the context of the study to follow, the selected mixed methods design is known as “concurrent triangulation strategy”, a typology described by the parallel use of the different quantitative and qualitative methods and the cross-validation of conclusions reached through the integration of results at the interpretative phase of the study (333). A concurrent strategy

with data integration after completion of the RCT was chosen to ensure a full dataset of results from 40 patients available for comparison to the interview findings. Earlier integration was not deemed appropriate as too few data may not have captured potential change and could have mislead the interpretation of the mixed method study findings.

5.5.3 Limitations of mixed methods approach

A purist stance would view the pragmatic mixed method philosophy as open to the development of "sloppy mishmash" (334) or as possible "method slurring" which contributes to loss of research value and rigour in the findings (335). Therefore, much debate has arisen at epistemological levels over the conceptual difficulties of combining the opposing paradigms and the possible lack of validity criteria in reporting a mixed methods study (336). The main barriers to mixing the methods would suggest that there is a potential loss of value and utility in the research results. Arguments stem from the decisions made about how to combine the results, the weighting of the data reported from the study methods and the failure to write up or publish the quantitative and qualitative components so that they are mutually illuminating (337). These issues are addressed by the guidelines for the Good Reporting of A Mixed Methods Study (GRAMMS) which aims to ensure that quality criteria exist within the reporting of a mixed methods study (338) These are reproduced in Table 21.

Table 21 Good Reporting of A Mixed Methods Study (GRAMMS) (338)

(1) Describe the justification for using a mixed methods approach to the research question
(2) Describe the design in terms of the purpose, priority and sequence of methods
(3) Describe each method in terms of sampling, data collection and analysis
(4) Describe where integration has occurred, how it has occurred and who has participated in it
(5) Describe any limitation of one method associated with the present of the other method
(6) Describe any insights gained from mixing or integrating methods

These guidelines were utilised in this mixed methods study to help guide the integration and interpretation of the data drawn from the quantitative and qualitative aspects of the study.

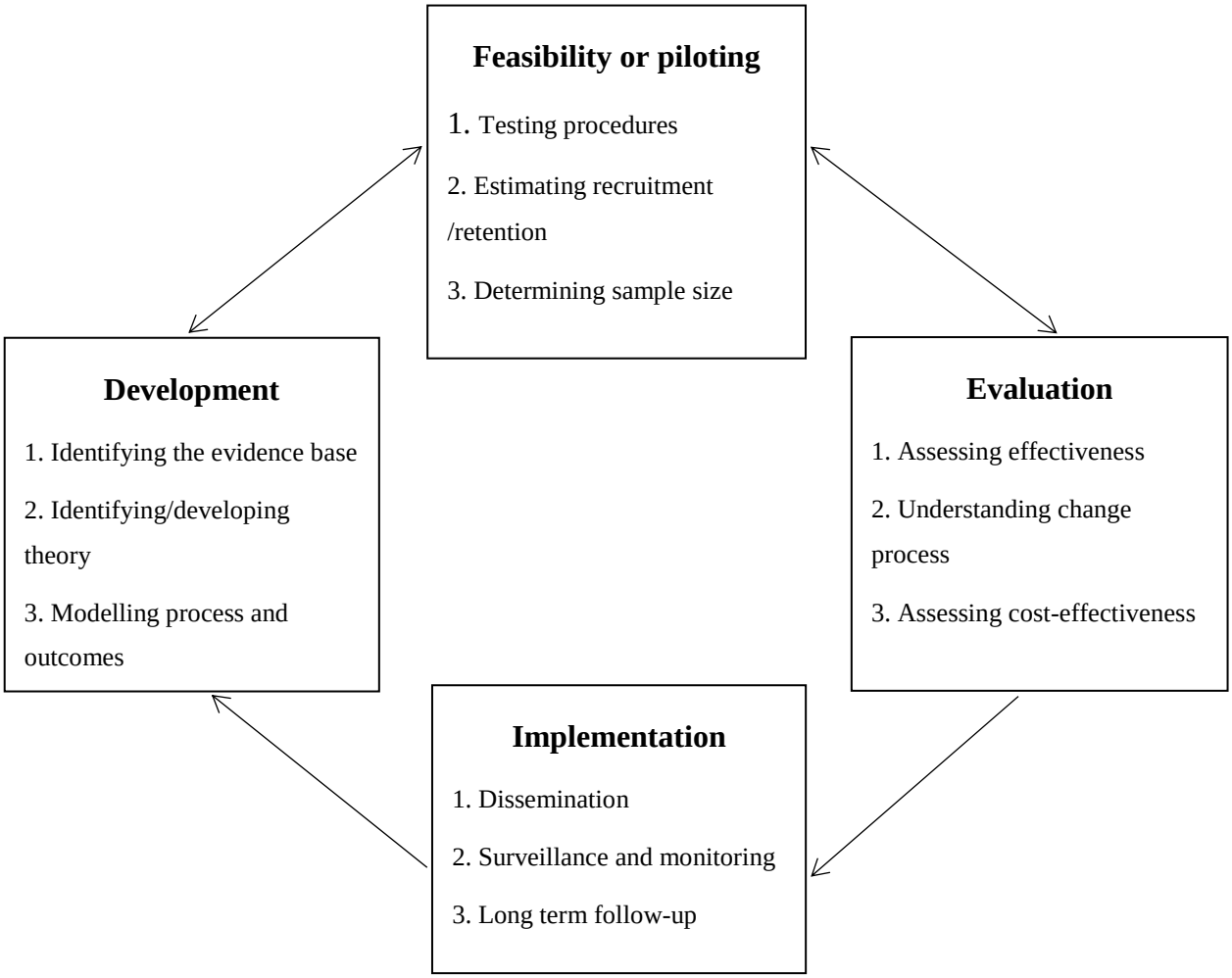
5.5.4 Complex Interventions

The mixed methods approach is identified in palliative care research as of particular value due to the complexity of the interventions under investigation and the inherently difficult problem of finding the correct outcome measures to reflect their effectiveness (339, 340). Complex interventions are defined by the updated Medical Research Council (MRC) framework in terms of their dimensions of complexity which may relate to;

- The number of, and interactions between components within the experimental and control interventions
- The number and difficulty of behaviours required by those delivering or receiving the intervention
- The number of groups or organisational levels targeted by the intervention
- The number and variability of outcomes
- The degree of flexibility or tailoring of the intervention permitted (281)

The key elements of the MRC development and evaluation approach are outlined in Table 22.

Table 22 MRC Complex Interventions (281)



Both the hand-held fan and the Calming Hand represent complex interventions in terms of the possible interactions between the interventions, the variability in the target population and the wide range of potential outcome measures. Therefore, there is the risk that the outcome measures selected will not identify or fully characterise all meaningful benefits or harms from the interventions. Using a mixed methods design to assess the complex interventions permits the patient's view to identify which outcomes are important and relevant. Furthermore, as one of the questions is to test the feasibility of the trial protocol, the patient's view will help inform the design of a future definitive trial by increasing the understanding of the

quantitative aspects of the study such as the acceptability of randomisation procedure to the patient and their usual clinician.

5.6 Summary of chapter five

This chapter has outlined the mixed methodological approach to answer the research questions effectively and the rationale for the methods chosen. The next chapter reports on the quantitative element of the mixed methods; the feasibility phase II, 2x2 factorial, pragmatic, RCT.

Chapter 6 The Calming Hand and Fan Feasibility study

6.1 Introduction

This chapter reports on the quantitative design; a feasibility, phase II, 2x2 factorial, pragmatic RCT to gain preliminary data and explore the effectiveness of two interventions (the hand-held fan and the Calming Hand) on chronic refractory breathlessness in the context of exercise and advice.

6.2 Research question

Is a phase III RCT to test the effectiveness of the hand-held fan and or the Calming Hand for breathlessness in people with chronic breathlessness feasible with regard to acceptability, recruitment and retention?

6.3 Methods

A concurrent strategy was used so that the data collection ran in parallel for the feasibility RCT and the semi-structured interviews. Integration of the data did not occur until after completion of all RCT data collection.

6.3.1 Design

This was a phase II, single site, 2x2 factorial, pragmatic, randomised controlled trial design comparing the effectiveness of:

- The hand-held fan and usual breathlessness care
- The Calming Hand and usual breathlessness care
- Both the hand-held fan and the Calming Hand and usual breathlessness care
- The usual breathlessness care only

for the relief of breathlessness from exercise in people with chronic refractory breathlessness from any cause. The 2x2 factorial design is illustrated in Table 23.

Table 23 2x2 factorial design

Factors	Hand-held fan		
Calming Hand	**Levels**	No fan	Fan
	No Calming Hand	- -	- +
	Calming Hand	+ -	+ +

The 2x2 factorial design results in the four study arms as shown in Table 24;

Table 24 Four arms of study

Usual breathlessness care	Hand-held fan + usual breathlessness care
Calming Hand + usual breathlessness care	Both hand-held fan + Calming Hand + usual breathlessness care

6.3.2 Participants

6.3.2.1.1 Inclusion criteria

The inclusion criteria were:

- Over 18
- Able to provide written or verbal consent to take part in the study
- Living in the community with or without a carer
- Intractable breathlessness from all causes, for whom all reversible components of breathlessness have been addressed
- Level 3 or higher on the Medical Research Council (MRC) Dyspnoea scale (94)
- Have not used the hand held fan or Calming hand for breathlessness over the past two weeks
- Willingness to engage with breathlessness care and study measures including:
    - attendance at breathlessness clinic on day 1
    - telephone call follow-up on day 14
    - attendance at breathlessness clinic or a home visit on day 28

6.3.2.1.2 Exclusion criteria

The exclusion criteria were:

- Too breathless to participate in the study as assessed by the opinion of investigator and/or patient
- Cognitively impaired and unable to understand the study
- Tri-geminal nerve damage/disease

6.3.3 Interventions

6.3.3.1.1 Hand-held fan

Participants allocated to the hand-held fan arm were taught how to use the hand-held battery operated fan in the context of general advice about breathlessness management, anxiety and exercise. Participants were encouraged to use the hand-held fan whenever they felt breathless from exercise, anxiety or other daily activities during the 28 day study period. A plastic, 3 flexible blades, high flow hand-held fan Marks and Spencer's (M&S) was used in this study. A minimum of 6 AAA batteries were given to each participant to allow for 2 new batteries to be installed weekly (Day 7, 14 and 21), or as and when the flow rate reduced from the battery running down, even if the hand-held fan was still functioning. The leaflet for the hand-held fan was developed by the Breathlessness Intervention Service (BIS) at Addenbrooke's Hospital, Cambridge for this study and was used with their permission. All leaflets developed by the BIS have gone through extensive user feedback and their institutional review process.

6.3.3.1.2 Calming Hand

Participants allocated to the Calming Hand arm were instructed how to perform the coping strategy in the context of general advice about breathlessness management, anxiety and exercise. Participants were encouraged to use the Calming Hand whenever they feel breathless from exercise, anxiety or other daily activities during the 28 day study period. They were given the procedure in the patient intervention information sheet, Appendix 11, and the diagram which is reproduced in Appendix 12. The Calming Hand diagram and procedure were developed by Marjorie Coulthard, Dorothy House Hospice Care as a component of their "Breathlessness Management Toolbox".

6.3.3.1.3 Usual breathlessness care

Participants allocated to the usual breathlessness care arm were taught practical techniques and given guidance on how to manage their breathlessness with the use of breathing control exercises, positions for recovery from breathlessness and advised about the importance of exercise. The practical and theoretical information was reproduced in an education leaflet and provided to all of the participants to help them remember and reinforce the practical use at

home during the study period. The information leaflet for the intervention arms also included advice on using the hand-held fan or the Calming Hand as outlined above. All of the Patient intervention information sheets are reproduced in Appendix 11.

6.3.4 Outcome measurements

6.3.4.1.1 Primary outcome measure

The primary outcome measure were:

- The recruitment rate (including screening/consent ratio)
- The attrition related to the intervention and to follow up outcome measures

6.3.4.1.2 Secondary feasibility measures

The secondary outcome measures were stated as:

- The data completion

- The variance or standard deviation of the other secondary outcome measures in order to perform a sample size calculation

6.3.4.2 Other Secondary Outcome measures

Other secondary outcome measures were the patient reported outcomes as shown in Table 25. The outcome for breathlessness intensity during recovery from the ISWT following maximal breathlessness tolerance from exercise was documented separately as shown in Table 26.

Table 25 Other Secondary Outcome Measures

Outcome Measures Symptoms (average over past 24 hours)	**Day1 Baseline Assessment**	**Day14 Telephone Assessment**	**Day 28 Exit Assessment**
NRS unpleasantness	*	*	*
NRS intensity	*	*	*
NRS distress	*	*	*
Function			
Life-space questionnaire	*		*
ISWT, distance, time, shuttles, speed	*		*
MRC dyspnoea scale (part of eligibility criteria)	*		
Participant Self-efficacy and psychometric			
General Self efficacy scale (GSES)	*		*
Carer Self efficacy and burden			
General Self efficacy scale (GSES)	*		*
Zarit caregiver Burden Interview	*		*

Table 26 NRS Breathlessness intensity during recovery from ISWT

Time	**Baseline**	**Maximal**	**Recovery from exercise to baseline following intervention(s) use over time**									
	(T0)	*(Tmax)*	*(T1)*	*(T2)*	*(T3)*	*(T4)*	*(T5)*	*(T6)*	*(T7)*	*(T8)*	*(T9)*	*(T10)*
NRS breathlessness intensity	*	*	*	*	*	*	*	*	*	*	*	*

(T0) = start time, *(Tmax)* = time of maximal breathlessness, *(T1)* = 1 minute recovery time, *(T2)* = 2 minutes recovery etc.

6.3.4.2.1 Demographic measures

The demographic measures were recorded at baseline as shown in Table 27 Demographic data measures.

Table 27 Demographic measures

	Day One Baseline Assessment
Age, sex, post code, DOB	*
Primary diagnosis	*
Hospital admissions (last 6/12)	*
Home oxygen therapy	*
Use of mobility aids	*
Live in carer (relationship)	*
Charlson Co-morbidity Index	*
General question: "when you move about, what stops you? Breathlessness or leg weakness or both?"	*

6.4 Procedures

All baseline assessments were undertaken on Day One at a Breathlessness clinic appointment. The study investigator took the measures and assessments as outlined in the Appendix 4 Case Report Form (CRF).The clinic visit was also recorded within the participant clinical file, along with any instructions or changes regarding on-going management. As part of the baseline measures assessment the study investigator taught and demonstrated;

- How to perform an Incremental Shuttle Walk Test (ISWT) including the reasons for stopping walking
- How to score their breathlessness using the NRS
- How to adopt a comfortable forward sitting recovery position when feeling maximal breathlessness tolerance from exercise.

Each participant was given adequate opportunity to listen to the instructions for the walking test until they felt competent and understood what was required of them. Participants were asked to avoid talking or making significant changes to the recovery position after the ISWT. Participants were shown the NRS and asked to rate their initial breathlessness intensity score *(T0).* Participants were asked to walk up and down a ten metre course along a corridor on a flat surface, externally and incrementally paced by an audio signal, with their walking aid if normally required, in the context of an ISWT. Details of an ISWT protocol test procedure are reproduced in the Table 28 (297).

Table 28 Modified ISWT protocol and test procedure (297)

Equipment
Flat, no slippery surface , at least 10m in length CD player and ISWT CD Suitable foot wear Measuring tape to measure 10m course Marker cones placed 0.5m in from each end to avoids need for any abrupt direction change
Preparation
Explanation to patient standardised on CD, repeated verbally "Walk at a steady pace aiming to turn around at each end when you hear the signal. You should continue to walk until you feel that you are unable to maintain the required speed due to breathlessness"
Starting the Test
There is a triple bleep to start. Thereafter the CD emits single bleeps at regular intervals. The subject should aim to be at the opposite end to the start by the time the bleep sounds After every minute the speed of walking is increased by a small increment so the patient walks progressively faster and is indicated by the triple bleep Each level lasts for 1 minute; the first speed of walking is Level 1, the second is Level 2 and so on Each level contains a number of shuttles which is determined by the speed of that level The patient is accompanied by the investigator to help establish the first very slow speed of Level 1
End point of Test
The end point of the test is determined by the patient - when they become too breathless to maintain the required speed Indication for the investigator to end the test is failure of the patient to complete the shuttle in the time allowed and they are more than 0.5m away from the cone If the patient is less than 0.5m away from the cone when the bleep sounds another shuttle is performed – if they are unable to make the cone for the next bleep then the test is discontinued

The study investigator followed the participant during the walk, guiding their pace and timing, while also monitoring for participant safety and any potential problems that would indicate an immediate stop such as sudden chest pain, dizziness or leg cramp. At the point, the participant perceived their worst or maximal breathlessness tolerance, or the study investigator stopped the ISWT due to the participant's failure to maintain the incremental speed, they were asked to give a NRS breathlessness intensity score, time of maximal breathlessness *(Tmax)*. Participants were instructed to sit down and adopt a comfortable forward sitting position during recovery. Participants were then asked for further NRS

breathlessness intensity ratings after every minute during the subsequent 10 minutes or until breathlessness was relieved *(TI, T2, T3, T4, T5 to 10)* as shown in Table 26 NRS Breathlessness intensity during recovery from ISWT.

After the baseline measures were completed the participant was randomised to the hand-held fan and usual breathlessness care, the Calming Hand and usual breathlessness care, both, hand-held fan and Calming Hand and usual breathlessness care, or the usual breathlessness care only. Participants were taught:

- Correct use of the hand-held fan in relation to the direction of airflow and distance from the face
- Correct performance of the Calming Hand exercises
- Correct performance of the usual care advice and exercises

They were given the hand-held fan, and/or the Calming Hand exercise sheet and/or the usual breathlessness care instructions and asked to continue with the intervention(s) and the usual breathlessness care at home for the next 28 days whenever they felt breathless from activity or anxiety.

Participants were also given a copy of the NRS to take home to assist in the rating of average/past 24 hours, breathlessness unpleasantness, intensity and distress on Day 14 by telephone. On Day 14 the study investigator phoned and asked the participant for their breathlessness unpleasantness, intensity and distress NRS. They also checked and documented if the participant had any problems or concerns arising from the study intervention(s).

Participants visited the clinic a second time on Day 28 to complete the follow- up assessments and perform another ISWT. On the Day 28 ISWT participants were instructed to adopt a comfortable sitting position and use the intervention(s) during recovery from maximal breathlessness tolerance from exercise as follows:

- Hand-held fan + usual breathlessness care
- Calming Hand + usual breathlessness care
- Hand-held fan + Calming Hand + usual breathlessness care

- Usual breathlessness care (breathing control) only

The study investigator recorded all the measures and assessments as outlined in the CRF. Alternatively, to minimise data loss the follow-up assessment on Day 28 was offered as a home visit appointment if the travel to clinic was too burdensome or if the participant felt unable to repeat the ISWT. In this case, the study investigator recorded all the measures and assessments apart from those pertaining to the ISWT. The visit was also recorded within the participant clinical file, along with any instructions or changes regarding on-going management. All patients, including those in the usual care group, were offered a hand-held fan and a copy of the Calming Hand, including instruction sheets to take home at the end of the study.

6.4.1 Recruitment setting

Out-patients with chronic refractory breathlessness due to cardio-respiratory disease from any cause were recruited from key clinics at one tertiary NHS centre, Castle Hill hospital, Hull from 17th Dec 2012 to 15th Dec 2014. Recruitment was temporarily suspended from Sept 2013 to Jan 2014 due to the ill-health of the study investigator during this time. Members of the investigative team interacted with key services at the participating site including oncology, palliative care and respiratory medicine.

6.4.2 Approach

Potentially eligible participants were approached and screened by the patient's usual clinician. If agreeable to finding out more about the study, the potential participant was provided with a Patient Information Sheet to take home (see Appendix 5). Potential participants were then contacted by the study investigator by telephone to discuss if they wished to participate in the study, or if they preferred a routine breathlessness clinic appointment. The study investigator requested the verbal consent of the patient so they were able to access their medical notes to complete the eligibility screening form if interested in study participation.

6.4.3 Written Consent

The patient information sheet was used as a basis for the discussion. In compliance with the recommendations of the Declaration of Helsinki and the ICH-GCP guidance, each participant was adequately informed of aims, methods, anticipated benefits, potential hazards and discomforts that the study may entail. The participant's right not to participate and to withdraw at any time was stated. The study investigator was responsible for administering informed consent and informing the subject's General Practitioner of their participation with the participant's agreement. The participant was given the opportunity (in time and physical capacity) to consider the study and formulate questions. Any questions were addressed and answered fully. An actual time period was not specified as this was determined in part by the person's condition and breathlessness at the time, but usually exceeded 24 hours. If an occasional potential participant in clinic wished to enter the study immediately, the study investigator used their judgement as to whether it was better to prevent the patient from having another journey and to allow consent at this earlier stage. All signed consent forms were completed by the study investigator, documented and stored in accordance with local ethics requirement:

- the original copy was given to the participant,
- one copy was inserted into the medical file
- one copy was filed in study file.

GCP training was completed by the study investigator involved in the consent procedure. The consent form was signed and dated by the participant in front of the witness. The witness was anyone who observes the participant signing the consent form, and was able to say that the participant was signing of their own free will. The patient consent form is displayed in Appendix 6.

6.4.4 Carer consent

Written informed consent was also obtained from the carer if they agreed to participate in the study in relation to exploring carer burden and self-efficacy. The process for consent followed the same procedure as for the participant, with the exception that the carer was

given their own Carer Information Sheet and consent form, (see Appendices 7 and 8). If the carer did not wish to participate this did not exclude the participant from study participation.

6.4.5 Randomisation

Participants were sequentially allocated a unique identifying number (ID) on referral to the study. This ID number was used for all subsequent study documentation for that participant. Each participant was allocated to the interventions and/or usual care according to a block randomisation schedule generated by a web-based random number sequence generator using a 1:1:1:1 ratio: Hand-held Fan and usual breathlessness care, versus Calming Hand and usual breathlessness care, versus both hand-held fan and Calming Hand and usual breathlessness care, versus the usual breathlessness care only. Block randomisation ensured the even allocation to each arm. The Hull academic oncology Clinical Trials Unit were responsible for generating the block randomisation tables and they were contained within sequentially numbered, opaque, sealed envelopes. The allocation of the randomisation codes at the site were managed by the Hull Clinical Trails Unit (CTU). The study investigator telephoned the Hull CTU in order to discover which arm the study participant was to receive as soon as consent was given and did not have access to the envelopes.

6.4.6 Cessation of study

Participants were able to withdraw their consent from the study such that all data was removed, or they stopped such that their data remained in the study with permission granted to use the already collected data. Participants were also withdrawn if they were not well enough to continue in the study in the opinion of the study investigator or their usual clinician.

6.4.7 Post study treatment

All participants who completed or withdrew from the study were treated according to the treating physician's discretion. Withdrawal was documented in the PIS and it was stated that this would not compromise the patient quality of care. If any participant wished to leave the study, the study investigator completed a "Withdrawal Study Case Report Form" (CRF) and documented the reasons for the study withdrawal. At the end of the study all participants

were given a hand-held fan and a copy of the Calming Hand diagram, with accompanying instruction leaflets.

6.4.8 Ethics and Research Governance

The study was conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines and the Research Governance Framework for Health and Social Care. The protocol, procedures, patient and carer information sheets, consent forms and questionnaires were approved by the Leeds (West) Ethics committee (REC ref: 12/YH/0410). Ethics approval is displayed in Appendix 9. Institutional permission were granted by the R&D Department, Hull and East Yorkshire Hospitals NHS Trust (R&

6.4.9 Changes to methods and protocol

An amendment was made to the study protocol to offer a second ISWT at baseline, and to increase the number of recruits if possible to 53 following protocol deviation in relation to the baseline ISWT measurements. The Ethics amendment is displayed in Appendix 10.

6.4.10 Statistical methods and analyses plan

As this was a feasibility study the aim was to generate basic information on outcome estimates for powering a future phase III study, therefore there was no formal hypothesis to test, instead the following descriptive analyses were conducted using SPSS Version 22:

- Descriptive analysis of recruitment at single site
- Descriptive analysis on the completion of endpoints
- Calculation of the variance of change associated with the study outcome measurements.

Continuous variables were expressed as means and standard deviations. All randomly assigned participants were included in the Intention-to-Treat analysis. All sample size calculations were made using PS power and sample size calculation software (341).

Recovery time was defined as the time taken for the participant to return to their baseline NRS breathlessness value from the point of maximal breathlessness, or when the ISWT was stopped, measured at 1 minute intervals as displayed in Table 26.

6.5 Results

6.5.1 Participant numbers and flow through the study

The study recruited between Dec 2012 and Dec 2014. Recruitment was full time during the following periods: Dec 2012 to Aug 2013 and Feb 2014 to Dec 2014; a total of 20 months. It was suspended from Sept 2013 to Jan 2014, a total of 4 months due to the ill-health of the study investigator. The recruitment rate for the study varied from 1.4/month to 1.28/month. During the first recruitment period; 9 months, 21 participants were screened and 15 were recruited. During the second recruitment period; 11 months, 32 participants were screened and 25 were recruited.

Of 53 screened participants a total of 13 were excluded; 2 participants did not meet the inclusion criteria (cognitively unable to understand the study or seen recently in the Breathlessness clinic) and a further 11 declined to participate for various reasons (carer duties, hospitalisation, other co-morbidity problems, felt the study was too much or had no transport).

40 were randomised and 40 completed the trial. There were no missing data apart from the ISWT data; two participants did not take part in the walking test on day 28 and the baseline ISWT data from 13 participants were also excluded due to a protocol violation (Baseline ISWT collected after randomisation in error). In addition, no data were collected for the amended study protocol as all of the participants declined the offer of a second ISWT on day on deeming the extra exercise test as too much effort. A pragmatic decision was taken not to recruit beyond the original planned sample size of 40 due to constraints within a PhD. studentship, the feasibility nature of the study and because the inadmissible data only related to one outcome measure where baseline variability was still possible for 27 participants.

All other baseline measures were collected before randomisation and were therefore included in the analysis. See Figure 11 CONSORT flow-diagram of participants through the study. Two adverse event forms were completed during the study; one patient experienced an episode of severe right side chest pain that resolved over-night. She was advised to see the GP if there was any re-occurrence. The second patient experienced increased breathlessness with chest/heart pain. They were admitted via an emergency visit to hospital, diagnosed with

pulmonary oedema and re-started on diuretic treatment. Therefore they were withdrawn from the ISWT and data for Day 28 were collected as a home visit.

Both were considered unlikely to be related to the study interventions and were documented as unexpected events. The adverse events did not result in any participant withdrawal, although the Day 28 ISWT was not considered appropriate for one participant.

14 carers were recruited and 13 completed the study. Data was missing from only one carer as they were unable to attend the Day 28 appointment.

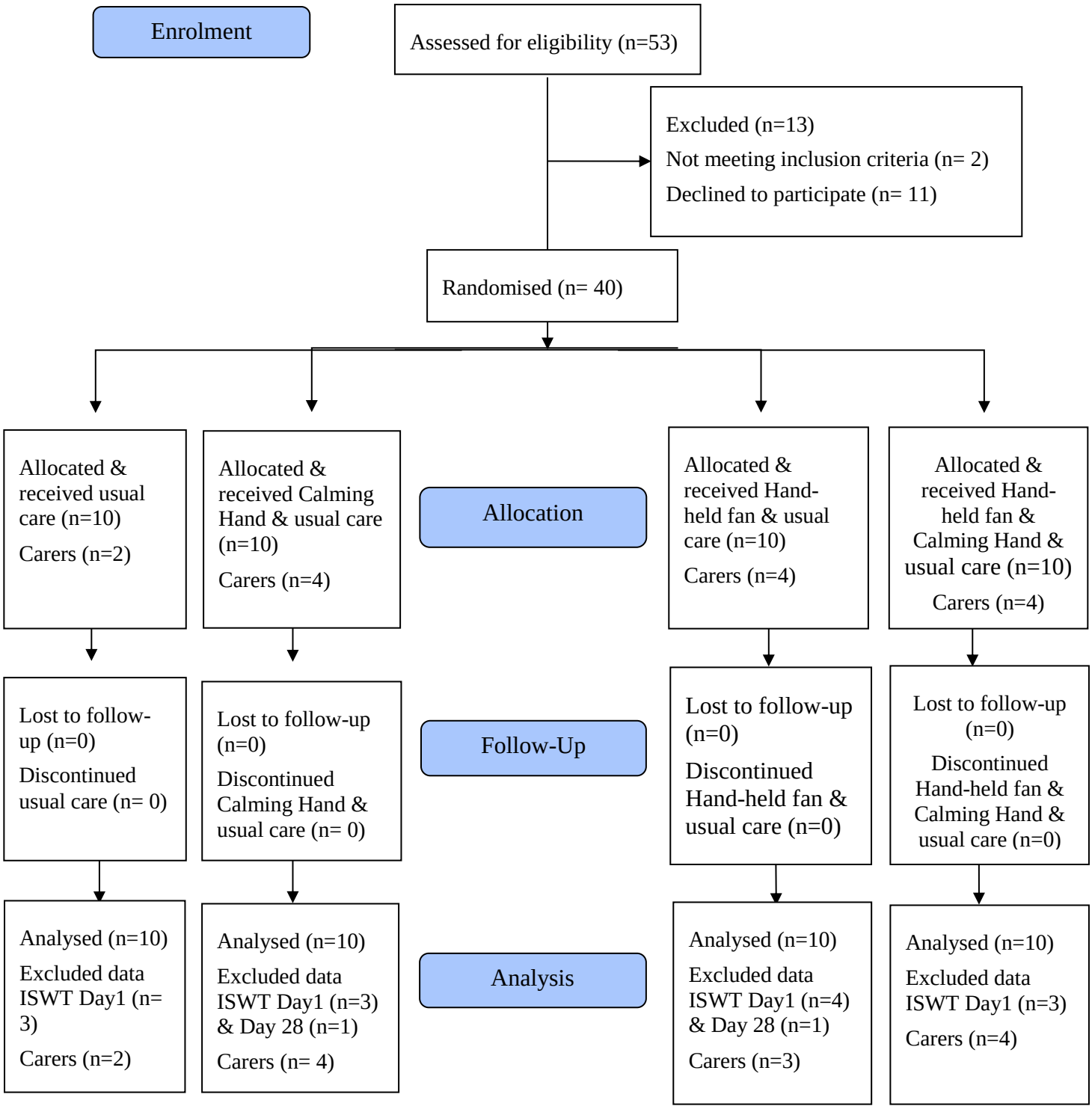


Figure 11 CONSORT Flow-diagram of participants through the study (342)

6.5.2 Participant Characteristics

Most of the study sample screened were from pulmonary fibrosis clinics (n=34) and there were no participants from oncology. The screening to consent ratio was 1.4/1, for pulmonary fibrosis and 1.1/1 for participants sourced from the CTU as displayed in Table 29 Screen/consent ratio.

Table 29 Screen/consent ratio

Source of participant	Screened	Recruited and consented	Screen/Consent ratio
Pulmonary fibrosis clinic	34	24	1.4/1
General respiratory clinic	3	1	3/1
Clinical trials unit	15	14	1.1/1
Patient referral	1	1	1/1
Oncology clinic	0	0	0

Characteristics of the study population can be seen in Table 30 Baseline data. The mean age of the 40 study participants was 72 years (SD 9.8). This was similar in all four arms, apart from the Calming Hand group which had a mean age of 79 years (SD 12.1) and also the oldest participant at 91 years. Over 50% of those sampled had a primary diagnosis of Pulmonary Fibrosis; these participants were randomised by chance mostly to two arms of the study, usual care (n=7) and usual care & Calming Hand (n=9). All of the other demographic variables were similar across the four arms indicating that the block of four randomisation was effective. Most participants were male 70% (n=28). Only a third (37%) had an informal (family) carer which was a spouse or partner for all apart from one. Just over a quarter of the sample stated that they had a hospital admission in the six months prior to the study. A mobility device was required by 15 participants, with 14 using a walking stick and one patient that used a three wheeled walker. Four of those sampled had home oxygen therapy. The Charlson Co-morbidity index score frequencies for participants were as follows: 50%: 1 point, 25%: 2 points, 20%: 3 points and 5%: 4 points. Breathlessness was reported as the first symptom that would stop movement in 55% of the sample, while 40% found that both

breathlessness and leg weakness prevented further movement and only 5% reported leg weakness as the primary symptom that limited movement.

All of the outcome measures; the NRS scores for breathlessness intensity, unpleasantness and distress average over the last 24 hours and breathlessness intensity at worst in the last 24 hours, the Life-space questionnaire, General Self-efficacy Scale (GSES), Incremental Shuttle Walk Test measures, recovery time (displayed in graph 1), and the carer GSES score were comparable across the four study arms, apart from imbalance for NRS breathlessness distress at worst over the last 24 hours and the Zarit caregiver burden. Values varied considerably for the NRS breathlessness distress at worst over the last 24 hours with nearly a 3 point difference between 2 of the 4 arms at baseline; the Calming Hand and usual care, mean 4.1 (SD 3.41), range 0-9 in comparison to the hand-held fan and usual care, mean 7.0 (SD 2.94), range 0-10. Since this was a feasibility study, this could be attributed to the low number of participants, 10 in each arm, rather than ineffective randomisation. Similarly, a five point difference in the Zarit caregiver burden, Usual care, 8.5 (SD 4.95) versus Usual care & both Calming Hand & hand-held fan, 3.5 (3.0) was attributed to the small number of carers in each arm.

Table 30 Baseline data

Demographic data	**Usual care** (n=10)	**Hand-held fan & Usual care** (n=10)	**Calming Hand & Usual care** (n=10)	**Hand-held fan & Calming Hand & Usual care** (n=10)	**Total** (n=40)
Age: Mean (SD), Range	70 (11.2), 53-86	70 (7.2), 61-84	79 (12.1), 59-91	71 (5.9), 56-71	72 (9.8), 53-91
Gender: Male	6	8	7	7	28
Formal Carer: Yes	2	5	4	4	15
Carer relationship					
Spouse/partner Child	2	5	3 1	4	14 1
Primary Diagnosis					
COPD Pulmonary Fibrosis ILD Asthma Sarcoidosis	1 7 1 1 -	5 3 - 2 -	1 9 - - -	5 3 1 - 1	12 22 2 3 1
Hospital admissions last 6 months					
1 admission 2 admissions	3 2	5 -	2 -	1 -	11 2
Home Oxygen Yes:	2	1	1	-	4
Mobility Aids Yes:	4	4	5	2	15
Type of mobility aid					
Walking stick: 3 wheeled walker:	4 -	3 1	5 -	2 -	14 1

Table 30 Baseline data

Charlson Co-Morbidity Index score frequency					
1 point:	5	5	6	4	20
2 points:	3	3	2	2	10
3 points:	1	2	1	4	8
4 points:	1	-	1	-	2
Stop movement					
Breathlessness:	7	5	4	6	22
Leg weakness:	-	-	1	1	2
Both:	3	5	5	3	16

Table 30 Baseline data

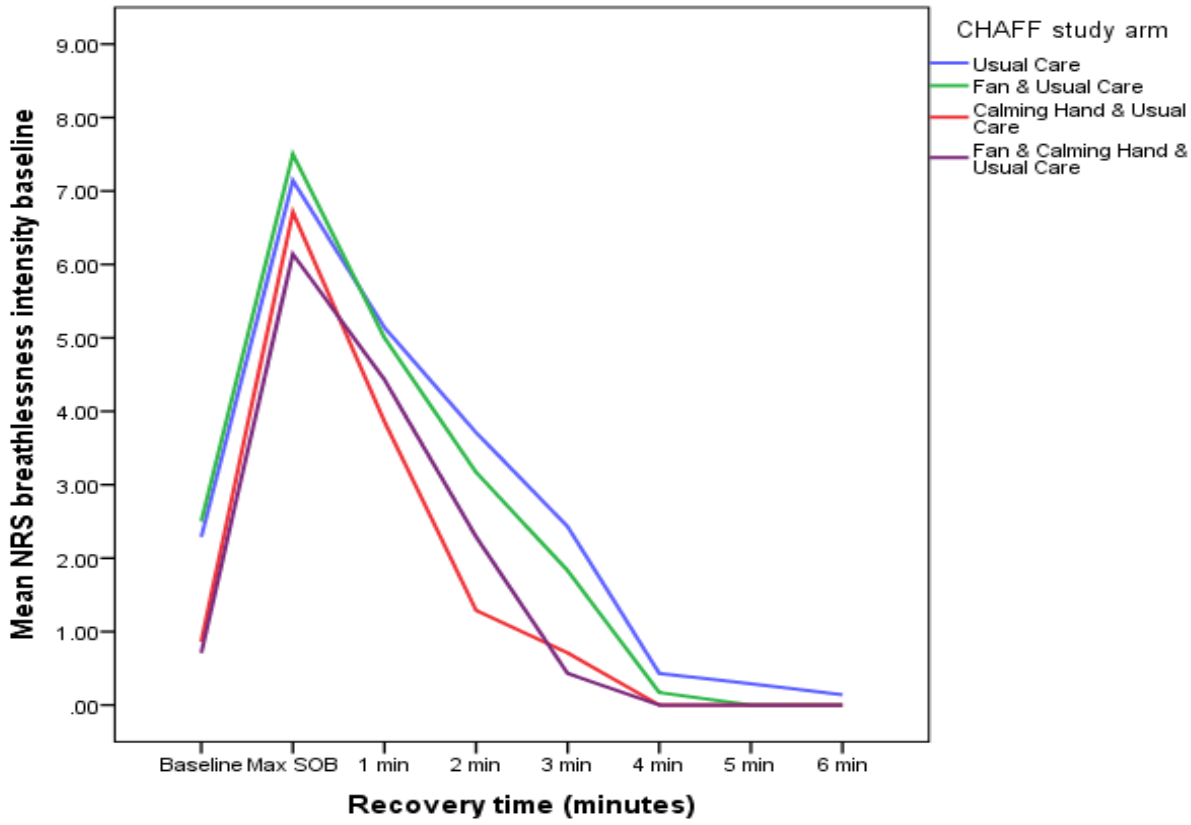
	Usual care (n=10)	**Hand-held fan & Usual care** (n=10)	**Calming Hand & Usual care** (n=10)	**Hand-held fan & Calming Hand & Usual care** (n=10)	**Total** (n=40)
Patient report measures					
NRS Intensity Average last 24 hours Mean (SD) range	5.0 (2.11) 2-8	5.5 (1.43) 4-8	4.7 (1.77) 2-8	4.8 (1.13) 3-7	5.0 (1.62) 2-8
NRS Distress Average last 24 hours, Mean (SD) range	4.8 (3.26) 0-9	5.6 (2.55) 0-9	3.7 (3.37) 0-9	3.3 (2.63) 0-8	4.35 (3.0) 0-9
NRS Unpleasantness Average over last 24 hours, Mean (SD) range	6.1 (2.68) 1-9	6.3 (2.16) 3-10	5.7 (2.26) 3-9	5.9 (2.18) 3-9	6.0 (2.25) 1-10
NRS Intensity At worst last 24 hours, Mean (SD) range	7.3 (1.7) 3-9	7.8 (1.32) 5-9	5.9 (2.28) 3-9	6.9 (1.66) 4-9	6.97 (1.85) 3-9
NRS Distress At worst last 24 hours, Mean (SD) range	6.1 (4.04) 0-10	7.0 (2.94) 0-10	4.1 (3.41) 0-9	4.3 (3.13) 0-9	5.37 (3.49) 0-10
Life-space questionnaire score, Mean (SD) range	54.45 (24.74) 20-100	60.85 (22.69) 20-96	47.05 (13.9) 29-69	55.5 (19.37) 12-78	54.46 (20.4) 12-100
General Self-efficacy Scale (GSES) score Mean (SD) range	30.30 (5.44) 19-38	28.8 (6.53) 21-38	31.7 (6.31) 19-40	33.3 (4.90) 24-40	31.03 (5.85) 19-40

Table 30 Baseline data

	Usual care (n=10)	**Hand-held fan & Usual care** (n=10)	**Calming Hand & Usual care** (n=10)	**Hand-held fan & Calming Hand & Usual care** (n=10)	**Total** (n=40)
Incremental Shuttle Walk Test measures					
Recovery time ISWT (seconds) Mean (SD), range, MD	179.0 (69.14) 98-303 MD = 3	164.0 (70.18) 90-291 MD = 4	140.29 (36.75) 91-201 MD = 3	163.57 (47.44) 85-232 MD=3	161.63 (55.57) 85-303 MD=13
Distance walked (metres) Mean (SD): range, MD	192.86 (138.05) 70 – 430 MD =3	126.67 (81.65) 30 -210 MD =4	121.43 (90.26) 40 -300 MD =3	187.14 (85.97) 80 – 290 MD =3	158.15 (102.02) 30 – 430 MD=13
NRS Breathlessness Intensity maximal *(Tmax)* Mean (SD):range, MD	7.14 (2.19) 3-9 MD = 3	7.5(1.05) 6-9 MD =4	6.71 (1.98) 3-8 MD = 3	6.14 (1.95) 4-9 MD = 3	6.85 (1.83) 3-9 MD = 13
NRS Breathlessness Intensity after 3 mins recovery time *(T3)* Mean (SD):range, MD	2.43 (2.37) 0-5 MD = 3	1.83 (1.94) 0-5 MD = 4	0.71 (1.11) 0-3 MD = 3	0.43 (0.53) 0-1 MD = 3	1.33 (1.75) 0-5 MD = 13
NRS Breathlessness Intensity Recovery Rate per minute (NRS *(Tmax)* – NRS *(T3)*/3mins)	1.57 (0.56) MD =3	1.89 (0.54) MD =4	2.0 (0.72) MD =3	1.9 (0.49) MD =3	1.84 (0.58) MD=13
Carer report measures					
Zarit caregiver burden score Mean (SD), range (n=)	8.5 (4.95) 5-12 (n=2)	8 (3.56) 3-11 (n=4)	7.25 (4.19) 1-10 (n=4)	3.5 (3.0) 0 - 6 (n=4)	6.57 (3.89) 0 - 12 (n=14)
Carer GSES score Mean (SD), range, (n=)	33 (2.83) 31-35 (n=2)	33.5 (3.11) 30-37 (n=4)	32.5 (2.89) 30-35 (n=4)	35.0 (3.56) 31-38 (n=4)	33.57 (2.95) 30 - 38 (n=14)

SD = standard deviation; MD = missing data; n = number included

Graph 1 Baseline data NRS breathlessness intensity during recovery from ISWT



6.5.3 Patient Report Outcome Measures; Variability of measure

The variability of measures, (the standard deviation; [SD]) at baseline were wide across the study groups for all of the NRS measures, the Life-space, GSES, recovery time from breathlessness and the ISWT, as well as the carer outcome measures; the Zarit caregiver burden and the GSES. The only measure that displayed a narrow SD at baseline was the NRS recovery rate per minute as displayed in Table 30.

6.5.4 Patient Report Outcome Measures; Mean change from baseline

6.5.4.1 NRS

There was little change in group mean from baseline for the NRS outcome measures at day 28. Improvement was recorded for the NRS unpleasantness average over the last 24 hours; -1.2, and NRS intensity at worst over the last 24 hours, -1.1, only in the hand-held fan & Calming Hand & usual care arm, mean change from baseline -20.3% and -15.9% respectively. Values were worse for the NRS unpleasantness average over last 24 hours; 0.9, in the Calming Hand & usual care arm, mean increase from baseline, 15.2%.

In contrast, there was more change in group mean from baseline for the NRS breathlessness intensity recovery rate per minute. Most improvements were found in the hand-held fan & usual care group, 0.64/minute faster; this equates to a 33.9% increase in speed of NRS recovery rate at day 28. Smaller group mean changes from baseline for NRS recovery rate were recorded in the other three arms; usual care 0.43/minute faster, Calming Hand & usual care 0.41, and hand-held fan &Calming Hand & usual care 0.1/minute faster. These represent 27.4%, 20.5% and 5.2% mean change from baseline respectively.

In addition, there was considerable mean change from baseline for the NRS Breathlessness Intensity after 3 minutes recovery time *(T3)* for the hand-held fan & usual care group, -1.33 minutes, which equates to -72.7% mean change from baseline. Lower group mean changes were found in the other study arms; usual care -1.1 minutes, Calming Hand & usual care -0.27 minutes, and hand-held fan &Calming Hand & usual care -0.13 minutes. These represent -45.3%, -38.0% and-30.2% mean change from baseline respectively.

The group mean at day 28 for all four study arms for the NRS recovery rate between maximal breathlessness and after 3 minutes recovery time are displayed in Graph 2. The change in group mean from baseline for the NRS recovery rate between maximal breathlessness and after 3 minutes recovery time are displayed in Graph 3, 4, 5 and 6.

6.5.4.2 Life-space

There was little group mean change from baseline with differences noted in only two of the study arms at day 28; the Calming Hand & usual care, 8.15, and the hand-held fan & Calming Hand & usual care, 5.55, improvements which represent 17.3% and 10% change from baseline respectively.

6.5.4.3 GSES

There was little group mean change from baseline, apart from the hand-held fan & usual care group, which demonstrated a 3.1 point mean change or 10.8% improvement from baseline.

6.5.4.4 Recovery time from breathlessness

There was more change in group mean from baseline with improvements in three of the study arms; usual care; -26.44 secs, hand-held fan & usual care; -33.5 secs, hand-held fan & Calming Hand & usual care;-40.27secs, These figures represent a change from baseline of -14.7%, -20.4% and -24.6% respectively. There was no improvement in the Calming Hand & usual care arm, a small increase in the length of time to recover was recorded; 5.71, 4.1% slower than baseline.

6.5.4.5 Incremental Shuttle Walk Test

Mean improvement from baseline was also shown in three of the groups; hand-held fan & usual care 55.33m, Calming Hand & usual care 18.57m, and hand-held fan & Calming Hand & usual care 31.86m.This represents a change from baseline of 43.7%, 15.3% and 17.02% respectively. In contrast, the ISWT distance at day 28 for the usual care group decreased, -19.53m, -10.8% less than baseline.

6.5.5 Carer outcome measures

The was little group mean change from baseline with the only changes documented for the hand-held fan & usual care group; GSES -2.5 points, and the Calming Hand & usual care group; Zarit carer burden; -2.25 points. Table 31 displays the Patient Report Outcome Measures for the group mean change at day 28 from baseline and the percentage.

Table 31 Patient Report Outcome measures at day 28 mean change from baseline and percentage

	Usual care		**Hand-held fan & Usual care**		**Calming Hand & Usual care**		**Hand-held fan & Calming Hand & Usual care**	
Patient Outcome measures	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %
NRS Intensity *Average over last 24 hours* Mean (SD): range, MD	5.2 (1.99) 1-8, MD = 0	0.2	6.1 (2.23) 3-10, MD = 0	0.2	4.8 (2.04) 2-9, MD = 0	-0.1	4.9 (2.56) 1-8, MD = 0	0.1
NRS Distress *Average over last 24 hours* Mean (SD): range, MD	5.2 (2.3) 2-8, MD = 0	0.4	5.3 (3.65) 0-10, MD = 0	-0.3	3.1 (2.02) 0-7, MD = 0	-0.6	3.8 (3.15) 0-10, MD = 0	0.5
NRS Unpleasantness *Average over last 24 hours* Mean (SD): range, MD	5.9 (1.91) 3-9, MD = 0	-0.2	5.8 (2.53) 1-10, MD = 0	-0.5	6.2 (2.20) 3-10, MD = 0	0.5	4.7 (2.75) 0-10, MD = 0	-1.2 -20.3%
NRS Intensity *At worst over last 24 hours* Mean (SD): range, MD	6.7 (1.34) 5-9, MD = 0	-0.6	7.5 (2.59) 2-10, MD = 0	-0.3	6.8 (2.25) 3-10, MD = 0	0.9 15.2%	5.8 (2.53) 2-10, MD = 0	-1.1 -15.9%
NRS Distress *At worst over last 24 hours* Mean (SD): range, MD	6.1 (2.47) 2-9, MD = 0	No change	6.5 (3.44) 0-10, MD = 0	-0.5	4.1 (2.99) 0-9, MD = 0	No change	4.9 (3.41) 0-10, MD = 0	0.6

Table 31 Patient Report Outcome measures at day 28 mean change from baseline and percentage

	Usual care		**Hand-held fan & Usual care**		**Calming Hand & Usual care**		**Hand-held fan & Calming Hand & Usual care**	
Patient Outcome measures	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %	Day 28	Change (day 28 – baseline) %
Life-space questionnaire Mean (SD): range, MD	54.0 (24.21) 25-100, MD = 0	-0.45	64.05 (19.23) 32-84, MD = 0	3.2	55.2 (14.67) 35-76, MD = 0	8.15 17.3%	61.05 (27.06) 20-100, MD = 0	5.55 10%
General Self-efficacy Scale (GSES) Mean (SD): range, MD	32.0 (5.96): 20-40 MD = 0	1.7	31.9 (4.36) 28-40, MD = 0	3.1 10.8%	31.8 (4.96) 23-40, MD = 0	0.1	32.4 (4.40) 22-40, MD = 0	-0.9

Table 31 Patient Report Outcome measures day 28 mean change from baseline and percentage

	Usual care		**Hand-held fan & Usual care**		**Calming Hand & Usual care**		**Hand-held fan & Calming Hand & Usual care**	
	Day 28	Change (day 28 – baseline; MD=3) %	Day 28	Change (day 28 – baseline; MD=4) %	Day 28	Change (day 28 – baseline; MD=3) %	Day 28	Change (day 28 – baseline; MD=3) %
Incremental Shuttle Walk Test Outcome measures								
Recovery time ISWT (seconds) Mean (SD): range, MD	152.56 (41.45) 111-224 MD = 1	-26.44 -14.7%	130.5 (64.60) 74-305 MD = 0	-33.5 -20.4%	146.0 (38.88) 89-200 MD = 1	5.71 4.1%	123.30 (24.93) 85-160 MD = 0	-40.27 -24.6%
Distance walked (metres) Mean (SD): range, MD	173.33 (124.9) 60 – 470 MD = 1	-19.53 -10.8%	182.0 (103.69) 50 – 340 MD = 0	55.33 43.7%	140.0 (84.41) 30 – 310 MD = 1	18.57 15.3%	219.0 (93.39) 120 – 410 MD =0	31.86 17.02%
NRS Breathlessness Intensity maximal (Tmax) Mean (SD):range, MD	7.33 (1.22) 5-9 MD = 1	0.19 2.6%	8.10 (1.59) 4-10 MD = 0	0.6 8%	7.67 (1.5) 5-10 MD = 1	0.96 14.3%	6.30 (2.91) 1-9 MD = 0	0.16 2.6%

Table 31 Patient Report Outcome measures day 28 mean change from baseline and percentage

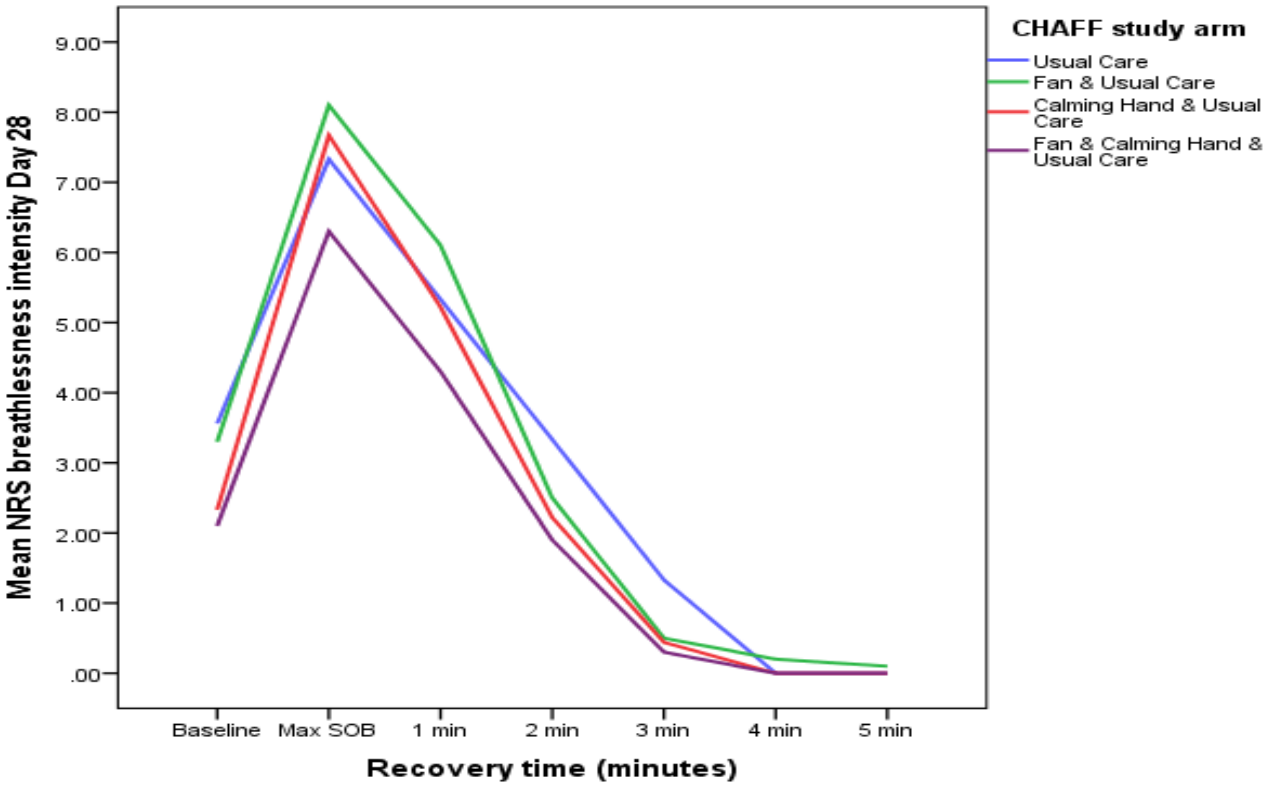
	Usual care		**Hand-held fan & Usual care**		**Calming Hand & Usual care**		**Hand-held fan & Calming Hand & Usual care**	
	Day 28	Change (day 28 – baseline; MD=3) %	Day 28	Change (day 28 – baseline; MD=4) %	Day 28	Change (day 28 – baseline; MD=3) %	Day 28	Change (day 28 – baseline; MD=3) %
Incremental Shuttle Walk Test Outcome measures								
NRS Breathlessness Intensity after 3 mins recovery time (T3) Mean (SD):range, MD	1.33 (2.39) 0-7 MD = 1	-1.1 -45.3%	0.5 (1.58) 0-5 MD = 0	-1.33 -72.7%	0.44 (1.01) 0-3 MD = 1	-0.27 -38.0%	0.3 (0.67) 0-2 MD = 0	-0.13 -30.2%
NRS Breathlessness Intensity Recovery Rate per minute (NRS (Tmax) – NRS (T3)/3mins)	2.0 (0.76) MD = 1	0.43 27.4%	2.53 (0.57) MD = 0	0.64 33.9%	2.41 (0.57) MD = 1	0.41 20.5%	2 (0.92) MD =0	0.1 5.2%

Table 31 Patient Report Outcome measures day 28 mean change from baseline and percentage

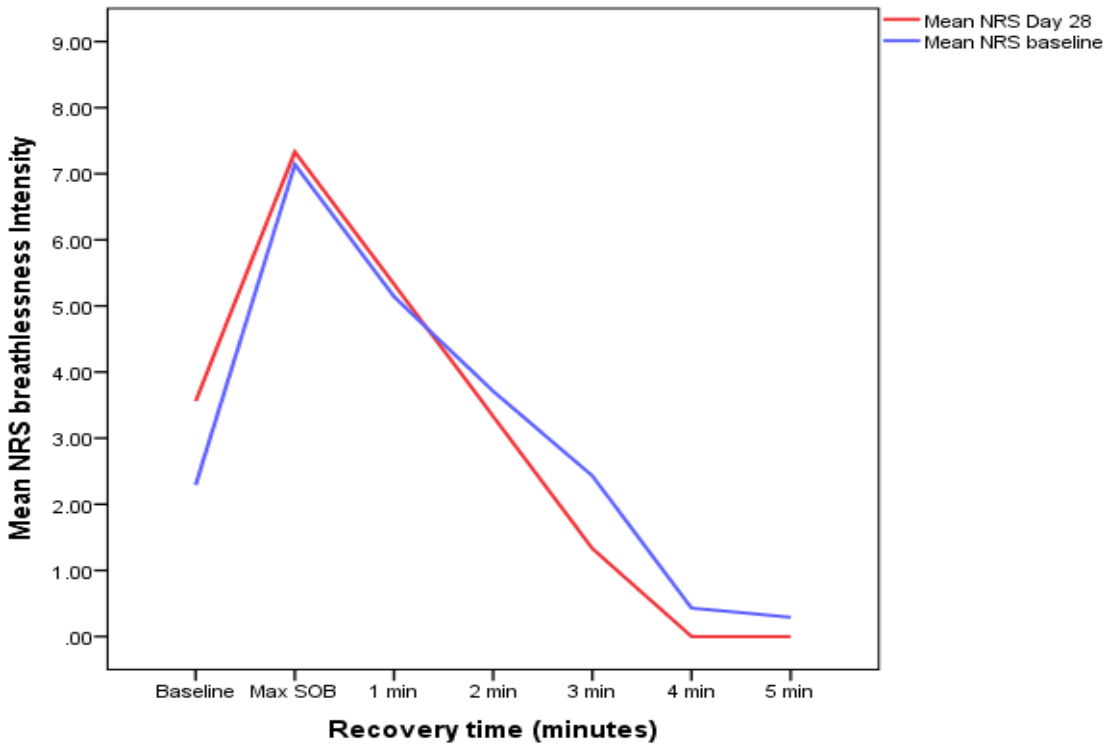
	Usual care		**Hand-held fan & Usual care**		**Calming Hand & Usual care**		**Hand-held fan & Calming Hand & Usual care**	
	Day 28	Change (day 28 – baseline)	Day 28	Change (day 28 – baseline)	Day 28	Change (day 28 – baseline)	Day 28	Change (day 28 – baseline)
Carer Outcome measures								
Zarit Carer burden Mean (SD): range, MD, (n=)	10.0 (1.41) 9-11 MD =0 (n=2)	1.5	8.75 (6.5) 0 – 15 MD = 0 (n=4)	0.75	5.00 (6.08) 1-12 MD = 1, (n=3)	-2.25	3.75 (2.63) 0-6 MD = 0, (n=4)	0.25
General Self-efficacy Scale (GSES) Mean (SD): range, MD, (n=)	32.5 (3.54) 30-35, MD = 0, (n=2)	0.5	31 (4.69) 25-36, MD = 0, (n=4)	-2.5	32.67 (4.62) 30-38, MD = 1, (n=3)	0.17	36.75 (2.06) 35-39, MD = 0, (n=4)	1.75

SD = standard deviation; MD = missing data; n = number included

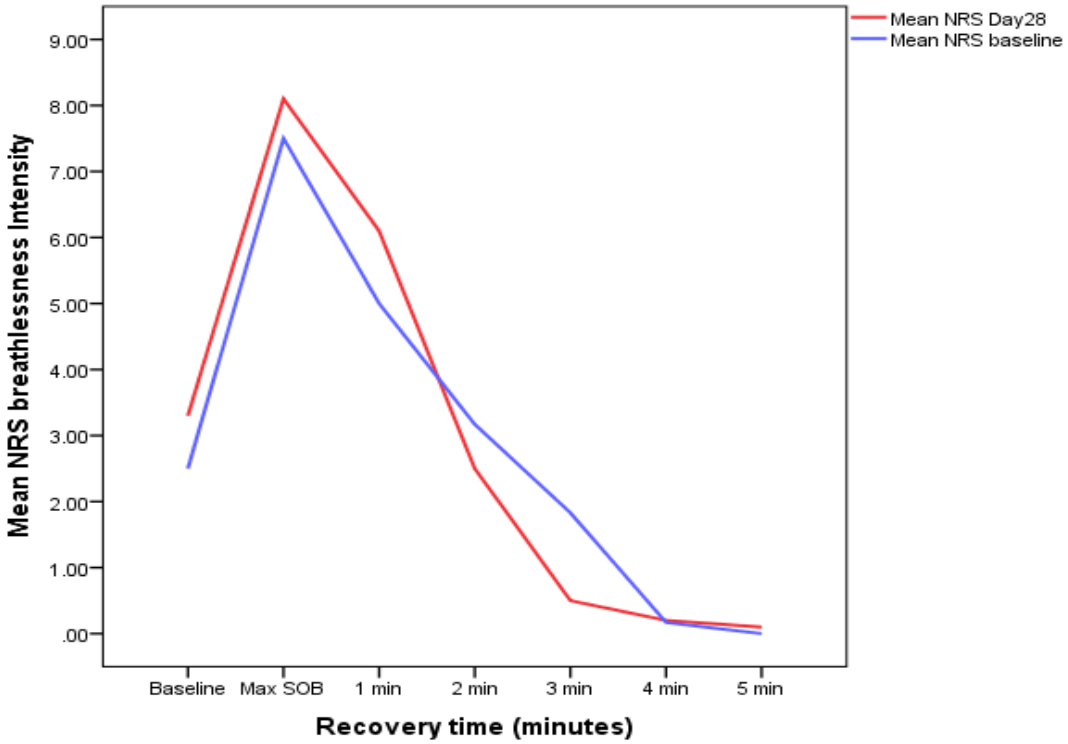
Graph 2 Day 28 NRS breathlessness intensity during recovery from ISWT



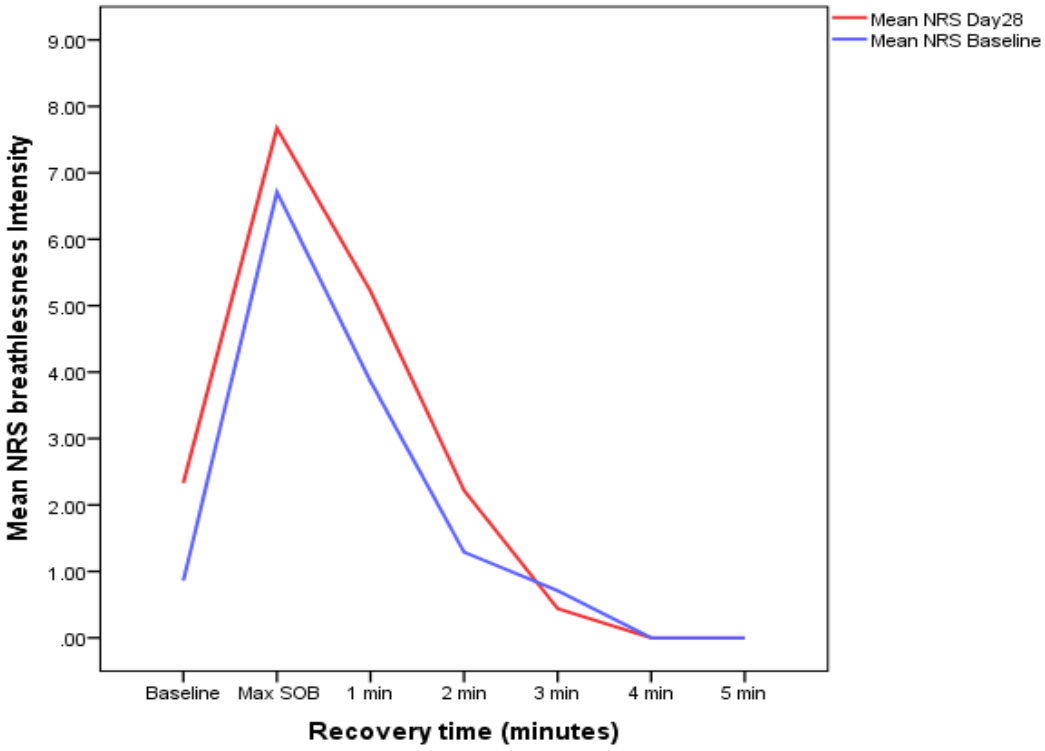
Graph 3 Day 28 and change from baseline NRS breathlessness intensity during recovery from ISWT; Usual care



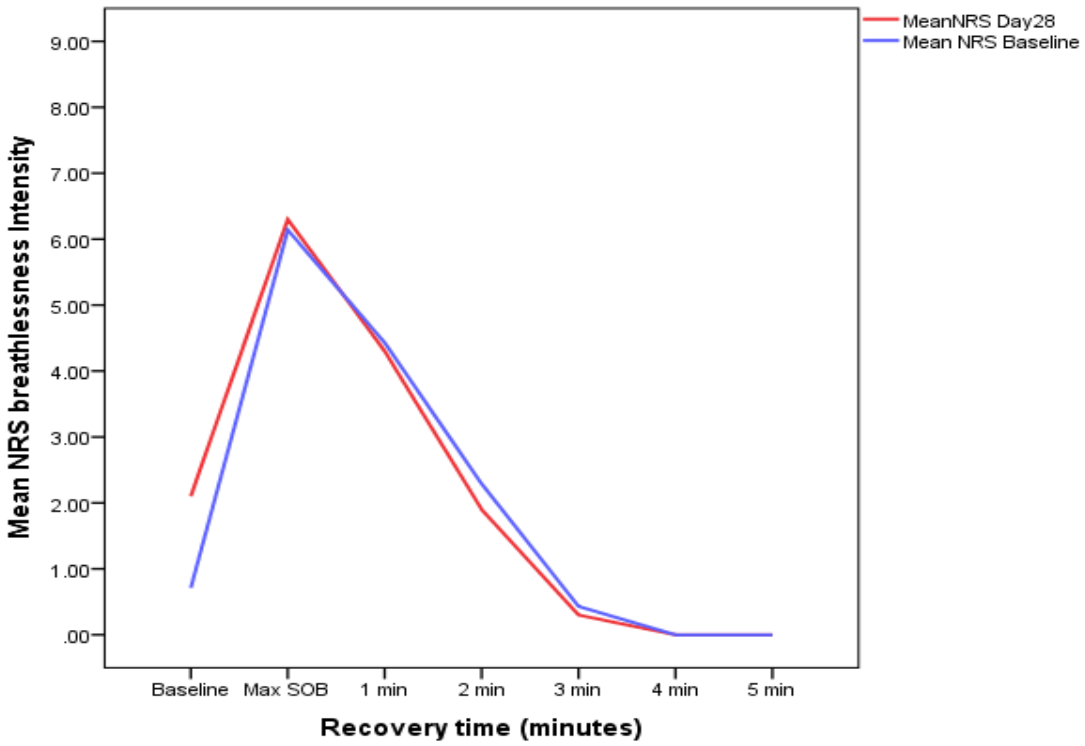
Graph 4 Day 28 and change from baseline NRS breathlessness intensity during recovery from ISWT; Hand-held Fan & usual care



Graph 5 Day 28 and change from baseline NRS breathlessness intensity during recovery from ISWT; Calming Hand & usual care



Graph 6 Day 28 and change from baseline NRS breathlessness intensity during recovery from ISWT; Hand-held Fan & Calming Hand & usual care



6.6 Discussion

6.6.1 Recruitment

Palliative care trials are traditionally thought to be difficult to recruit to with most of the documented challenges centred on ethical and logistical difficulties (282, 283, 343-345). Burden of the study measures and lack of transport for the participants, acceptability of randomisation, limited clinician time, gatekeeping, and inadequate facilities to support the research projects, in addition to expected participant deterioration or death due to disease progression are all cited as potential issues that could undermine successful study completion and increase the risk of underpowered results (282, 283, 343-346).

However, in this feasibility study recruitment was relatively easy, one reason being that the clinicians and patients seemed to be keen to be involved due to the limited opportunities for breathlessness management. This may have been because a large proportion of patients had a diagnosis of IPF. Therefore, patients were unable to access pulmonary rehabilitation in the same way as COPD patients, where it is recognised as standard care (347), (as described in chapter 2.2.2), and there was only one breathlessness clinic accessible to patients with any diagnosis in Hull; a unique service held at Dove House hospice one morning a week, with a waiting list due to demand. In consequence, the extra option of a breathlessness study was readily received by patients and the medical team. In addition, patient recruitment was supported and facilitated through the close collaboration with the research staff in the Clinical Trials Unit, Academic Respiratory Medicine at Castle Hill hospital, and the use of the facilities was crucial to the completion of the ISWT. It is also likely that the detailed planning of the protocol helped to make study participation an easy acceptable patient option. Careful attention to the study design, duration and assessment of burden has been identified as a successful strategy to improve recruitment of patients in palliative care trials (348).

These results indicate the suitability of recruiting patients with IPF to clinical trials for chronic refractory breathlessness, but in addition reflect a problem with the access to breathlessness management and a lack of service provision for this patient group.

6.6.2 Attrition/missing data

Furthermore, the feasibility of recruiting patients diagnosed with IPF and/or COPD for chronic refractory breathlessness research projects was highlighted by the lack of attrition. Follow up was complete for all 40 participants which suggests a relatively clinically stable population, and the short study duration, 28 days meant there were no deaths or withdrawals due to deterioration. There were only two adverse event forms completed. Both were considered unlikely to be related to the study interventions and did not result in any participant withdrawal. Carer attrition was also minimal with data missing from only one carer as they were unable to attend the day 28 appointment due to work restrictions.

The small amount of missing data may be attributed to the short trial duration and the protocol design. Shortened formats of outcome measures such as the Zarit 6 caregiver burden and a limited number of questions were asked. It is known that larger missing data proportions are associated with increasing numbers of questions and tests requested, odds ratio (OR, 1.19; 95% CI 1.05 to 1.35) and with longer study duration (OR, 1.09; 95% CI 1.02 to 1.17) (349). The data loss was also minimised by the flexibility of the study protocol as the day 28 appointment was offered as a home visit. In addition, the participant was supported during trial participation with verbal telephone contact and help readily available from the investigator to guide all of the data completion.

6.6.3 Randomisation

This was considered effective as all four arms had similar baseline data, although participants with Pulmonary Fibrosis were randomised mostly to two arms of the study, usual care (n=7) and usual care & Calming Hand (n=9), and there was also baseline imbalance in the values for NRS breathlessness distress at worst over the last 24 hours and the Zarit 6 caregiver burden. Since this was a feasibility study, these differences were attributed to the small number of participants, 10 in each study arm, rather than a problem with the randomisation process. However it is possible that this could have introduced bias if participants with Pulmonary Fibrosis in the usual care, or the Calming Hand and usual care arms responded differently to the study interventions, in comparison to the other two arms of the study.

6.6.4 Feasibility and usefulness of patient study outcome measures

The study was not designed with power to discard the null hypothesis, however, results were examined for signal to suggest that they might be useful outcome measures and to use the data to calculate a sample size

6.6.4.1 NRS

There was little mean change from baseline in any of the NRS outcome measures, although improvements were documented on day 28 for the hand-held fan & Calming Hand & usual care study arm with NRS breathlessness unpleasantness average over last 24 hours, -1.2, and intensity at worst over the last 24 hours, -1.1. These differences are consistent with the minimal clinical important difference (MCID), known to be a -1 point NRS difference in breathless patients with a variety of conditions (4). But, since there was little other signal from the other NRS scores for breathlessness after 28 days it would appear that it does not appropriately reflect any improvement in breathlessness in the context of everyday general activity, although it is important to remember that this study was not designed with power to discard the null hypothesis. In addition, as previously discussed in chapter two, breathlessness scores may remain static or worsen after the initial introduction of an intervention to alleviate symptoms because patients are able to exert themselves to the same level of breathlessness without realising the difference in their exercise tolerance (273). The feasibility data displayed mean group improvement from baseline for both the ISWT distance walked and the maximal NRS breathlessness intensity experienced after the ISWT at day 28 in two of the study arms; the hand-held fan & usual care, and the Calming Hand &usual care as shown Table 31 and in Graph 4 and 5. This result may in part reflect that the ISWT is a more appropriate and suitable walking test to induce a patient's maximal exertional breathlessness tolerance.

Most of the participants commented about the difficulty they had assigning a number to their breathlessness intensity due to the regular fluctuations of the symptom. Therefore it may be more appropriate to combine the NRS presentation with the four-level categorical Verbal Descriptor Scale (VDS), a practical tool that correlates strongly with the NRS (290) that could facilitate easier completion.

However, the study protocol also measured the NRS breathlessness intensity during recovery from the ISWT at repeated minute intervals and used the data to calculate a novel outcome; the NRS breathlessness intensity recovery rate per minute. These measurements showed promise of a breathlessness outcome likely to reflect a worthwhile change from using the hand-held fan. The NRS breathlessness intensity recovery rate per minute in the hand-held fan &usual care group was 0.64 points/minute quicker than baseline, an improvement of 33.9%. This was coupled with a -1.33, mean change from baseline for the NRS breathlessness intensity at 3 minutes recovery time, which equates to a -72.7% improvement. In contrast, the group mean change from baseline for the NRS breathlessness intensity recovery rate per minute was less in the other three study arms; usual care -45.3%, Calming Hand & usual care -38% and hand-held fan & Calming Hand &usual care -30.2%. Similarly, group mean changes for the NRS breathlessness intensity after 3 minutes recovery time were smaller; usual care 27.4%, Calming Hand & usual care 20.5% and hand-held fan & Calming Hand & usual care arm 5.2%. These results signal that the NRS breathlessness intensity recovery rate per minute could be an outcome measure likely to reflect a discernible change in exertion induced breathlessness from use of the hand-held fan and therefore should be considered a potential primary outcome in a future study that assesses the intervention effectiveness with exercise related breathlessness. Both of these outcomes are shown in Table 31, and the change in speed of mean recovery rate at day 28 in comparison to baseline for the four groups are displayed in graphs 3, 4, 5 and 6.

6.6.4.2 Life-space

Normative data results from 3032 participants surveyed in Australia found that the mean Life-space score was 98.3 (SD 20.3); range 6-120 with only 4.6% of respondents scoring less than 60 (350). In comparison the mean group baseline Life-space scores for the feasibility study participants were 54.46 (20.4); range 12-100. These data reflect the sample chosen as Life-space score decline is associated with being older, female, low socio-economic status and a higher number of chronic conditions ($R2 = 0.35$, $P < 0.001$) (350).

At day 28, the mean group changes from baseline for the Life-space questionnaire were small with only two of the study arms showing any difference; the Calming Hand & usual care, 8.15 and the hand-held fan & Calming Hand & usual care, 5.55. Figures that represent a 17.3% and 10% change from baseline respectively. It is not known if these changes would be

of clinical significance, but since Life-space scores decreases after the age of 55 years (350), it is possible that the level of improvement shown, even though a small change, could equate to worthwhile patient benefit.

However, it also was noted that Life-space questionnaire change could be influenced by seasonal variation, such as the likelihood of going away on a short trip in summer as opposed to winter, therefore it may be more suitable as an outcome measurement for longer-term assessment, at least 6 months. Another area of feasibility concern were the American phrases within the Life-space questionnaire. Since the investigator were present at all times it was easy for participants to ask for help or clarification of what was meant by any of the questions. This has relevance for a future design as it may be a potential source of missing data if no-one is available to assist with the questionnaire and the suitability of the outcome measure could be further compromised, unless adapted to reflect the terminology of the UK population.

6.6.4.3 General Self-Efficacy Scale

Similarly, there was little mean group change from baseline for the GSES, apart from the hand-held fan & usual care group which demonstrated a 3.1 point improvement from baseline. This equates to 10.8% change, although it is not clear if this improvement equates to a significant change or if it was discernible to the patient as little is known about the MCID. In addition, participants commented that the statements were too general and not clearly related to breathlessness. However, since self-efficacy is linked to how effectively patients manage difficult symptoms and their quality of life (351), it is important to retain an outcome measurement that can accurately reflect the patients ability to self-manage breathlessness.

Therefore it would seem more appropriate to replace the GSES in a future trial with a measurement of the level of self –mastery over the symptom such as the CRQ, particularly as recently published data suggests that this outcome would be more likely to reflect any discernible change in self-efficacy and the patient's ability to cope with breathlessness. Significant improvements in the CRQ self-mastery of breathlessness domain have resulted from a complex multi-factorial approach to breathlessness management that includes the hand-held fan (9, 132).

6.6.4.4 Recovery time from breathlessness

The results for recovery time from exertion induced breathlessness demonstrated that nearly all of the participants were fully recovered from the ISWT after 4 minutes, as displayed in Graph One. These figures align with previous data that examined the recovery time from an ISWT in 57 thoracic cancer patients by rating breathlessness severity on a modified Borg scale at repeated minute intervals (276). The median time for breathlessness to return to baseline was found to be 4 mins (range 1-7mins) (276). Therefore the preliminary data suggest that patients with a diagnosis of IPF, COPD or chronic asthma rapidly recover from breathlessness in a similar time to cancer patients, even after performing a progressive walking test to maximal breathlessness. This is clinically relevant and important as it serves to reassure patients that this is the usual case and counters beliefs that breathlessness is harmful. Any improvement in patient confidence may help negate the fear of exertion induced breathlessness and reduce the perpetuation of a vicious circle of deconditioning through exercise avoidance (as previously described in chapter 2.2.2).

The time to recovery from exertion induced breathlessness was also identified as a potentially useful future outcome measurement to assess for benefit from hand-held fan use, along with the NRS breathlessness intensity recovery rate per minute as outlined earlier. Data from both of the groups allocated to the hand-held fan displayed faster mean recovery times on day 28; hand-held fan & usual care arm; -33.5 seconds, and hand-held fan & Calming Hand & usual care -40.3 seconds. These figures represent mean group change from baseline of -20.4% and -24.6% respectively and could potentially represent a worthwhile change for the patient. A quick recovery after exertion induced breathlessness may help patients to negate a strategy of exercise avoidance and improve their confidence to undertake activity, safe in the knowledge that there is a device available that offers a speedy recovery whenever needed.

In contrast, the recovery time for the Calming Hand & usual care arm was slower; 5.71secs, which represents a 4.1% increase from baseline. It is possible that an instructed sigh could potentially inhibit and slow recovery from breathlessness. Prior study found that an instructed sigh seemed to inhibit recovery of both muscle tension and respiratory variability (247) (as previously outlined in chapter 2.5.2). The preliminary outcome data therefore suggests that the Calming Hand may be an unsuitable intervention to help speed recovery from exertion induced breathlessness.

6.6.4.5 ISWT

The ISWT demonstrated improvement from baseline with changes observed in all four study arms; in particular, the distance walked for the hand-held fan & usual care arm on day 28 increased by 55.33 metres, an improvement that exceeds the MCID for the ISWT which is known as 47.5metres (352). Furthermore, the participants reported the ISWT as an acceptable method for measuring exercise performance. This is in keeping with previous findings from patients with chronic respiratory disease and cancer (294, 297). Only two participants did not complete the ISWT on day 28; one participant, the oldest at 91 years, declined, feeling the walking was too much, and the exercise was not considered appropriate for the other participant in view of an unexpected adverse event; pulmonary oedema during the study period. Both of these patients were visited at home instead to collect all of the other clinical outcomes thereby helping to prevent possible participant attrition and missing data.

In contrast, no data were collected from the amended study protocol to include a second ISWT at baseline. All of the participants were reluctant to do this, deeming the extra exercise test on the same day too much effort. The possibility of asking the patients to come back again on another day to perform a second baseline ISWT was also considered, however the clinical stability of the patients were still uncertain and consequently there was concern that this could unnecessarily increase patient burden and cause potential attrition.

Therefore, it is possible that the results are due to a training effect, in that participants learnt how to perform the ISWT at baseline, therefore they were able to improve the distance walked on the second occasion, day 28, from the knowledge and experience they had gained from the first exercise test. Previous research identifies a possible learning or training effect and the necessity of repeating the first baseline measurement to avoid bias (296, 353). The study investigator also noted that participants were often apprehensive before the first ISWT, yet afterwards they felt more confident about the second walking test and commented on how they had enjoyed the experience.

However, if learning bias had occurred then an improvement in walking distance should be observed in all four of the study arms, this was not the case as the distance walked at day 28 in the usual care arm decreased from baseline, -26.44 metres. Therefore, it is possible that participants may not have remembered the test as well as they thought due to the length of

time between the first and second walk. More importantly, as a feasibility study the main objective was not to test for benefit, but to understand the acceptability of the walking test. Since data support the ISWT as a reproducible, safe and acceptable exercise test, as well as an outcome measure likely to reflect benefit from using the hand-held fan, it would be an important consideration to ensure that a future trial design does not involve participants performing two exercise tests on the same day. Instead an extra visit to perform a second baseline ISWT could be feasible given the lack of attrition indicates that IPF patients are a relatively clinically stable population.

6.6.5 Carer outcome measures

Carer burden is well documented, research identifies a high level of distress and unmet need from caring for a breathless person (112-114), as outlined in chapter 1.8.4. A previous cross-sectional survey of lung cancer and HF caregivers data found mean 11.1 (SD 8.7); 95% CI 8.6–13.6, (n=47), and mean 9.6 (SD 9.0); 95% CI 7.0–12.2, (n=48) respectively for the Zarit caregiver burden (113). In comparison, the feasibility figures mean score at baseline were slightly lower; mean 6.57 (SD 3.89), range 0-12 (n=14). This could indicate that the caregivers for IPF and COPD suffer less from living with a breathless patient, however it is more likely to result from few data and the small number of participants in the study arms, particularly as baseline imbalance was noted between the hand-held fan & Calming Hand & usual care group; mean 3.5 (SD 3.0) range 0 – 6, (n=4) in comparison to the usual care group; mean 8.5 (SD 4.95) range 5-12, (n=2).

Furthermore, there was very little mean group change from baseline documented for the Zarit caregiver burden and the carer GSES. Both failed to provide any clear signal of an outcome that would be useful and likely to reflect clinically important change. Again, it is a likely consequences of the small numbers in each study arm and therefore insufficient data to capture any change. Since the qualitative results from the BIS phase III mixed method RCT indicate that carers gain most benefit from being listened to and having their experience of living with a breathless person validated (8), it is also possible that the carer gained little help from the interventions delivered to the patient during the 28 day study period. In contrast, the interview at follow up may have provided worthwhile benefit if this interview was perceived as beneficial and therefore an active intervention, an issue recently identified in the findings of the BIS phase III RCT mixed methods design (325).

6.6.6 Sample size calculations for full scale trial

Sample size calculations for full scale trial

From these preliminary data three potentially viable continuous outcome variables were identified for sample size calculations. These were;

- NRS breathlessness intensity recovery rate per minute
- ISWT distance
- Recovery time from maximal breathlessness

Sample size calculations were for an independent t-test design, based on Type I error $p<0.05$ and power at 0.8 and assumed normal distribution for a parallel two arm study comparing the hand-held fan & usual care versus the usual care only. The ISWT mean difference was informed by the known MCID values (352), and the SD was based on the feasibility results. For the NRS breathlessness intensity recovery rate per minute and the recovery time estimates of the mean difference and SD were informed by the feasibility data. Although there were no participant withdrawals in the feasibility study, it is still probable that there would be attrition; 10% was considered an appropriate value for a definitive trial of people with chronic refractory breathlessness from any diagnosis.

- NRS breathlessness intensity recovery rate per minute; Mean difference 0.65 point (SD 0.55) = 24 + 10% = 28
- Recovery time; Mean difference 30 seconds (SD 60) = 128 + 10% = 142
- ISWT distance; Mean difference 47.5 metres (SD 80) = 92 + 10% = 102

Based on the sample size calculations the total sample size required to be able to reject the null hypotheses are;

- NRS breathlessness intensity recovery rate per minute; Total = 28, (n=14 per arm)
- Recovery time; Total = 142, (n=71 per arm)
- ISWT distance; Total = 102, (n=51 per arm)

These figures suggest that the NRS breathlessness intensity recovery rate per minute should be the primary outcome for a future trial, and the recovery time and the ISWT distance considered secondary outcomes. But the value of information needs to be evaluated given the weight of evidence available from two Phase III complex intervention studies (8, 9), and the results from a recently published feasibility study of the hand-held fan with activity (311).

6.6.7 Limitations

It is recognised that the lack of blinding of both the participants and the investigator could have introduced bias. Reporting bias is possible if participants felt reluctant to offend the investigator and tell the truth about how they experienced the interventions, although blinding was not considered appropriate due to the known difficulties in providing a realistic comparator for the hand-held fan (219). Ascertainment bias was also possible from myself as the sole investigator delivering both the interventions and the outcome measurements for the trial. My beliefs and pre-conceptions about the hand-held fan and the Calming Hand in terms of perceived benefit (or not) could have influenced the delivery of the interventions to the patients. However, since this was a feasibility study the main objective was to assess for variability of the outcome measures, therefore if any bias had occurred it would be consistent for all of the participants.

Further potential bias, if present, would likely relate to the ISWT data; investigator error meant that results for only 27 participants were collected at baseline instead of 40 and the possibility of learning bias cannot be excluded as the exercise test was not repeated at baseline. It is also acknowledged that there is statistical limitation and uncertainty with the sample size calculations as the study groups were not adjusted for baseline measures and little is known about the NRS recovery rate per minute or the time to recovery as outcome measures for breathlessness. The sample size calculations suggest that the NRS recovery rate per minute requires fewest participants for a future definitive study. However, the clinical relevance of using such a measure needs to be considered. It is plausible that the time to recovery is a more practical outcome and an understandable reason for patients and health care professionals to use the fan as an intervention for breathlessness problems.

In addition, there are other limitations associated with the use of an outcome based on recovery time. The recovery time is inherently linked to the patient’s exercise capacity and

therefore their ability to perform an ISWT to maximal breathlessness. It is possible that the recovery time may be influenced by other individual physiological and psychological determinants such as age, gender, lower limb skeletal muscle mass, nutritional status and level of distress.

6.7 Conclusions

The results confirm the feasibility of recruitment, data completion and acceptability of the outcome measures. Lack of attrition indicates the suitability of sampling patients with a diagnosis of IPF, COPD or asthma for chronic refractory breathlessness projects. There was little signal of activity, although a variety of outcomes were used to help inform a future design. This is consistent with the known challenge of selecting the appropriate patient outcome measures to accurately reflect a change in breathlessness (274, 354). However, the data did indicate that the ISWT outcome measures were of potential value. Of the three intervention study arms most improvements were consistently recorded for the hand-held fan & usual care arm. In comparison, there were smaller improvements in the hand-held fan & the Calming Hand & usual care group, and little indication from the Calming Hand & usual care group results to support worthwhile change from intervention use. Therefore, these preliminary data suggest discernible patient benefit from use of the hand-held fan to relieve exertion induced breathlessness. In contrast the Calming Hand appears to be an unsuitable intervention to assist breathless recovery after exercise.

6.8 Recommendations

A future multi-site parallel RCT design would test the effectiveness of the hand-held fan & usual care versus usual care only when used during recovery from exertion-induced breathlessness after an ISWT. Since the methods and design used in the phase II study were acceptable and feasible, a phase III trial would employ a parallel group design, but use an otherwise similar protocol, apart from an extra visit to perform a second baseline ISWT. This would ensure against the risk of learning bias and three visits are thought be achievable given the clinical stability of the patient population. In addition, the recovery time appears worthy of further investigation therefore it is possible to consider this measure as a potential primary outcome.

Future work would also recommend to explore if the Calming Hand is any value of with other sub-groups such as cancer diagnoses and investigate if this intervention is more appropriate for use with breathlessness experienced in other contexts such as at rest, or with anxiety, rather than recovery after exercise.

6.9 Summary of chapter six

This chapter has shown;

- a phase III RCT is feasible with regard to recruitment, attrition and data completion
- three potential outcome measures of interest from the quantitative results for the hand-held fan, these are:
    1. NRS breathlessness intensity recovery rate per minute
    2. time to recovery from ISWT
    3. and ISWT distance
- The sample size calculations for these outcome measures are:
    1. NRS breathlessness intensity recovery rate per minute; Total = 28, (n=14 per arm)
    2. recovery time; Total = 142, (n=71 per arm)
    3. ISWT distance; Total = 102, (n=51 per arm)
- These results support a future phase III RCT test of effectiveness for the hand-held fan with primary outcome; time to recovery from an ISWT a relevant clinical measure, and secondary outcomes; NRS breathlessness intensity recovery rate per minute and ISWT distance.
- The preliminary data for the Calming Hand did not provide a clear signal of potential activity or outcome measures of interest and suggest it is not a suitable intervention to assist patients with exertional breathlessness

Chapter 7 Patient and carer experiences and beliefs of the Calming Hand and Fan Feasibility study

7.1 Introduction

This chapter reports on the qualitative element of the mixed method design; a series of in-depth interviews that were conducted with consented patients and their family carers to explore the acceptability of the feasibility design, methods and interventions. The interviews were embedded in the quantitative study and were held once the trial participants had completed the 28 day study. The qualitative data provided valuable information about who was likely to be attracted to and could benefit from the use of the hand-held fan and/or Calming Hand and assisted with the quantitative data interpretation to help plan a subsequent definitive study.

7.2 Research question

1. What are the patients' and carers' perceptions and beliefs in relation to the hand-held fan and Calming Hand for the management of chronic refractory breathlessness?
2. What are the patients' and carers' experience of the hand-held fan and Calming Hand during the trial and how do they use the interventions for the management of chronic refractory breathlessness?
3. What are the patients' and carers' preferences and beliefs about different treatments for chronic refractory breathlessness, and what effect do these factors have on their experience of healthcare treatment and subsequent outcomes.
4. Is the trial design feasible and are the procedures and outcomes used acceptable to the patients and carers?

7.3 Methods

7.3.1 Identification

Participants were selected from those in the RCT. The possibility of participating in an in-depth interview was explained in the Participant Study Information leaflet for the RCT, and consent for this part of the study was specified in the consent form. Therefore participants were able to take part in the RCT only or both the RCT and an interview as well. Carers were identified through participating patients, who gave permission to approach their carer to see if they wished to be involved in the RCT and/or a separate interview. Patients could participate in an interview whether or not their carer wished to take part in the interview sub-study.

7.3.2 Participants

16 interviews were conducted in total;

- A purposive sample of 11 patients drawn equally as possible from participants who had given consent to be interview from the four study groups.
- A convenience sample of 5 carers willing to participate.

In order to capture and map the diversity of the participant profile, a sampling frame was used with sampling criteria that included all four arms of the feasibility RCT, gender and whether patients had a formal carer or not (See chapter four Table 21 and 22, Sampling framework for patients and carers). The demographics of the patients and carers interviewed are displayed in Table 32 and 33.

Table 32 Demographics of patients interviewed

Participant number	Age	Gender	Diagnosis	Formal Carer	Interview with carer	Smoker	Study arm
9	65	F	IPF, emphysema	Yes	Yes	Yes	Fan + usual care
10	75	F	COPD, sarcoidosis	No	No	No	Fan + C.H+ usual care
11	82	M	IPF, pacemaker	Yes	Yes	No	Usual care
12	73	M	COPD, asthma	No	No	Yes	Fan + usual care
14	53	F	Asthma	Yes	Yes	No	Usual care
15	88	M	IPF	Yes	No	No	C.H + usual care
17	74	M	IPF	No	No	Yes	Fan + C.H + usual care
18	74	M	Emphysema	Yes	No	No	Fan + C.H + usual care
19	61	M	COPD, asthma	Yes	Yes	Yes	Fan + usual care
22	87	F	IPF	No	No	No	C.H + usual care
24	74	M	COPD	No	No	Yes	Fan + C.H + usual care

Table 33 Demographics of carers interviewed

Carer of patient number	Age	Gender
9	54	M
11	75	F
14	50	F
19	56	F
23	74	F

7.1 Data collection

Interviews were held at the participant's home, at a time which was convenient to the participant. Interviews with the participants and carers were conducted individually with the exception of one interview where the environment did not permit a separate room, in this instance the participant and carer were interviewed in the presence of each other. An interview topic guide was used to cover the appropriate areas as outlined in Appendix 13. The questions were adapted for use with carers to examine their perception and experience of living with a chronically breathless person, how they felt about the interventions used in the study and how they thought the problem should be managed and/or improved. Before the interview commenced the investigator verbally confirmed participant consent to commence the audio-recording of an interview with the participant or carer and re-iterated the confidentiality and use of anonymised quotes only. Contemporaneous field notes were made and all interviews were transcribed verbatim.

7.2 Data analysis

The interviews were initially coded by the investigator Flavia Swan (FS) using a thematic analysis framework with methods as described by Braun and Clarke (322). This involved the following five phases as shown in Table 34 Phases of thematic analysis. Four transcripts were also independently coded by Miriam Johnson (MJ). FS and MJ discussed the codes and a working coding framework was drawn up. This framework was then used by FS to code the remainder of the transcripts. The Grounded theory method of constant comparative as first described by Glaser and Strauss (317) and modified by the subsequent guidelines of Strauss and Corbin (320) were utilised throughout the coding of the dataset. This was a recursive process that involved the systematic coding of the interviews to develop and organise the data into categories, which were then saturated with appropriate examples to illustrate the relevance to the research questions.

Table 34 Phases of thematic analysis modified from Braun and Clarke (322)

Phase	Description of the process
1. Familiarising yourself with your data	Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas
2. Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code
3. Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme
4. Reviewing themes	Checking if the themes work in relation to the coded extracts (Phase 1) and the entire data set (Phase 2), generating a thematic map of the analysis
5. Defining and naming themes	Ongoing analysis to refine the specifics of each theme and the overall story the analysis tells, generating clear definitions and names for each theme

7.3 Findings

Four main themes were found during the coding and analysis process of the interview data, these were;

- Theme One: Patient and carer restriction and loss resulting from breathlessness
- Theme Two: Characteristics of breathlessness
- Theme Three: Patient and carer self-management
- Theme Four: How does the patient (and carer) use the interventions (Hand-held fan and Calming Hand)

The main themes, sub-themes and data codes are illustrated in Table 35.

Table 35 Main themes, sub-themes and data codes

Main themes	Sub-themes	Data codes
Theme One: Patient and carer restriction and loss resulting from breathlessness	Physical	Decrease mobility, exercise, walking, ability to do ADL's - around house eg cleaning, hoovering, personal ADL's eg bathing, decrease upper limb activities eg unable to lift or carry, weight gain, diet restriction
	Psychological	Decrease ability to cope and self-efficacy, frustration, anger, bereavement, distress, fear, sadness, depression, panic, embarrassed, guilt, decrease personal space, loss of role, loss sense of self
	Social	Decrease social contact family and friends, decrease life-space and social or joint activities, hobbies, loss of role, job, friends, decrease ability to communicate, loss of holidays and ability to travel
Theme Two: Characteristics of breathlessness	Exertion induced breathlessness	After all physical activities, walking, stairs, doing all personal ADL and things around the house, Upper limb activity - hoovering, making bed, carrying washing out
	Episodic breathlessness	Short periods of breathlessness
	Triggers: weather, seasonal, emotions, smells, food, "out of the blue"	Windy, hot/cold, humidity sudden temp change, pollen, cut grass, blossom on trees, flowers, panic, stress, pain, perfume, animals, cigarette smoke, garlic, onion, dairy - milk, bread, pastry, tiredness, driving
	Continuous breathlessness	Breathlessness background all the time, increases with talking, increases with eating

Table 35 Main themes, sub-themes and data codes

Main themes	Sub-themes	Sub-theme data codes
Theme Three: Patient and carer self-management	Patient and carer beliefs about breathlessness management	Therapeutic nihilism: symptom versus disease (no treatment for symptom): symptom therefore incurable, hopelessness, no choice, learn to live with it Trial participation: altruism, value, influence of co-morbidities, focus on symptom welcome Healthcare professionals: Experience, credibility, value Burden: medications, hospital appointments Exercise: bad, makes you out of puff, fear
	Adaptation	Avoidance of breathlessness, stop attempting, disguise Pace, slow down, prioritise, plan, organise, stop and wait, learn signs, control, re-adjust, re-train
	Carer role	Physical presence, role as therapist, extra duties, stoicism, obligation, adaptation, constant worry, trust 24/7 job or role for life time, life changing, no life

Table 35 Main themes, sub-themes and data codes

Main themes	Sub-themes	Sub-theme data codes
Theme Four: How does the patient (and carer) use the interventions (Hand-held fan and Calming Hand)	Hand-held fan:	A tool in the toolbox: physical object or article to hold in hand, feel sensation, medical device; complex intervention; panic attack or "out of blue" breathlessness, severity and level of breathlessness, length of time used; instrument, tool, physical object, adjunct, between nebulisers, instead of Ventolin; extra intervention or prop, another device to try Physical effects: coolness, cold or fresh air, force air in, push in extra oxygen, blowing, Psychological effects: "doing something", self-efficacy, confidence, best help I can get is that fan Valuable/use – improve recovery from breathlessness, increase Life-space, different uses day, night, after exertion, walking up/down stairs, gardening, shopping, DIY, with bowling, in public, private at home, in car, in pocket, out shopping
	Calming Hand:	Common sense; disregarded, not used, nothing new, things already known or tried

7.3.1 Theme One: Patient and carer restriction and loss resulting from breathlessness

Restriction and loss resulting from chronic refractory breathlessness were prominent. The physical, psychological and social effects of breathlessness had an enormous impact on the everyday life of patients and carers. Physical restriction was evident in all of the interviews with patients most obviously in relation to mobility, personal activities of daily living such as bathing, housework duties around the home such as cleaning and hoovering, hobbies and the ability to continue with their employment. Exertion induced breathlessness played a major role in preventing the patients from engaging in most normal activities.

Table 36 Physical loss and restriction resulting from breathlessness

Patient 9 "I couldn't do the job…I couldn't keep up the pace"
Patient 10 "I can't do what I usually do 'cos I haven't got the puff to do it"
Patient 12 "walking any distances created problems so I stopped walking"
Patient 14 "I can't do things I used to be able to do…just silly little stuff like playing with [child]….I can't do that because mummy can't breathe properly now"
Patient 22 "I can't hoover, no way can I push…and it's one of those lightweight ones and I still can't use it"
Patient 24 ""I can't go fishing, I can't go bowling, I just can't get me breath to do anything, any activity"
Carer of patient 23 "he cannot get into the bath…he has to have a shower which I've got to see to"

Psychological difficulty and a wide range of emotions in response to the breathlessness were common and often intertwined with the physical consequences of breathlessness. Patients

described a range of situations where the breathlessness experience had compromised their self –efficacy and decreased confidence to perform a task again in the future, or had precipitated other emotional responses such as fear or anger.

Table 37 Psychological loss and restriction resulting from breathlessness

Patient 9 "I think it's one of the most frightening'ist things you can have"
Patient 10 "If I'm going to do something I do get a wee bit anxious now because I know it's going to take a lot of effort
Patient 11 "I feel guilty of not being able to go to football with X"
Patient 12 "when the breathing gets difficult and the frustration kicks in err I've lost the ability to manage that panic or stress and so I identify that as kind of a panic attack"
Patient 14 "I get annoyed and irritable because I can't do things I used to be able to do"

Similarly, social loss and restriction resulting from the physical effects of breathlessness were a consistent theme. Strong language was used to describe such affects, e.g. described by one patient as a "bereavement". It was also very apparent that carers were also significantly affected, reporting restricted socialisation, decreased magnitude of time and movement away from the patient to such an extent that their life-space was largely confined to being at home.

Table 38 Social loss and restriction resulting from breathlessness

Patient 9 "when you can't breathe it's very frightening because for what thirty years I've never had a holiday"
Patient 10 "as well as losing your job, you're losing your comrades at work"
Patient 12 "it's my own bereavement"
Patient 15 "you become a social outcast"
Patient 17 "me only brother died phew about a month ago, but he moved to Wales and I couldn't go because I couldn't drive….so the wife had to go to represent us"
Patient 22 "I haven't a social life 'cos I don't go nowhere" (laughs)
Carer of patient 9 "I can't do stuff and can't go nowhere, I can't do this and I can't do that, yeah"
Carer of patient 19 "it's a big change you know from us both a few years ago, going out and earning a good wage and having good jobs to sort of…not being able to go out, not being able to socialise….we haven't been on holiday for a few years now"
Carer of patient 23 "there's such a lot of things we can't do now….we can't go away it would be so difficult"

Moreover, the carers in particular reported that the effects of living with a person suffering from chronic refractory breathlessness were devastating and had dramatically changed their experience of everyday ordinary life.

Table 39 Carer restriction and loss of lifestyle resulting from breathlessness

Carer of patient 14 "Sometimes just wish the world would stop so we could both get off and just have a normal day."

Carer of patient 19 ""I'm fifty-seven this year and I feel as though….there's no life there."

Carer of patient 23 "You're in a sort of different sphere….you know to what your life was before, you just can't compare it, there's no comparison whatsoever."

7.3.2 Theme Two: Characteristics of breathlessness

Patients identified exertion induced breathlessness as one of the most common characteristics of their daily breathlessness experience. This theme featured strongly throughout the data set, along with triggers for episodes of breathlessness. The triggers for breathlessness were many, although most commonly the patients described these in terms of the weather and seasonal smells such as pollen or blossom.

Table 40 Characteristics: Exertion-induced breathlessness

Patient 10 "Anything with exertion brings on breathlessness."
Patient 11 "If I try and walk somewhere, I go so far and then I'm out of breath."
Patient 18 "Even just walking, the more and more you walk the more breathless you get."
Patient 19 "If I try and walk too far too quickly I'm getting outta breath straight away."
Patient 22 "If I do anything, and I've got to be careful what I do, otherwise I'm puffing and panting."
Patient 24 "I just know exerting me-self in any way is gonna affect me breathing."

Table 41 Characteristics: Triggers for episodes of breathlessness

Patient 10 "When it's hot you tighten up and you can feel that…but when it's really, really cold that can be a bit difficult."
Patient 14 "Its windy today and there's no way I could get a bike out 'cos I wouldn't be able to breathe."
Patient 15 "Sometimes I've gone too far maybe, or the wind's too strong…so I find myself quite puffed."
Patient 17 "I couldn't keep up with them and of course what with the change in temperature…"
Patient 19 "Why do I have to get in this state when the weather changes or I pass afield fulla rapeseed, or the blossom like coming off the trees now and the pollen…it's so quick to trigger"
Patient 22 "If it's windy, if I see the trees swaying outside I know, I'm not going out."
Patient 24 "As soon as you get a vast change, like too hot or very, winter, too cold...from then on I struggle."

7.3.3 Theme three: Patient and carer self-management

Patients appeared to believe that there was little or no help for their breathlessness problem as the lung disease was incurable. Therapeutic nihilism seemed to be apparent and this led to a sense of hopelessness in relation to any treatment of their breathlessness symptoms over and above treatment for the disease causing it.

Table 42 Patient beliefs about breathlessness management: Therapeutic nihilism

Patient 10 "Obviously there's not much anybody can do for me really with it being lung disease…I will never get better."
Patient 11"It doesn't get any worse and it doesn't get any better…I've resigned me-self to that fact"
Patient 15 "So there's nothing they can do, [Doctor] said there was no known cure for this….and he said all they can see is at the next visit whether it's increased or decreased or staying as it is."
Patient 17 "He says "we don't know what causes it, we don't know how to get rid of it so" he says "you've got to learn to live with it" and that's what I took on."
Patient 18 "I just sort-a plod on the way I am you know...I mean [Doctor] says what you've got , its incurable, you've got to learn to live with it."

Beliefs about healthcare varied among the patients and carers, however a similar view of therapeutic nihilism was a common feature in many interviews. Healthcare management was seen by the patients and carers to offer treatment that was primarily focused on the disease with little attention given to the problem of the symptom. Hospital appointments were perceived to be burdensome or of little value. Prominent beliefs were also voiced by the carers about healthcare professionals and their ability to manage breathlessness. The credibility of the clinician was important to patients and carers in terms of their "hands on" understanding of the patient's experience of breathlessness; an approach which seemed to be

driven by book knowledge only and was not informed by a clear desire to understand the impact of breathlessness on the patient's life was dismissed as irrelevant. Credibility was also improved if the clinician was perceived to be available and able to focus and listen to the problems of the symptom rather than the disease only.

Table 43 Patient and carer beliefs about breathlessness management: Healthcare services

Patient 9 Q: "What do you feel about the treatments for breathlessness or how breathlessness is managed in hospitals? A: "Well I've never had any except coming to you...I've never had anything in hospital."
Patient 15 "you don't go to the dentist if you can put up with the pain."
Patient 18 Q: "How do you feel about the services you're offered? A: Well I am happy enough in one way I mean as [doctor] explained to me there's not a lot can be done for it apart from getting you to regulate your own breathing."
Patient 24 A: "No, No input, no 'elp, no nothing from the GP or nurse. Once a year I get called in for a lung function test…last time I was dreading it 'cos I knew I'd been getting worse, when I did the test the nurse said "Oh well you're very much the same as last year." Q: "Right. And how did you feel about that?" A: "I felt it was a waste of time going."
Carer of participant 11:"Well, I don't know, what is there, what could help, I don't know…I think it's just a case, its old age."
Carer of patient 14 ""You have to plan things around hospital visits, I mean on a bad week we've got three or four…when you see [patient's] resignation look on her face and it's "Oh! God I've got the hospital again."
Carer of patient 19 "Yer life seems to just revolve around appointments and like you know, physios and doctors every month and this clinic and hospital appointments and that's it."

Table 44 Patient and carer beliefs about breathlessness management: Healthcare professionals

Patient 12 Q: "What you're sort of saying is, it's not just about the intervention that we're giving you it's also about the effect of the clinician." A: "Yes" Q: "Am I right?" A: "You're right, you're very right."
Patient 24 "You're looking for something different that might help with my breathing, whereas in the last eight years nobody's been looking…nobody gives a shit they just give me a prescription."
Patient 24 "If nobody tells you there's any help you're never gonna know, you just accept what happens at your GP or your nurse."
Carer of patient 9 "Dr's know nothing…it's all bookwork…it just goes in one ear and comes out the other ear, and I think yeah you don't know what you're talking about you've never lived it."
Carer of patient 9 "If you go to A&E it's the same thing they don't understand it, they should have a doctor there what's actually got it then he'll understand what you're going through."
Carer of patient 19" It's just the norm [patient] got a bad chest, he's a bit chesty, give him some antibiotic, give him some steroids and off you go."

The sense of hopelessness also seemed to perpetuate the belief amongst patients that they would gain little symptomatic benefit for their breathlessness from taking part in the trial. There were low expectations of help prior to the study and altruistic motives were often cited by patients as the rationale for their involvement in the research.

Table 45 Patient beliefs about breathlessness management: Trial participation - altruism

Patient 9 "Well when I first went I just thought another err just go and see whatever they tell me and I'll try it and I thought Oh! Here we go again, but with the fan giving me the cool air it…it's a good job I went."
Patient 14 "I'm up for anything to make it; if it doesn't make it easier for me it may make it easier for somebody else. So like I'm quite happy to be a guinea pig; you never know it might work for me one day." (laughs)
Patient 17 "So you know, I'm not as they quite correctly point out to me ,I'm not going to get anything out of it, you know apart from shall we say the satisfaction to know that someone's interested."

In contrast, after the trial most patients did report an increase in their confidence and ability to manage breathlessness, even if the level of benefit was perceived to be small or influenced by the presence of other co-morbidities. In addition, although the trial patients felt that they could possibly walk further if they wanted too, or may try to go out and about more, most still expressed the belief that exercise was bad for you.

Table 46 Patient beliefs about breathlessness management: Trial participation - value

Patient 9 "I would like to go but I'm thinking next year now's too late because winters coming, but next year I will go away for a weekend"
Patient 12 "Whether it's going to make a life changing difference I don't know but I certainly feel a damn sight more comfortable with it than without it."
Patient 15 Q: "Have you found the trial useful?" A:"Well it hasn't helped my condition, it's helped me how to cope with it and what not."
Patient 17 Q: "Ok so what's helped the most?" A: "What apart from seeing you? (laughs)…Shall we say I feel more confident."
Patient 18 "Well I would just say you maybe feel slightly better, but then again you see, I've that many other things wrong with me, (laughs) you don't know are you just having a good day with 'em?"
Patient 24 "I'm glad it's all happened because it's given me more confidence when I'm breathless. I don't have the view that this is the time I'm gonna collapse"

Table 47 Patient beliefs about breathlessness management: Exercise

Patient 10 Q: "Do you think your exercise helps your breathlessness?" A: "No it makes me out of puff."(laughs)
Patient 12 Q: "Does it help you with breathlessness after exercise?" A: (Pause) I haven't really tested that because I haven't done that much exercise…I'm a bit fearful of umm if I push myself too far I know just how far to go."
Patient 18 Q: "Do you feel you're able to do more, or has it changed how far you would consider going?" A: "No, I wouldn't say so, I wouldn't say so"…Q: "Do you perceive exertion as bad?" A: "It's bad for me chest (laughs), it's bad for me breathing."

In terms of how the patient's self-managed breathlessness adaptation was a key theme across the data set. One of the main strategies for managing breathlessness was described by participants as avoidance, or simply to stop doing the activities that provoked the breathlessness. This was consistently reported in the whole dataset and linked with the main first theme, loss and restriction resulting from breathlessness.

Table 48 Patient self-management: Adaptation - Avoidance

Patient 12 "I probably stopped attempting things which I could have done umm walking any distance created problems so I stopped walking."
Patient 15 A: "Another thing I try to do is life is life and if you can do something about it then do it, if you can't then try and forget it…So if I know I'm going to be puffing and blowing then like I don't go out for a walk" Q: "So just to summarise you're saying you avoid things if you know it's going to make you out of puff" A: "Yes that's right yeah."
Patient 17 A: "I try to work within me bounds and not become breathless." Q: "So you avoid breathlessness?" A: "I try to avoid…you, you can never achieve it, but you try…"
Patient 24 A: "I've never been the martyr type right…if something's hurting I'll stop doing it." Q: "So are you telling me you've stopped doing things really?" A: "So I've stopped doing the things that I used to love doing."

Secondly, most patients reported pacing as the other important strategy used for managing breathlessness day to day. Commonly the patients practiced pacing by moving slower, breaking down or re-adjusting activities into stages, or stopping to rest at intervals. Prioritising, planning and task organisation were also reported by patients, along with the monitoring of their breathlessness signs.

Table 49 Patient self-management: Adaptation - Pacing

Patient 9"…strip one bed go for a rest, then strip the next bed go for a rest and then I hoover one bedroom I come for a rest and then the next day I hoover the next bedroom…I pace me-self."
Patient 10 A: "…I mean I do things when I'm breathless because I have to do, but I'm uncomfortable" Q: "Is there anything you do to make yourself more comfortable?" A: "Stop." Q: "Stop?" A: "Just stop and rest."
Patient 15 "I don't rush, I just slow down and stop."
Patient 17 "I'm working at a much slower pace now than I used to….I've had to re-train myself."
Patient 18"sometimes I'll get halfway and have to stop, 'cos it's going up a slight incline; get to the shop, take a coupla minutes getting me breath back in there and I can usually walk home."
Patient 22 Q: "How do you manage with the cooking?" A: "Oh not too bad, I keep doing a bit and sitting down. I do all me vegetables first thing in the morning… I keep going in and doing one thing , then I come back for five minutes, sit in me chair then I go back"
Patient 24 "I've got to plan it…I've gotta think right I'll do that bit first and then I'll have a cuppa tea or whatever and then I'll do that."

Patients with carers in particular also reported that their carer was essential for the management of difficult episodes of breathlessness as well as ordinary activities of daily living.

Table 50 Patient self-management: Carer role as therapist

Patient 11 "I don't know what I would do without her like you know I mean I should be in a right pickle." (laughs)
Patient 12"Most people who are suffering or distressed want the physical contact…[wife] put's her hand on my back and she sort of soothes me and it helps enormously."
Patient 14 "She is my Calming Hand…I come down a lot quicker when [partner] is around she knows straight away when I'm getting into trouble…I don't know what I'd do without her."

The patients' view concurred with how the carers reported their management of breathlessness. The key-themes of a 24/7 role, along with the importance of their physical presence, extra duties, stoicism and a strong sense of obligation were described. Carers also reported that managing and caring for a breathless partner caused them to feel constant worry.

Table 51 Carer self-management: 24/7 job and obligation

Carer of patient 9 "It's just like full-time to me now…it's like a 24/7 job… it's my job to look after me wife that's the way I look at it."
Carer of patient 11 "Well it would be nice not to think will he be fit to go anywhere tomorrow…I don't know what to do, whether to leave him, tie him to this chair, what can I do?"
Carer of patient 14" …at the back of your mind you're always thinking is she too cold is she too hot."
Carer of patient 19 "He'll never work again so therefore I can't go out and work because I've got to look after him."
Carer of patient 19 "You feel as though when you're out, you're looking at yer watch…I often think I can't be too long anyway because in the back of me mind I always think is he alright you know because he's by his-self."
Carer of patient 23 Q: "So you're worried about what will happen to X when you're in hospital? A: "I know for a fact he's going into residential care…Yeah the doctor insisted. She said there is no way anybody else is gonna be able to cope with him at home now."

Carer adaptation to the management of breathlessness was reported as a lived daily experience that involved going into a known routine and playing out a rehearsed coping strategy during acute episodes of breathlessness.

Table 52 Carer self-management: Stoicism and role adaptation

Carer of patient 9 Q: "What do you normally do when she's breathless? A; "Well it's just a case of being patient and talking to her and calming her down…" Q: "How does that affect you?" A: "I don't think it does affect me now 'cos I've just got used to it, doing it…so it's become a normal thing."
Carer of patient 14 "It's scary, but you have to sort of, you have to make sure you don't show that, you have to sort of try and be the calming hand or the, the steady influence."
Carer of patient 19 Q: "What does it make you feel like when you see him really breathless?" A: "...it doesn't frighten me now, it doesn't you know it's just, I just go into this mode where I get on with it you know I do his peak flow , I set his nebuliser up and things like that."

Finally, most patients believed that their medication were burdensome and welcomed a non-pharmacological option for the treatment of breathlessness. This in part may have related to the influence of co-morbidities as some patients were taking a lot of medication for other health problems, however there are other reasons as to why taking medication was interpreted to be problematic to the patient.

Table 53 Patient and carer beliefs about breathlessness management: Burden - medication

Patient 10"…I can only use the nebuliser say 4 times a day because obviously the drugs will affect me if I take too many."
Patient 11 "…but with all these tablets I've got in a box there what are they all for?"
Patient 12 "Oh I don't want to be dependent on anything other than myself I mean I hate taking my pills and I, I hate I really do." (Sigh)
Carer of patient 14 "[Patient's] not one that likes to take tablets, she takes them out of necessity and if she can get out of taking them, she would do."
Patient 17 "And of course I've always been opposed to taking unnecessary tablets and all the rest…I don't like taking unnecessary medication."
Patient 18 "Well I'm on that many different tablets, the less I have to take the better"
Patient 19 "I've been on these inhalers since the day they came out and before that I was on the tablet form of steroids. So really I'm sicka taking tablets and medication, and I'm all for anything that don't involve medicine."
Patient 24"I take Ventolin inhaler…you take two puffs and you sit and wait and nothing's happening and you're just hoping it's going to work."
Carer of patient 19 "It's very, very rare I use my blue Ventolin; and as I say [husband] gets one a month and he ends up using mine as well, my Ventolin, cos obviously I don't use it."

7.3.4 Theme four: How does the patient (and carer) use the interventions (hand-held fan and Calming Hand)

The hand-held fans were used by all patients interviewed and included those who were not allocated to the fan arm, but had received the device subsequently at follow up, as well as one of the carers. However, there was wide variation in how individuals used it which was in keeping with a complex intervention. Some patients selected the hand-held fan specifically according to the severity of breathlessness, the circumstances of the breathlessness and designated a certain timeframe for use, while others found that the hand-held fan could be used for a variety of purposes and served for many different breathlessness situations. Day or night time, after exertion or different activities at home, in private or outdoor, as well as for panic attacks were all commonly identified as times when the hand-held fan had been used to help resolve breathlessness problems.

Table 54 Patient (and carer) use of the hand-held fan: Complex intervention

Patient 9 "I always use me fan so my breathing's at ease when I lay down and go back to sleep."
Patient 10 "I have used it once or twice during the night if I've woke up rather than have a nebuliser I just put the fan on, but that's not a regular thing."
Patient 12 Q: "So it works in the context of helping you manage an anxiety attack" A: "Yes it does" Q: "related to your breathlessness?" A: "Yes it does."
Patient 14 "I can't have that fan full in my face, it has to be off to the side, if it's full in my face then I, I struggle to breathe."
Patient 15 Q: "So the fan would be used if you're moving round the house or if you go for a walk?" A: "Well basically it's difficult to use if you're moving around the house…I'll be honest with yer I only use it when I've come back from walking."

Table 54 Patient (and carer) use of the hand-held fan: Complex intervention

Participant 17 A: "Once I'm in horizontal I switch on the fan, 'cos I then progress, start the breathing" Q: "So when you get horizontal you use the fan, the fan is on while you're clearing your chest?" A: "Yeah."
Patient 18 Q; And you're using the fan after you're walking? A: Yes, yeah even maybe only for a few seconds, not for any length a time."
Patient 19 "I'm breathless now talking to yer, but I've got me fan ready for when I need it."
Patient 19 " now and again she [wife] pinches my fan (laughter)…she does use it if she gets breathless, 'cos she's asthmatic"
Patient 22 Q: "When do use the fan then?" A: "Well I used it a bit this morning."
Patient 24 Q: "How long would you use the fan for when you put it on then?" A: "Oh maybe ten/twelve breaths you know."
Carer of patient 19 Q: "[Husband] mentioned that you've be using the fan…" A: "Oh I have, yeah." Q: "…so as an asthmatic have you found it useful?" A: "Yes, I've found it useful as well, yeah I often pick (laughs) I often pick it up."
Carer of patient 23 Q: "Is he happy to use it? A: "Yeah, he is, even sort of when we're having a meal he'll use it, which is something he wouldn't do with the other, with the Ventolin you know…"

Patients and carers described the hand-held fan use in terms of a portable intervention that was often taken when going out shopping.

Table 55 Patient use of the hand-held fan: Portable

Patient 9 "If I go shopping I take the fan with me…I can walk round when I take the fan. When I get out of breath I just stand still for five minutes, take the fan and then I can continue with me little journey."
Patient 10 "When I've been shopping I take the fan with me and I get back in the car and I'll use the fan then just for a few minutes."
Patient 11 "I've been going a bit further just recently since I've had me fan thing"
Patient 19 "If I'm at home like…in me garden and I'm doing a bitta digging or DIYing I've always gorrit near hand and if I find I need it I'll just sit…put the fan six to eight inches away from me face on an angle so if I want it to go up me nose as well I can...I find coupla minutes it does take the breathlessness down."
Patient 22"I'd take it if I was visiting me family and that like, but I wouldn't take it if I was just going shopping." Q: "Right so is the fan something you do privately, in private you would use but in public?" A: "Not in public."

Table 55 Patient use of the hand-held fan: Portable

Patient 24 " I went shopping, one small bag of shopping…be time I got to me car, I sat in me car and I was breathless and I got the fan out and I just sat that minute calmed me down, I put it back in the glove compartment and drove away."
Patient 24 "I don't mind doing me inhaler in public cos I'm used to do, and lots of other people know cos they have inhalers; I don't see many people with this (fan)"
Carer of patient 23 "it's neat, its tidy he can carry it everywhere with him without a problem."

The hand-held fan use was also described in terms of a medical device or a prop instrument that was used in replacement for a Ventolin inhaler or as an adjunct between nebulisers. It was also identified as an extra "device" that they had added to their "toolbox" of strategies for coping with different episodes of breathlessness.

Table 56 Patient use of the hand-held fan: Medical device

Patient 10 "I carry it around with me and I'll use it you know because I feel a bit out of puff because it's between nebulisers, I can't take too many nebulisers so that acts as a prop in between."
Patient 12 " I've been using the fan instead of Ventolin"
Patient 19 A: "If I wake up in a morning real breathless I will take me Ventolin which I'm supposed to. But during the day, whereas I'd be using it three/four times, I'm maybe only using it once now 'cos I've got the fan" Q: "So you're using the fan instead of the inhalers during the day?" A: "Yes."
Patient 24 "Now I have the alternative, i.e. the fan, where I used to grab me inhaler and have two puffs, wait and hope something gets better; instead of that I get the fan…I'm not using my inhaler half as much as I did."
Carer of patient 19 "If you took the fan away from him now he'd just go, go back to his Ventolin….But as I say, he uses his fan more than he uses the Ventolin"
Patient 22 "If he saw that [fan] I'd say "No, you don't touch that , it's from hospital, love, you mustn't touch that"

Table 57 Patient use of the hand-held fan: Extra intervention for toolbox

Patient 14 "I don't use it often I tend to keep it in the car because there is nothing else, I don't take my nebuliser with me so that would be the thing I would use is the fan when I'm out."
Patient 18 "I don't know why I started cos I wasn't exerting me-self as such I don't know why I started sorta gasping and I thought right fan and after a few seconds back to normal"
Patient 19 "Got me fan in me pocket and I've got me inhaler in me pocket so that I know if I ever go anywhere I've got more, more bases covered now I've got me fan as well"
Patient 24 A: "If I've been a bit breathless, not bad enough to use the fan or me inhaler, I have just done the breathing exercises…" Q: "So what you're saying is there's levels…the fan would be at the top…" A: "Yes" Q: "…for the worst breathlessness…" A: "Yes definitely." Q: "…and then you would come down with other different strategies… A: "Yeah, yeah." Q: "to cope with breathlessness…" A: "Yes."

Patients voiced strong beliefs about the effects of the hand-held fan. Physical and psychological effects were thought to operate and these featured commonly. In particular, patients thought that the physical properties derived from the fan such as the cooling sensation or the "blowing", or even a "driving in" of cold air could be attributed to any improvement they found in their breathlessness.

Table 58 Patient beliefs about the hand-held fan: Physical effects

Patient 9 "I feel that it's the coolness of the fan that gives me a little bit more air in me lung."
Patient 10 A: "but using an article in your hand and the cold air…" Q: "Do you think the cool air is maybe..? A: "Yes I think the cool air does help. Yeah I'm sure it does."
Patient 11 "You're just brea, breathing in aren't you, the cooler air?"
Patient 12 "You've got a filter in your throat and so you've got to push air through it and the fan helps that."
Patient 15 "It does have a cooling effect."
Patient 18 "It must push extra ox, extra oxygen into yer so that's what helps."
Patient 19 "with a fan you're not, there's nothing entering into your system, it's just fresh air in't it?"
Patient 22 Q: "And how do you find the fan?" A: "I find it's very good." Q: "What do you like about it?" A: "I think it's more relaxing, 'cos it's cooling you down as well."
Patient 24 Q: "So why do you like the fan?" A: "I think it helps to, I, I'll say force the air in when I'm out of breath…"

Psychological effects were regarded as an equally important part of the intervention and were commonly mentioned. The physical nature of having an object to hold in the hand, the action of "doing something", as well as feeling the sensation from the fan were important. These patient views interlinked with the belief that they were using the hand-held fan like a medical device or another tool to use for episodes of breathlessness which helped self-efficacy.

Table 59 Patient beliefs about the hand-held fan: Psychological effects

Patient 9 "When I lose my breath and I do panic it's [husband] that calms me, but now I've got the fan I don't need him as much as I did."
Patient 10 Q: "when you've got something in your hand, you've got to press the thing to switch it on and you've got to think what you're doing"
Patient 11 "It just seems to relax me a bit and you know, I can close my eyes or whatever and it just seems to make the breathing a bit easier."
Patient 12 "the fan it's physical, err but significantly one holds the fan in one's hand so there is a combination of the two"
Patient 12. "The reason most people smoke cigarettes is because they're using their hands and it's an object and that's a hard habit to get out of…It's the very rare philosophers who have to sit there with their eyes closed and solve all their problems"

Table 59 Patient beliefs about the hand-held fan: Psychological effects

Patient 14 Q: "What happens?" A: "…we're going back to the prop,…you've got something in your hand… it's a visual comfort thing you know , it's there, it's doing something"
Patient 17 "a little instrument or a tool you know…it's a functional thing, it is a bit of equipment, not an idea yeah? You feel, once it's switched on ….it is a physical thing , you can feel the effect of it"
Patient 24 "I also think there's a psychological end to that 'cos you can feel that something is happening… with the fan you can feel it working, it gives you confidence and you calm down quicker."

The hand-held fan was identified as a valuable intervention with key improvements described by patients in terms of physical, psychological and social changes. Benefits from using the hand-held fan were identified in nearly all of the patient and carer interviews. One of the key attributes was the change in the recovery time from episodes of breathlessness. Patients consistently identified a faster recovery rate when using the hand-held fan. This influenced the patient's sense of control and the confidence to manage their breathlessness symptoms. In addition, this affected their self-efficacy and how they felt about going away from the home environment.

Table 60 Patient beliefs about the hand-held fan: Recovery time

Patient 11 "It just seems to make the breathing a bit easier, relaxes you more than your thing [Calming Hand]."
Patient 12 Q: "so quicker recovery?" A: "around 10 breaths" Q: "you feel recovered after 10 breaths?" A: "I begin to feel more easy with it, umm yeah, about 10 breaths"
Patient 18 "I think the fan is a good thing to bring yer back to what I call normal; without it I would well, you'd be suffering a little bit longer….the best help I can get is that fan."
Patient 22 "I would say the fan is a bit quicker than the Calming Hand at doing the easing."
Patient 24 "the recovery is quicker…it's fifty percent I believe the air is being pushed in and fifty percent I'm confident as to what's happening so I calm down quicker."

Table 61 Patient (and carer) beliefs about the hand-held fan: Valuable intervention

Patient 9 "I can walk round when I take the fan…which I find very nice as I have never done it…this is a really big change…I can walk round [the shop]I can look at everything and I can read everything and it's wonderful"
Patient 10 "I just feel a bit more comfortable afterwards as I say I don't know if it's psychological or what it is, but as long as it works (laughs) that's all I'm worried about."
Patient 12 "when I'm gasping for breath that fan has stopped me gasping for breath…it works so I'm going to use it."
Patient 14 "I just tipped it off to the side, like I've shown you and it worked, it helped and that."
Patient 17 "What we're saying is do you find the fan helpful really, that's what we're after isn't it? And the answer is yes, you know it, it does help."
Patient 19 "I've got the fan, and the fan does help a big, the fan does make a big difference."
Carer of patient 9 "Well since she's got the fan, the fan helped a bit, quite a bit really to tell you the truth, yeah"
Carer of patient 19 "he does seem better, I mean he don't seem to be gasping and really wheezing as much, as much as he was before…I think he is settled more because he's, he's like got two things to have a go at now"

In contrast to the hand-held fan, the Calming Hand was used rarely with few patients reporting any intervention benefit, therefore it was often disregarded as an intervention for breathlessness.

Table 62 Patient use of the Calming Hand: Disregarded

Patient 9 "I haven't really tried the "Hand" thing as I say when I lose my breath and I do panic it's [husband] that calms me."
Patient 10 Q: "The Calming Hand?" A: "Don't like it" Q: "You don't like it?" A: "No I've tried it a few times and I don't find it of any benefit at all."
Patient 11 Q: "Do you find it helps using your hand when you're breathless? A: "Not really." Q: "Not really?" A: "I haven't noticed it." (laughs)
Patient 14 Q: "The Calming Hand was the other coping strategy, how did you find that? A: "Don't think we've use it…to me a Calming Hand is I talk myself into easing down…or I have [partner] who will talk"
Patient 17 "The Calming Hand…I didn't pursue that at all."
Patient 18 "I read the Calming Hand once and more or less disregarded it."
Patient 24 "I stopped doing the Calming Hand thing 'cos to me that was a case of regimentation…I don't need to do that to know there's a list to go through."

In line with the lack of intervention use, patients believed the Calming Hand was something they already knew and it was perceived as a self-help strategy that had been tried in the past. The key sub-themes that emerged were that the intervention was "common sense" and "nothing new".

Table 63 Patient beliefs about the Calming Hand: Common sense

Patient 10 Q: "What do you get with the "Hand"?" A: "Nothing." Q: Nothing? A: "No the "Hand" are things I do myself any how if I feel very breathless… so that's nothing really new."
Patient 12 "The Calming Hand is a good piece of advice, but practically it's quite hard to apply it because of all the other constraints and restrictions"
Patient 15 Q: "The Calming Hand which you were given in the trial…how did you find that?" A: "Well, common sense, its common sense."
Patient 17 "The Calming Hand, I didn't think it was really of much value…I think I could find a lot of better ways of calming me-self down."
Patient 18 Q: You had the fan, but you also had the Calming Hand so…?" A: "…I would think it's a common sense thing that's the way I looked at it."

7.4 Discussion

7.4.1 Theme One Restriction and loss resulting from breathlessness

The first theme of restriction and loss reflects how the patient and carer experience the effects of living with chronic refractory breathlessness. Patients with IPF, asthma and COPD, along with their respective carers all exhibited physical, psychological and social patterns of loss and restriction resulting from breathlessness (Table 36, 37 and 38 physical, psychological and social patterns of loss and restriction resulting from breathlessness), and as described in further detail in chapter 1.8. These effects are reflected in the updated ATS statement that highlights the experience of breathlessness as

> "deriving from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses" (26).

The theme is also consistent with a wealth of data derived from previous qualitative research that has documented the daily lived experience of breathlessness as profoundly frightening, disabling and restrictive in COPD, cancer, heart failure and MND (100-103, 112, 355-357). In COPD, patients have described an inexorable reduction and loss of activities related to job, sport, and tasks around the home and garden (355). Physical limitations force them to stop meaningful activities and become confined to the house, thus imposing social isolation (100, 101). Moreover, the patient's experience of being inactive and housebound due to breathlessness has been described as "physical stagnation" and discussed in ways analogous to the loss of freedom experienced by prisoners (102). The authors identify two core concepts that captured the patients experience of activity and proposed a model of "Stagnation – movement" (102). This model is discussed in further detail in Theme four, Beliefs and uses of the hand-held fan and is reproduced in Figure 12, Stagnation – movement model in Chronic Obstructive Pulmonary Disease (102). Likewise, HF patients have reported "living a restricted life" and feelings of imprisonment that then enmesh with psychological, social and existential issues, such as the frustration and embarrassment of not being able to do everyday things (103, 356).

Consistent with previous findings, carers in this study adopted stoical approach to cope with the demands of the symptom and the patient's perception that the carer was a therapist and a

key prop needed during the management of acute episodes of breathlessness (Table 52, Carer self-management: Stoicism and role adaptation). The dependency on the carer performing extra duties was also cited as a concern as patients felt unable to cope without their partner's caring duties (Table 50, Patient self-management: Carer role as therapist). This was mirrored in the carer interviews as they felt they had to manage breathlessness on a 24/7 basis leading to substantial losses such as job, social life, holidays as well as the everyday strain of feeling heightened alert in case of an acute episode (Table 51, Carer self-management: 24/7 job and obligation).

Likewise, another prior study of COPD patients found that the carers experienced similar losses to the patient and significant burden from adopting multiple roles, as well as a lifestyle that becomes entangled in the illness (355). Furthermore, an earlier study by Booth et al that examined the breathlessness experience in cancer and COPD identified high psychosocial needs of carers that were not adequately addressed or recognised (112). This resonates with the data presented and how the carers described their existence with a breathless person (Table 39, Carer restriction and loss of lifestyle resulting from breathlessness). The impact was so great that everyday life had become unrecognisable and was deemed to be *"no comparison to before"*, or as *"there is no life"* in alignment with the reported far-reaching and devastating effects of the symptom.

7.4.2 Theme two Characteristics of breathlessness

The second theme concurs with the findings from a previous study by Simon et al (85). In particular, the participants frequently identified the characteristics of exertion induced breathlessness (Table 40 Characteristics: exertion-induced breathlessness) and short episodes of breathlessness with certain triggers (Table 41 Characteristics: triggers for breathlessness). These mirrored the specific terminology used by Simon et al and adds support to their proposed categorisation of breathlessness based on patient experiences by time and triggers (85). The proposed categorisation of breathlessness is discussed in further detail in chapter 1.7 and the Categorization of breathlessness by time and triggers based on patient experiences and the List of triggers for breathlessness are reproduced in Figure 3 and Table 4 respectively.

7.4.3 Theme three Patient and carer self-management

7.4.3.1 Beliefs about breathlessness management -therapeutic nihilism

At diagnosis patients usually received the message that they had an "incurable disease" and they had "to learn to live with it" which appeared to feed into the belief by patients that there is no treatment for the symptom of breathlessness (Table 42 Patient beliefs about breathlessness management: therapeutic nihilism). This mirrors earlier work as patients lived with the assumption that as their lungs were damaged beyond repair they could not be helped (358). It is also possible that the diagnosis of "COPD" or "IPF" may mean little to the patient and carer in comparison to the well-known and publicised word of "cancer" in which death plays a prominent role. This is confirmed in earlier qualitative interviews of 18 COPD patients that found at the point of diagnosis there were limited understanding of the words "COPD" and an "empty label" of little significance were perceived by patients, who also expressed relief that it was not a diagnosis of cancer (359). These patient interviews also demonstrated that healthcare professionals did little to acknowledge or merit the breathlessness problems and as such the concept of "invisibility" was deemed to fit the symptom experience (360). An issue endorsed by these results as patients and carers believed that healthcare services and professionals offered irrelevant or limited input that did little or nothing to support their daily experience of breathlessness (Table 43 and Table 44 Patient and carer beliefs about breathlessness management: healthcare services and professionals).

A further literature review of qualitative studies synthesized similar conclusions, suggesting that the information provision in COPD was minimal and often coupled with lack of routine open discussion of the implications of the diagnosis and prognosis of the disease (361). This problem has been confirmed by healthcare professionals who feel a reluctance to communicate prognosis and find it difficult to discuss the trajectory of the disease (362). Consequently, if communication is limited regarding breathlessness management and non-pharmacological interventions are not offered then the patients will not realise there is the possibility of improving their breathlessness (Table 44 Patient and carer beliefs about breathlessness management: Healthcare professionals). This is a view consistent with prior qualitative study; Habraken *et al* found that patients did not know that their breathlessness experience could be improved as the respiratory physician had told them that there was nothing more that could be done (358). Therefore, the patient's perception of the disease at

diagnosis and the information communicated by the healthcare professional may perpetuate therapeutic nihilism and influence whether the patient chooses to seek any help (or not) with the symptoms of chronic refractory breathlessness. More importantly, if neither the patient nor the clinician sees the breathlessness as a therapeutic target then the problem is ignored leaving the patient to self-manage and miss out on evidence based management of the condition (363).

In addition, qualitative study by Gysel *et al* identified an unhelpful pattern of health seeking actions, in that the COPD patients postponed contact with healthcare until a crisis point was reached (359). This difference in health seeking behaviour and the late presentation of patients may compound the perspective that little can be done for their breathlessness symptoms and may be aggravated if they feel at fault for their condition as a smoker. A recent systematic review that examined the consequences of tobacco smoking related stigma identified that smokers felt shame, guilt and embarrassment and applied words such as "lowlife" and "pathetic" in reference to their own smoking behaviour (364). This suggests that a smoker could experience lower self-esteem and feel that they don't deserve treatment for their breathlessness as they have smoked themselves into this position. A view previously identified by Gysels *et al* as the COPD patients interviewed felt guilty about their breathlessness and expressed responsibility as it was self-inflicted from cigarette smoking (357).

Equally it is possible that the patients smoking status may not be a relevant issue if they adopt a stoical approach in order to manage their breathlessness (Table 43 Patient and carer beliefs about breathlessness management: Healthcare services), a finding that resonates with another prior qualitative study (112). It is also possible that patients may regard the problems they experience as normal. An earlier study that explored the silence of patients living with end stage COPD found that the patients did not actively express a wish for help as they did not perceive their limitations to be something out of the ordinary and as such there was not a valid reason to go and seek help (358). According to Cornwell's categories of health problems it suggests that patients may classify COPD as a health problem that is not an illness (365). This may in part be due to the trajectory of the disease and the nature of breathlessness in COPD; identified as a slow and insidious onset, hardly noticeable at first, easily allowing patients time to adapt to small deteriorations and silently accept the restrictions in their day to day living (357).

The onset and progression of illness in COPD was also examined by Pinnock *et al* in a longitudinal qualitative study; the patients reported a passive acceptance of the breathlessness situation as a way of life, rather than a distinct illness (366). The patients interviewed also told a "chaos narrative" typified by a directionless story that enmeshed the illness into their life and as such the problem of breathlessness lacked a clear beginning and had an unpredictable ending (366).

The authors proposed that the patient's passivity and the low demand for breathlessness treatment may stem from a lack of "biographical disruption" (366). The term "biographical disruption" describes how a person experiences a high level of disruption during the development of a chronic illness and has to re-think their biography and self-concept (367-369)). However, in COPD and other respiratory conditions such as chronic asthma and IPF there is no dramatic sense of disruption, particularly if the breathlessness is regarded as unavoidable part of the aging process and similar to the pain felt with age related arthritis it is something to be coped with. Moreover, in comparison to others the patient may perceive that at their age most people of their generation have some sort of chronic illness or condition. A view clearly captured by one of the carers interviewed (Table 43 Patient and carer beliefs about breathlessness management: Healthcare services), and consistent with previous qualitative study amongst COPD patients in Barnsley, Yorkshire that reported, "you get old, you get breathless, and you die" because "bad lungs" were believed to be a normal part of the ageing experience (370).

Finally, the patient's views before trial participation also attest to the problem of therapeutic nihilism and would suggest that patients did not know that there were any possibilities to improve their breathlessness situation. Prior to study involvement they expressed little expectation of benefit for their breathlessness symptoms. Altruistic motives were often cited by patients as the rationale for research participation (Table 45 Patient beliefs about breathlessness management: trial participation - altruism). A finding confirmed by previous qualitative work that analysed 108 interviews and explored the preferences and expectations among patients with various diagnoses and carers regarding their contribution to palliative care research (314).

7.4.3.2 Adaptation - avoidance

Consequently, it is likely that at the point of diagnosis the patient is already deconditioned as a result of reduced exercise and it is possible that they will have already experienced a breathlessness crisis. They will have typically learnt to avoid all activities that trigger breathlessness and have formed their own beliefs about how to manage exertion induced breathlessness. Avoidance has previously been confirmed as one of the two main strategies used to cope with the limitations of breathlessness due to COPD (358). Also the motivation for older adults to exercise was strongly influenced by their previous experience of unpleasant sensations associated with the activity, such as breathlessness and this was sufficient to discourage the participant from continuing with the exercise programme (86). Likewise, the interview data show how patients have tried to manage their exertion induced breathlessness by avoiding activities, stopping attempting, or doing less and less in an effort to control the breathlessness (Table 48, Patient self-management: Adaptation - Avoidance). The characteristics of exertion induced breathlessness as described in theme two exemplify how the patients' avoidance of activity to reduce their breathlessness has perpetuated a situation where many find minimal exertion causes breathlessness (Table 40 Characteristics: exertion-induced breathlessness).

This indicates that the patient will already have known restrictions in terms of their exercise capacity and it is likely that they will feel less able to engage in increased exercise or changes to their normal exertion induced breathlessness. This again is reflected in the interview data as patients felt little had changed after the trial in relation to their experience of exertion induced breathlessness and the belief that exercise was not good for you as it induced breathlessness symptoms was also expressed (Table 47 Patient beliefs about breathlessness management: Exercise). It is also possible that adopting a strategy of avoidance allows the patient to hide their breathlessness and combined with the invisibility of the lung damage they can easily continue to convince themselves that it is not a real illness (365).

7.4.3.3 Adaptation - Pacing

Pacing was identified as the other most commonly adopted self-management strategies; it was used by nearly all patients to differing degrees to control the level of exertion-induced breathlessness experienced during activities (Table 49 Patient self-management Adaptation -

pacing). Pacing has previously been identified in a prior survey that examined the frequency of use and perceived benefit from different self-management techniques among 79 patients with COPD. The results demonstrated that moving slower were utilised frequently to relieve breathlessness 91% (n=72), along with staying stationary 86% (n=68) (164). In a subsequent study of 30 COPD that used a mixed method design these strategies were also perceived to be 74% (n=21) and 79% (n=19) effective respectively (163). Likewise, qualitative studies have also reported pacing as an important coping strategy with patients modifying or taking breaks during activity (358).

7.4.3.4 Beliefs about breathlessness management – medication burden

Medication was perceived to be burdensome by most of the patients. This may have resulted from how many tablets were prescribed, the frequency the medication needed to be taken to relieve breathlessness coupled with the fact that relief was not always given and the limitations as to how many times the medication could be used on a daily basis (Table 53 Patient and carer beliefs about breathlessness management: Burden - medication). Concern was expressed over the long-term use of medication due to the possibility of future side-effects, making a non-pharmacological intervention such as the hand-held fan an appealing option.

7.4.4 Theme four: How does the patient (and carer) use the interventions: hand-held fan

7.4.4.1 Complex Intervention

The hand-held fan was used by all of the patients and also one of the carers in a complex manner and as an intervention to help the self-management of chronic refractory breathlessness, distinct individual preferences were stated in terms of the time of day, location, severity and type of breathlessness when patients would use the intervention (Table 54 Patient (and carer) use of the hand-held fan: Complex Intervention). This mirrors the findings from another fan and activity study in people with chronic breathlessness where the fan was found to be used in a complex manner as part of other strategies (311), and is in keeping with the updated MRC definition of a Complex Intervention and their proposed dimensions of complexity (281). The hand-held fan demonstrated key dimensions of

complexity in relation to the range of possible outcomes, the high level of variability and differences in behaviours in the target population and the degree to which the intervention could be tailored to specific personal requirements (281). The MRC definition of a Complex Intervention and further details of the dimensions of complexity can be found in chapter 4.1.3.

7.4.4.2 Portable

In particular the hand-held fan was frequently used in the morning, night, after exertion and at home, or in a private environment. Interestingly, some patients expressed concern about using the fan in a public place as they felt the hand-held fan, although was not publicly known as an intervention, signified the visibility of their health problem. It was also noticeable that in terms of a portable device the patients associated the hand-held fan as a tool that could be used inside the car rather than outside (Table 55 Patient use of the hand-held fan: Portable).

The problem of intervention adherence has also previously been identified in a prior study that evaluated the effect of a rollator over 8 weeks in patients with severe COPD (371). The authors found a sub-group of patients, 8 out of 18, who were infrequent users utilising the device less than 3 times a week, despite indicating their preference for walking with the rollator. Furthermore, since outdoor walking and activities away from the home were identified as when the rollator was most commonly used, it suggests a similar patient reluctance to use the device in public due to feelings of self-consciousness from what others may think.

It is not known if this perception applies only to this group of patients interviewed, or if there is potentially a wider problem in the population that could undermine the use of the hand-held fan in a public place and prevent adherence to the intervention. If the latter applies then the notion of a novel plastic object needs to be challenged as a lack of confidence to use the hand-held fan in a public place could limit how much the patient could potentially benefit from the intervention and serve as a constraint on increasing their personal living space in terms of their ability to go out and about in public. This is supported by Booth and Farquhar et al; both have indicated the importance of how the intervention is delivered and the

clinician's role, given the delineation of the hand-held fan as a non-pharmacological intervention and a common everyday object (8, 166).

7.4.4.3 Medical device

However, patients also described how they had used the hand-held fan similarly to the way they used a medical device. It was taken instead of a Ventolin inhaler thereby reducing medication intake, or it was an adjunct between daily nebulisers. More importantly, in some cases the hand-held fan was reported to be as good as, or nearly as effective as the medication (Table 56 Patient use of the hand-held fan: Medical device).

Furthermore, the hand-held fan was viewed as an *"instrument"*, *"device"*, *"prop"*, or an *"actual piece of equipment",* rather than an everyday object, terms that mirror the EU definition of a medical device as,

"Any instrument, apparatus, appliance, material or other article, whether used alone or in combination together with any accessories or software for its proper functioning, intended by the manufacturer to be used for human beings in the diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap…This includes devices that do not achieve their principal intended action in or on the human body by pharmacological, immunological, or metabolic means"(372).

The patient's views indicate that the hand-held fan could fit the specifications of a medical device and one patient even suggested how a future design could accommodate an arthritic hand, or incorporate a neck-strap or wristband. At present the hand-held fan is not recognised as a medical device, therefore this maybe the next step to change how the hand-held fan is perceived and challenge the universal representation of an everyday object. It is possible that as a "prescription", the hand-held fan could have more credence as an intervention to relief breathlessness. However, if the device became regulated manufacturing costs might increase and the hand-held fan would no longer be a cheap intervention that is easily available to all patients. It could imply the existence of a safety problem and perpetuate a situation where patients are unsure if they can use a non-prescription version. In addition, it would influence the planning for future clinical trials of the hand-held fan as these would be subject to the MHRA regulations for medical devices.

7.4.4.4 Extra intervention for toolbox

Patients identified how the hand-held fan represented an extra treatment option that had been added to their "toolbox" of strategies for coping with different episodes of breathlessness. The provision of a range of interventions which includes the hand-held fan has previously been identified as important to patients (8).

In addition, the level or attributes of the breathlessness experience were cited as influencing the decision as to whether the hand-held fan or another type of self-management strategies were used (Table 57 Patient use of the hand-held fan: extra intervention for toolbox). This aligns with previous mixed methods research that identifies COPD patients employing multiply strategies to help effectively self-manage their various episodes of breathlessness (163, 164). Likewise, a Cochrane review that examined the content of self- management training programmes for patients with COPD confirms that the diversity amongst the interventions means that it is not possible to interpret which of the self-management components are most effective, although the outcomes from the included studies are associated with decreased breathlessness and improved health related quality of life (351).

Interestingly, patients described selecting the hand-held fan as a strategy for breathlessness associated with panic or episodes arising "out of the blue", this suggests that it should be identified as a key tool in any breathlessness crisis plan. A proposal confirmed by a recent ATS statement that reports the management of breathlessness crisis in terms of the "COMFORT" mnemonic (167). The approach identifies "F" as the fan to face, illustrating the important consideration of the device during crises situations of breathlessness for the patient and their carer (167). Further details of the COMFORT mnemonic are shown in Table 6, chapter 2.2.4.

7.4.4.5 Physical effects

The use of the hand-held fan during an emergency situation implies that the intervention has important attributes needed in the response to a panic or crisis episode of breathlessness. This is reflected in the patient beliefs as they identified prominent physical effects of the hand-held fan centred on two properties; the cooling sensation from the air, and the belief that the air was being forced or pushed into the lungs (Table 58 Patient beliefs about the hand-held fan –

physical effects). These beliefs resonate with the results from prior mixed methods studies that also found cold, fresh air an effective and frequently selected option among the self-management strategies in COPD patients (163, 164). Similarly, the proposed model of "Stagnation – movement" as displayed in Figure 12, identifies fresh air and the flow of air as integral to the patient's perception of breathlessness, which in turn lessens the experience of physical limitations and promotes psychological and social well-being. In contrast the patient's perception of air within the confines of their home was stale and still, thereby increasing the perception of breathlessness and feelings of suffocation, which in consequence compounded the sense of physical, psychological and social stagnation (102).

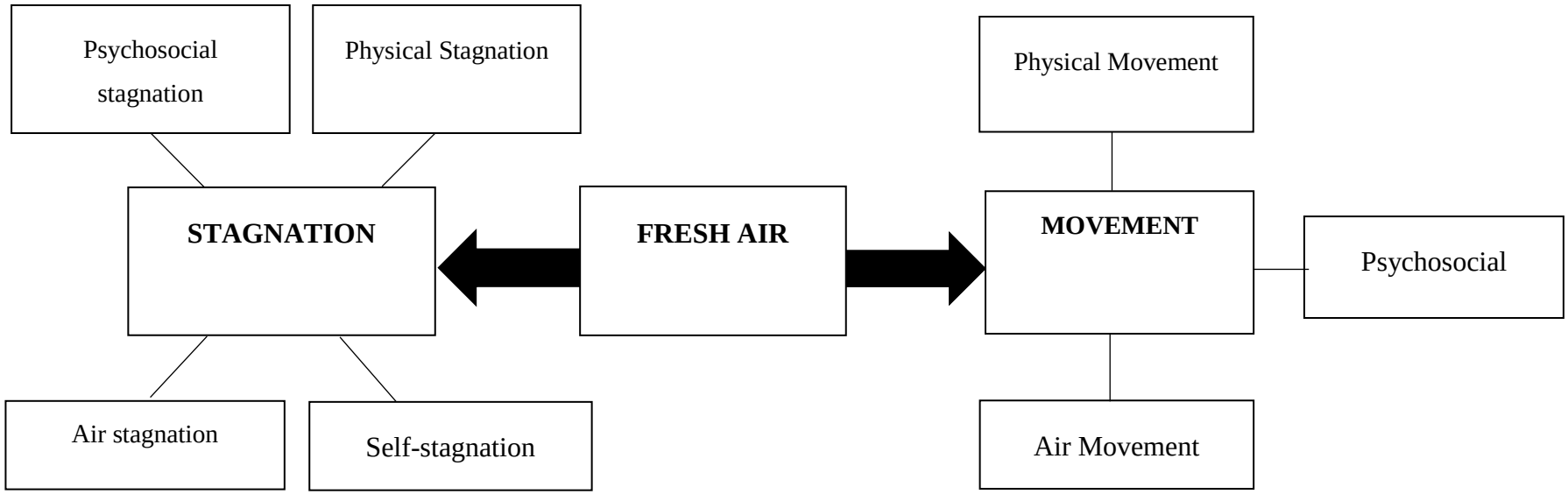


Figure 12 Stagnation and movement model in COPD (102)

7.4.4.6 Psychological effects

The psychological effects seemed to stem from the patients belief that the hand-held fan represented a medical device (Table 59 Patient beliefs about the hand-held fan - psychological effects). Three key components were identified in the patient's interpretation of the hand-held fan.

1. The physical activity or routine of something to do,
2. A prop object to hold in the hand,
3. A tangible sensation felt on the operation of a button.

The significance of having a prop object in the hand was also likened by one participant to the need for a physical device when smoking (Table 59 Patient beliefs about the hand-held fan - psychological effects). It is possible to speculate that the use of an e-cigarette as a replacement for tobacco smoking may offer the patient a similar prop or device that is held in the hand, the performance of a physical action and an inhalation that is followed by vapour visible to the user. However, at present little is known about how patients perceive the importance of a piece of equipment to hold in the hand or having a physical device to use.

7.4.4.7 Valuable

Finally the hand-held fan represented a valued and acceptable intervention that was used by all of the patients interviewed. One of the main views consistently confirmed by the patients was that the hand-held fan had worked as an intervention to speed recovery time from episodes of breathlessness (Table 60 Patient beliefs about the hand-held fan: Recovery time). This in consequence had helped to increase patient confidence and their ability to manage episodes of breathlessness (Table 61 Patient and carer beliefs about the hand-held fan: Valuable intervention), a finding in keeping with the BIS recent Phase III mixed methods randomised controlled trial. The follow up interviews identified the hand-held fan as a valued intervention that influenced patient self-mastery and confidence to manage breathlessness (8).

7.4.5 Theme four: How does the patient (and carer) use the interventions: Calming Hand

7.4.5.1 Disregarded

In contrast to the hand-held fan, the Calming Hand was used infrequently and quite often patients disregarded the intervention (Table 62 Patient use of the Calming Hand: Disregarded). This could be interpreted in a number of ways; first, if the patient has suffered from breathlessness for a long time period of time and the problem is chronic and refractory then it is likely that some of the techniques that are employed as part of the Calming Hand will already have been tried in the past. In this context the Calming Hand would appear to be common sense and the value of the intervention is thereby reduced (Table 63 Patient beliefs about the Calming Hand: Common sense). Secondly, if the patient found the hand-held fan to be a valuable asset in their management of breathlessness then this intervention could have been used in preference to the Calming Hand. Finally, in contrast to the Calming Hand, the hand-held fan offered physical properties and required little or no thought control, therefore it is possible that this was viewed as the easier and simpler of the two interventions to use. This indicates that the Calming Hand needs to be targeted at patients as a self-management strategy after careful assessment of their needs and should be introduced earlier in the management of breathlessness problems such as during pulmonary rehabilitation. There are significant differences in the use and effectiveness of breathing exercises as a self-management strategy for breathlessness between those who had attended pulmonary rehabilitation and those who had not (164).

7.5 Limitations

The findings from these interviews are based on data from a small number of patients and carers living in a single geographical regional and should not be generalized. Indeed, as with all qualitative work it is not intended to be generalized, as patients from other locations may experience breathlessness and the interventions differently. However, given that many earlier studies from diverse settings and different patient diagnoses result in similar narratives and findings, it does support the notion of common experience. The patients were only interviewed on one occasion therefore the interpretation is limited to a single snapshot of the patient's experience. It may be possible to achieve a deeper understanding of breathlessness

and the interventions with repeated interviews. Nonetheless, the findings do provide valuable insight and important preliminary information about the patient's perception and use of the hand-held fan and Calming Hand that can be used to guide and plan future research studies.

7.6 Reflexivity

I took great care to be neutral when teaching the hand-held fan and Calming Hand and I felt able to convince the patients that the interventions were credible given my previous clinical experience which involved the delivery of these two interventions regularly. No judgements were made about the interventions during the trial and the interviews were all approached with an open-minded attitude. Nonetheless, I was aware that there was already some published research studies suggesting the effectiveness of the hand-held fan at rest, while no evidence and only a little grey literature to support the Calming Hand. It was also apparent that using a concurrent strategy for the data collection meant I became aware of the patients views and experience of the interventions during the ongoing feasibility RCT. Therefore, it was evident that there was a clear difference in the patient's perception and use of the hand-held fan in contrast to the Calming Hand. This changed my pre-conceived ideas about the interventions and my later view of the hand-held fan and Calming Hand could have potentially introduced bias if it influenced the line of questioning during any of the interviews. However, I also took great care to use questions that were open-ended and I reflected back what the patient had said about the interventions to ensure complete clarity and understanding of their perceptions and experience.

7.7 Conclusions

The main themes identified in the dataset resonate with many former qualitative studies and add weight to the evidence of how chronic refractory breathlessness is experienced, characterised and self-managed by patients with asthma, IPF and COPD, as well as their carer's.

The findings provide preliminary insight into patient's beliefs about the hand-held fan and Calming Hand, along with their experience of using these non-pharmacological interventions during the course of a 28 day feasibility trial and subsequently at follow up.

Patients and carers appreciated a trial that was focused on breathlessness and not the disease. There were high acceptability of the outcome measures including the use of the ISWT to test maximal exercise capacity. Of the outcome measures tested recovery from exertional breathlessness, the confidence and ability to self-manage breathlessness and Life-space were deemed important and of most value to the patients and carers.

The perception and use of the hand-held fan and Calming Hand were found to vary widely, each patient defined and individualised use of the interventions according to their own breathlessness experience. Overall the hand-held fan was felt to be more useful and credible for the management of breathlessness, while the Calming Hand was of less value and often disregarded. Patients associated the hand-held fan with a faster speed of recovery from exertional breathlessness, which helped to improve confidence and their sense of control, during episodes of breathlessness. Patients derived psychological support from a prop object that provided the physical sensation of air "blowing" or "cooling" on the operation of a button. These attributes were considered important in the patient's interpretation of a potential medical device, as well as a valued and acceptable extra intervention to replace the carer role in the management of breathlessness.

The healthcare management of COPD, IPF and asthma were perceived to primarily focus on the monitoring of the respiratory system with little attention to the symptom. Lung function results do not match the patient's experience of breathlessness or indicate the possibility of symptom treatment (Table 43*).* Medication prescribed for breathlessness were perceived as burdensome in that it did not always alleviate the symptoms and may need to be used frequently, or can only be given a limited number of times during the day, as well as the possibility of side-effects from long term use (Table 53).

7.8 Implications

Healthcare professionals such as physiotherapists need to be aware that they are teaching breathlessness management and delivering non-pharmacological interventions to patients against a background of therapeutic nihilism and hopelessness. Similarly, the perceived burden of the medications prescribed for breathlessness may influence the patient's view of

any proposed non-pharmacological options. It is possible that the patient will understandably feel sceptical as to the potential benefits of using such treatments and have low expectations particularly if they feel that the interventions are *"things already known" [Patient 10]*, or are perhaps the last healthcare option with little or no evidence to support effectiveness. This underlines the importance of the clinician's role and how the intervention is delivered (8, 166).

Furthermore, the timing of delivery of a non-pharmacological programme for breathlessness may be important in preventing the patient from adopting avoidance as a self-help strategy. The patients interviewed found that little had changed in relation to their exertion induced breathlessness or their ability to exercise more, often citing a reluctance to increase activity based on the belief that it was bad for you (Table 47). Avoidance of breathlessness does little to help the symptom as exercise tolerance reduces and the de-conditioning process perpetuates further breathlessness.

Therefore, if the hand-held fan were delivered to patients earlier in their disease trajectory, preferably before an acute exacerbation such as in conjunction with a pulmonary rehabilitation programme then it may support the possibility of continuing with exercise after pulmonary rehabilitation has finished, given the problems of activity adherence and maintaining the benefits of pulmonary rehabilitation long-term (86, 139, 152, 153). This also promotes the likelihood of pacing as a patient self-help strategy because the hand-held fan can be used with any exertion induced breathlessness and as it is also portable the patient can have it readily available for any circumstances. Crucially, the device would then be delivered in the context of use with activity in an environment that endorses and also promotes the benefits of continued exercise.

7.9 Summary of chapter seven

This chapter has demonstrated that recovery time from exertional breathlessness was an important outcome and helped give patients a sense of control and self-mastery over their breathlessness. Such ability and confidence to self-manage breathlessness with everyday activity was identified by patients as particularly valuable, rather than a change in exercise capacity alone.

Patients voiced strong beliefs about the effects of the hand-held fan. Physical and psychological effects were thought to operate. Physical properties were linked to the cooling sensation and air being forced or pushed into the lungs. Psychological attributes were defined in terms of the physical activity, or routine of something to do, coupled with a prop object to hold in the hand and a tangible sensation felt on the operation of a button. These effects contributed to the interpretation of;

- A medical device
- A complex intervention
- An extra intervention for toolbox
- A replacement, instead of Ventolin inhalers or carer help

Patients felt the Calming Hand was not suitable to help with the recovery from exertional breathlessness after activities and they did not identify any benefits with the ability or confidence to self-manage breathlessness. The intervention was perceived as "*common sense",* or "*things already tried",* therefore it was often *"disregarded"* and not used in preference for the hand-held fan, or carer help with breathlessness management.

Therapeutic nihilism was a consistent theme. Patients and carers perceived that healthcare services were focused on the disease and not the patient or carer experience of living with breathlessness. In consequence, clinicians were perceived as not understanding breathlessness management with no time to listen or provide adequate support for the far-reaching consequences of the symptom. Medication was perceived as burdensome and often of little help therefore, patients and carers felt sceptical about the potential benefits from non-pharmacological intervention use in the management of chronic breathlessness. Therefore

research that focused on breathlessness as a symptom and the use of non-pharmacological interventions were welcomed by participants.

Chapter 8 Thesis summary synthesis and discussion

8.1 Introduction

The overall aim of the thesis was to undertake a preliminary investigation to inform about two non-pharmacological interventions; the hand-held fan and Calming Hand for the management of exertion-induced breathlessness in people with chronic breathlessness. Chapters three to six have presented the findings from i) a systematic literature review and meta-analyses of airflow for the relief of chronic refractory breathlessness, and ii) a feasibility, 2x2 factorial RCT with embedded qualitative semi-structured interviews with participants and their carers to test acceptability and address the main uncertainties for a future definitive trial.

This chapter will synthesise the findings from each methodological approach in relation to the research questions addressed by this thesis.

8.2 Research questions

8.2.1 Overarching Question

What is the effectiveness of two non-pharmacological interventions which are currently used in clinical practice (cool facial airflow, and the Calming Hand) with regard to exertion-induced breathlessness management in people with chronic breathlessness and implications for clinical practice and future research?

Specific questions are summarised below:

1. Does airflow from a hand-held fan or use of the Calming Hand provide benefit for breathlessness when used for exertion-induced breathlessness?

2. Does airflow from a hand-held fan or use of the Calming Hand help patients' functional abilities?

3. Does the use of a hand-held fan or the Calming Hand influence the carer level of burden or ability to cope with the patient's breathlessness problems?

4. What are the most important outcome measures to the patient and what will appropriately reflect any patient benefit from using the hand-held fan or Calming Hand?

5. Is a phase III RCT to test the effectiveness of the hand-held fan and or the Calming Hand for breathlessness in people with chronic breathlessness feasible?

8.3 Integration and summary synthesis of findings

The key findings are summarised in Table 64 and will form the basis for the discussion. The discussion will firstly address to what extent the specific questions have been answered. Lastly, there will be a summary discussion about how well the overarching aim of the thesis has been achieved.

8.3.1 Question one. Does airflow from a hand-held fan or use of the Calming Hand provide benefit for breathlessness when used for exertion-induced breathlessness?

Airflow systematic review and meta-analysis data demonstrated significant relief of breathlessness intensity from hand-held fan use, at rest, in a mixed population of patients with mild or normoxaemia; Standardised Mean Difference [SMD] -8.5, 95% CI -12.9 to -4.1, $p<0.0001$, a change in VAS breathlessness equivalent to the MCID (4). However, there was only probable benefit to breathlessness intensity when the hand-held fan was used in relation to general activity, and it was not possible to clarify any clear improvement with exercise. The 6MWT was identified as a limitation to the interpretation of breathlessness intensity change in the systematic review studies. This measurement of exercise capacity permits patients to pace their walking therefore they can limit their breathlessness intensity to a known level, particularly if fear prevents them from pushing beyond this point of breathlessness intensity. A view highlighted in the patient beliefs about breathlessness management and exercise, as displayed in Table 47.

It is recognised that measurement of breathlessness intensity after exercise or general activity may not demonstrate improvement as patients are able do more activity before reaching the same level of intensity, or may even have been able to tolerate higher levels of breathlessness intensity, enabling greater exertion, due to improved mastery over breathlessness without realising there is any benefit (273). However, the feasibility data displayed mean group

improvement from baseline for both the ISWT distance walked and the maximal NRS breathlessness intensity experienced after the ISWT at day 28 in two of the study arms; the hand-held fan & usual care, and the Calming Hand & usual care as shown Table 31 and in Graph 4 and 5. This results may in part reflect that the ISWT is a more appropriate test to induce a patient's maximal exertional breathlessness tolerance. The ISWT offers a different and more stringent protocol to the 6MWT, which is incremental and externally paced (373). Recent systematic review identifies a strong relationship between ISWT distance and peak oxygen uptake (VO^2 peak), or work rate on a cardiopulmonary exercise test (CPET) and concludes that the ISWT is a valid and reliable measure of cardiopulmonary exercise capacity in chronic obstructive pulmonary disease (373).

In contrast, there was no signal from any of the feasibility study NRS breathlessness outcomes when measured as an "average over the last 24 hours" to suggest discernible change in symptom intensity, distress or unpleasantness after 28 days use of the hand-held fan with activity. This mirrors the systematic review findings, results from the longitudinal studies identify inconsistent changes and wide variability in CRQ or Borg breathlessness scores when airflow from cylinder air or the hand-held fan is used with general activity over time (219, 262, 266, 267). Breathlessness intensity is known to fluctuate considerably over a 24 hour period (85), as highlighted by the categorisation of breathlessness characteristics, previously described in chapter 1.7 and this may not be usefully captured in an average daily measure.

However, measurement of breathlessness "right now" at minute intervals during recovery from the ISWT indicated worthwhile benefit with use of the hand-held fan. Calculation of the NRS breathlessness intensity recovery rate per minute indicates a possible novel outcome measure that was more responsive to change with use of the hand-held fan. An improved NRS breathlessness intensity recovery rate, 0.64 NRS points per minute faster than baseline was found for the hand-held fan & usual care arm. Results for the variability of the measure; a narrow SD at baseline across all four study arms, indicates the potential suitability of the outcome measure to accurately pinpoint breathlessness intensity change. Similarly, qualitative findings emphasize minimal hand-held fan use to achieve a full recovery from exertion related breathlessness, as shown in Table 60; a theme consistent with the recently published results from a feasibility trial of the hand-held fan with activity (311).

Data from both of the groups allocated to the hand-held fan displayed quicker mean recovery times on day 28; hand-held fan & usual care arm; -33.5 seconds, and hand-held fan & Calming Hand & usual care -40.3 seconds. These figures represent mean group change from baseline of -20.4% and -24.6% respectively. This was mirrored by the qualitative findings as patients defined their experience of the hand-held fan in terms of speeding up breathlessness recovery as highlighted in Table 54 and Table 60, and is consistent with patient interviews from prior studies that identify the hand-held fan as an aid to recovery (8, 311).

There were no published relevant data regarding recovery time in the systematic review, however, these preliminary data support the use of the hand-held fan to relieve the intensity of exertional breathlessness experienced after exercise or activity.

Limited data from a prior study of 57 cancer patients found a median recovery time of 4 minutes (IQR 2-5); range 1-7 minutes after an ISWT with rest alone (276). Similarly nearly all of the participants in the feasibility study were fully recovered after 4 minutes. The mean recovery time at baseline for all participants, (n=27) was 2.42 (SD 0.56) minutes, range; 1.25-5.03 minutes. The results suggest that patients with a diagnosis of COPD, IPF or asthma experience a similar rapid recovery from exertional breathlessness, even after performing a progressive walking test to maximal breathlessness. This is clinically relevant and important as it serves to reassure patients that this is the usual case and counters beliefs that breathlessness is harmful.

The hand-held fan appears to be a pragmatic, and easily administered intervention (276). Furthermore, a reduction in recovery time may reflect that cool airflow changes respiratory sensation and interferes with the patient's perception of breathlessness. Results from a preliminary study that explored the feasibility of using MEG found a change and decrease in the pattern of alpha wave activity in the parietal–temporal regions when airflow was used during recovery from exercise which could be the mechanism involved in the reduced breathlessness intensity (228). Fear of breathlessness is a significant obstacle to exertion and exercise in people with chronic breathlessness. Therefore if the fan shortens recovery time and gives confidence to patients, enabling them to exercise to higher levels of breathlessness intensity, this would be directly relevant in clinical practice.

Such self –efficacy is an important concept (158), as detailed in chapter 2.2.3, and links to how effectively patients manage difficult symptoms and their quality of life (302, 351). The patient's experience of performance success or failure will likely validate or undermine their capabilities to cope with a given activity. Significant improvements in the CRQ self-mastery of breathlessness domain have resulted from a complex multi-factorial approach to breathlessness management that includes the hand-held fan (9, 132). Recently published feasibility data is also consistent that the hand-held fan is a helpful strategy and a useful component of self-management (311).

The mixed method data similarly identified improved patient confidence and the ability to self-manage breathlessness on a daily basis from hand-held fan use. Only the hand-held fan & usual care group GSES results demonstrated a mean improvement from baseline, 3.1 point. Since breathlessness is a multi-factorial problem any small improvement in the management, such as the addition of an extra intervention, may be sufficient to benefit a patient's psychological and physical function (9).

Likewise, the qualitative data endorse that hand-held fan use improves self-efficacy and confidence to manage symptoms. Key psychological effects were related to the physical activity or routine of something to do, a prop object to hold in the hand and a tangible sensation felt on the operation of a button, as displayed in Table 59. It was perceived as a medical device and considered a valuable extra intervention that was added to the patient's toolbox of coping strategies, as shown in Table 56, 57, and 61. The psychological effects were commonly interlinked to the physical effects. Patients commonly described the cooling sensation from the air, and the belief that the air was being forced or pushed into the lungs as shown in Table 58. These data align with the known potential peripheral source of respiratory sensation; the cooling of the tri-geminal nerve and nasal mucosa which are discussed in more detail in chapter 2.4.2 (26, 222). These views also resonate with prior mixed methods studies which found cold, fresh air an effective and frequently selected option among the self-management strategies in COPD patients (163, 164).

Therefore, the hand-held fan appears to be an intervention of significant value, but given the background of patients' therapeutic nihilism identified in the data, as shown in Table 42, these findings underline the importance of how the clinician recommends and presents the intervention (166). These data add weight to the evidence and support improvement of self-

efficacy and symptom mastery with use of the hand-held fan as part of a complex intervention for breathlessness management (8, 132, 311).

8.3.2 Question two. Does airflow from a hand-held fan or use of the Calming Hand help patients' functional abilities?

The quantitative and qualitative results for general activity contrasted. The mean ISWT distance at day 28 increased by 55.33 metres from baseline for the hand-held fan & usual care arm. This value exceeds the MCID, known as 47.5 metres (352), and suggests a discernible change in exercise capacity and functional ability. However, the qualitative analysis indicated patients felt limited change to exercise capacity and were still reluctant to increase activity, (Table 47), despite confirming the value of the hand-held fan with recovery from exertional breathlessness (Table 60). Better self-management of breathlessness symptoms experienced during normal activities was deemed more relevant, than a change in exercise capacity.

There are several possibilities for the conflicting results. It may reflect limitation from the study design, in that a learning effect was possible as the ISWT was not repeated at baseline, or it is plausible that the patient's exercise performance was influenced by the context. A hospital environment and the presence of a healthcare professional could provide re-assurance that it is safe and not harmful to exercise to maximal capacity. Furthermore, it is feasible that the exercise advice given with the study intervention(s) did not help patients increase activities or add exercise to their daily life. Measurement of daily steps using accelerometry has gained interest over the past few years and would give a measure of the activity patients do in their home setting without the watchful eye of a health care professional (374). Daily step count is also associated with important clinical outcomes in people with COPD such as survival and exacerbations (375, 376) and may prove a useful outcome measure in breathlessness research.

The qualitative data also identified that the hand-held fan was used in a manner consistent with a complex intervention that could potentially increase Life-space, another way of measuring day to day functional capacity. Patients individualised the use to their own personal needs and described how the portable nature of the hand-held fan made it a device suitable to support many functional activities, in particular, outside with gardening, or in the car after shopping (Table 54 and 55). The integration of the hand-held fan as a self-

management strategy into everyday breathless situations suggests that the hand-held fan does support the patient's functional abilities and concurs with the qualitative findings from a recently published mixed method feasibility trial of the hand-held fan and activity (311).

In contrast, to the findings for the hand-held fan it was not possible to confirm similar patient benefits from use of the Calming Hand for exertion-induced breathlessness or any improvement in functional abilities. There were limited evidence available and literature review were only able to identify conference presentation data from a survey of physiotherapists, a proxy view that suggested potential value, as outlined in chapter 2.5.1. The quantitative data did not signal any outcome measures that were likely to reflect worthwhile patient change or benefit from intervention use. Interestingly, the recovery time for the Calming Hand & usual care arm on day 28 was slower; 5.71secs, which represents a 4.1% increase from baseline. It is possible that an instructed sigh could potentially inhibit recovery of both muscle tension and respiratory variability (247), as previously outlined in chapter 2.5.2. These preliminary outcome data therefore suggest that the Calming Hand may be an unsuitable intervention to help speed recovery from exertion induced breathlessness, however, this study was not designed to detect a difference between the groups.

More insights, were provided by the qualitative data. Patients identified their experience of the intervention as *"things already known"* or *"common sense"*, as displayed in Table 63. The intervention were often *"disregarded*" after a preliminary try and patients reported little if any benefit, as seen in Table 62. The qualitative findings consistently suggested that the Calming Hand was not suitable to help with exertional related breathlessness and did not change functional abilities. Therefore, in conclusion, synthesis of quantitative and qualitative findings does not support the clinical use of the Calming Hand for patients experiencing problems with exertional breathlessness.

8.3.3 Question three. Does the use of a hand-held fan or the Calming Hand influence the carer level of burden or ability to cope with the patient's breathlessness problems?

The systematic review of airflow did not identify any studies that investigated the benefits of hand-held fan use in relation to carer burden, or their ability to cope with the patient's breathlessness problems as expected from the review inclusion criteria, and there were also

very little signal from the Calming Hand and Fan Feasibility (CHAFF) quantitative data to suggest any benefit. This result likely reflects too few carer data to capture any change, although it is possible that the carer gained little help from the interventions delivered to the patient during the 28 day study period. Benefit is consistently identified from being listened to and having their experience of living with a breathless person validated (8). Therefore, the interview at follow up may have provided worthwhile improvement to burden and distress if it was perceived as an active intervention, an issue recently identified in the findings of the BIS phase III RCT mixed methods design (325).

However, the qualitative data analysis provided preliminary indication of carer benefit. Carers perceived the hand-held fan as a valuable, extra tool that offered the patient a viable alternative option to depending on their assistance with breathlessness management (Table 61). The importance of the carer role and the 24/7 demands and obligation they felt were a key sub-theme identified in the data analysis, as shown in table 50 and 51. In particular, carers perceived that they were able to leave the patient alone, secure in the knowledge that they had another device to assist independent recovery from breathlessness if needed. This could potentially decrease carer distress and burden and provide incremental benefit to Life-space. These findings support the recent results from the BIS phase III mixed method RCT, carers consistently identified interventions such as the hand-held fan as helpful when delivered as part of a multi-disciplinary complex intervention for breathlessness management (8).

In contrast, none of the carers interviewed suggested any benefit from use of the Calming Hand and in some cases the carer his/herself was considered to be of more value in the management of episodes of breathlessness, as shown in table 50 "*She's my Calming Hand* ".

Therefore, the data synthesis for the interventions suggests that the hand-held fan may offer valuable carer benefit and assistance with breathlessness management, but does not support the Calming Hand as a suitable strategy to help with carer burden or distress.

8.3.4 Question four. What are the most important outcome measures to the patient and what will appropriately reflect any patient benefit from using the hand-held fan or Calming Hand?

A wide range of outcomes were incorporated in the study protocol to assess which may be appropriate for a definitive trial in terms of patient relevance, data completion and sample size required. Given the difficulty of selecting an appropriate tool to accurately reflect worthwhile change in the patients experience of breathlessness it is important that a relevant outcome is identified (274). The data synthesis were unable to identify any outcomes of potential relevance for the Calming Hand but there were three measures which showed potential with regard to possible future primary outcomes for a phase III trial for the hand-held fan. These were the NRS breathlessness intensity recovery rate per minute, the recovery time from exertional breathlessness and the ISWT distance.

Sample size calculations indicated fewest participants in total, (n=28), required for a future trial that measures breathlessness intensity recovery rate per minute data as a primary outcome. In combination with the results for the variability of the measure (a narrow SD at baseline across all four study groups, which suggest patients can accurately pinpoint a difference in breathlessness intensity), the NRS breathlessness recovery rate per minute was judged most likely to reflect benefit from the use of the hand-held fan and deemed an important novel patient outcome worthy of further study. Qualitative data also highlighted the relevance and value of a fast breathlessness intensity recovery time after exertion (Table 60). Therefore recovery time is something which can i) be measured, ii) is important to patients and iii) only needs a small sample size to provide adequate power in a trial.

Improved recovery time helped patients feel more confidence about their ability to self-manage breathlessness symptoms (Table 61), a prominent view that suggests the relevance and importance of a measurement of self-efficacy, or mastery over breathlessness for future studies. Furthermore, the data synthesis reflects recent studies, self-mastery of breathlessness was of considerable value to participants and able to reflect significant improvement when used as a primary study outcome (9, 311).

8.3.5 Question five: Is a phase III RCT to test the effectiveness of the hand-held fan and or the Calming Hand for breathlessness in people with chronic breathlessness feasible?

The good recruitment, lack of attrition, minimal missing data and acceptability of the protocol design and outcome measures to the patients and carers suggest that a phase III RCT is feasible to test the effectiveness of the hand-held fan or Calming Hand in people with chronic breathlessness. Of the two interventions tested the mixed method synthesis suggests that the hand-held fan is more suitable for use with exertional breathlessness and likely to reflect worthwhile benefit in recovery time and patient confidence to self-manage functional activities.

The mixed method results confirmed the suitability and acceptability of the ISWT as test of functional capacity and supports the value of using this exercise test to induce maximal exertional breathlessness in patients with IPF, COPD or chronic asthma. This is consistent with previous studies that found the ISWT a reliable, safe and reproducible method to measure exercise tolerance in patients with COPD, cancer and chronic heart disease (294, 297, 301). The qualitative data indicated that patients welcomed a trial focused on breathlessness symptoms rather than the disease (Table 44), a theme mirrored by a recent feasibility study of the fan and activity (311)

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
1. Does airflow from a hand-held fan or use of the Calming Hand provide benefit for breathlessness intensity when used for exertion-induced breathlessness?	**Breathlessness intensity** Fan: Exertion - No clear evidence General activity - Probable benefit At rest - Clear indication of benefit improved breathlessness using a "before and after" cohort design in a mixed population of patients with mild or normoxaemia with a significant benefit SMD -8.5, 95% CI -12.9 to -4.1, p<0.0001 Calming Hand: No evidence available	**Breathlessness intensity** Fan: Yes, improvement in NRS exertional breathlessness intensity recovery rate per minute. 0.64 faster per minute than baseline, 33.9% change from baseline Variability of the measure; a narrow SD at baseline across all four study arms potential suitability to accurately pinpoint breathlessness intensity change Calming Hand: Some improvement 0.41 faster per minute than baseline, 20.5% change from baseline.	**Breathlessness intensity** Fan: Yes, all patients identified benefit Calming Hand: No, only one patient identified benefit, but reported fan quicker recovery	**Hand-held fan** These data indicate worthwhile patient benefit to exertional breathlessness intensity, recovery time and improved self –efficacy to manage breathlessness with functional activities. The findings support the use of the fan with exercise and activity and as part of a complex intervention for breathlessness management

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
1. Does airflow from a hand-held fan or use of the Calming Hand provide benefit for breathlessness when used for exertion-induced breathlessness	**Recovery time** Calming Hand: No evidence available Fan: No clear evidence available	**Recovery time** Fan: Yes, faster breathlessness recovery time: -33.5 secs, -20.4% improvement from baseline Calming Hand: No, slower breathlessness recovery time: 5.71secs, 4.1% worse than baseline	**Recovery time** Fan: Yes, speeds up breathlessness recovery time Calming Hand: No change in breathlessness recovery time	**Calming Hand** The data does not indicate worthwhile patient benefit to exertional breathlessness intensity, recovery time or improved self –efficacy to manage breathlessness with functional activities. The findings suggest that the Calming hand is not a suitable intervention to help with exercise and activity related breathlessness as part of a complex intervention for breathlessness management
	Symptom mastery, or patient self-efficacy Fan: Limited data Calming Hand: No evidence available	**Symptom mastery, or patient self-efficacy** Fan: Yes, improvement GSES 3.1 point increase, 10.8% difference from baseline Calming Hand: No clear signal from data, GSES 0.1point little change	**Symptom mastery, or patient self-efficacy** Fan: Yes, contributes to self-efficacy and increased confidence with symptom control. May help increase Life-space - portable and used in car Calming Hand: No, things already known or tried in the past, common sense	

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
2. Does airflow from a hand-held fan or use of the Calming Hand help patients' functional abilities?	Fan: Little evidence available Calming Hand: No evidence available	Fan: Yes, ISWT distance increased 55.33 metres from baseline, exceeds the MCID, 47.5 metres 43.7% improvement from baseline, clear signal of benefit from data Calming Hand: Some improvement ISWT distance increased 18.57 metres from baseline 15.3% improvement from baseline no clear signal of benefit from data	Fan: Yes, helped maintain general activities and also used as a complex intervention, but no increase in exercise capacity Calming Hand: No patients disregarded the intervention and it was not used to help support functional abilities	**Hand-held fan** These data indicate that the hand-held fan helps to support the patient's functional abilities and the intervention was integrated into everyday use, but patients felt little change to exercise capacity. **Calming Hand** These data indicate that the Calming Hand is not a suitable intervention to help with functional ability or exercise capacity

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
3. Does the use of a hand-held fan or the Calming Hand influence the carer level of burden or ability to cope with the patient's breathlessness problems?	Fan: No evidence available Calming Hand: No evidence available	Fan: No indication from data Calming Hand: No indication from data	Fan: Yes, another extra valuable tool that can replace the role of the carer and help the patient independently manage breathlessness Calming Hand: No, carer more important and preferred help and support with breathlessness management	**Hand-held fan** These data indicate that the hand-held fan was a valuable extra intervention that helped carer burden. It was a suitable replacement for the carer role and supported the patient's independent management of breathlessness **Calming Hand** These data indicate that the Calming Hand is not suitable to help with carer burden or their ability to manage a breathless patient

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
4. What are the most important outcome measures to the patient and what will appropriately reflect any patient benefit from using the hand-held fan or Calming Hand?	Fan: Limited data, ISWT, recovery time Calming Hand: No evidence available	Fan: NRS breathlessness intensity recovery rate per minute, recovery time from ISWT and ISWT distance Calming Hand: No clear signal from results	Fan: Recovery time, symptom-mastery and coping with breathlessness, self-efficacy, life-space Calming Hand: No indication from data	**Hand-held fan** These data indicate that the breathlessness intensity recovery rate per minute, recovery time from ISWT and ISWT distance are able to reflect worthwhile patient benefit from use of the fan Patients consider symptom-mastery or the ability to cope with breathlessness, self-efficacy and life-space important measures **Calming Hand** These data are unable to confirm suitable outcome measures likely to reflect worthwhile benefit from use of the Calming Hand

Table 64 Main findings for the research questions

RESEARCH QUESTIONS	FINDINGS			
	Systematic Lit. Review	**Calming Hand and Fan Feasibility study: quantitative results**	**Calming Hand and Fan Feasibility study: qualitative results**	**Summary synthesis**
5. Is a phase III RCT to test the effectiveness of the hand-held fan and or the Calming Hand for breathlessness in people with chronic breathlessness feasible?	Not applicable	A phase III is feasible and acceptable; No attrition and minimal missing data for all patient reported outcome measures. ISWT safe and reproducible Fan: Feasibility data signalled worthwhile patient benefits for exertional breathlessness Calming Hand: Feasibility data did not signal any worthwhile patient benefits for exertional breathlessness	A phase III RCT is feasible, acceptable design and outcome measures, patients appreciated a trial focused on breathlessness symptoms Fan: Feasible patients identified a valuable intervention with discernible benefits Calming Hand: Feasible but not appropriate intervention was disregarded and not used. Patients considered it common sense and reported little benefit	**Hand-held fan** A phase III RCT to test the effectiveness of the hand-held fan for breathlessness in people with chronic breathlessness is feasible and acceptable but the value of the information needs to be considered given the weight of the data available. **Calming Hand** A phase III RCT to test the effectiveness of the Calming Hand in people with chronic breathlessness is feasible but not appropriate as the data suggests little patient benefit and an intervention that was disregarded

8.4 Strengths

These data confirm the value of a mixed method study design for the development and evaluation of a complex intervention for people with chronic breathlessness (281) and highlight the challenges of suitable outcome measure selection in palliative care research (339, 377). There were limited signal from most of the patient reported outcome measures in keeping with the feasibility design, therefore the strength of the qualitative findings were crucial in the interpretation of the quantitative results. This permitted insight of the patient's experience of the interventions and provided a clear understanding of which attributes were important to benefit the self-management of exertional breathlessness. Conducting the interviews at the end of the study prevented the risk that the interview itself was therapeutic, which could have influenced any benefit found from the interventions. The selection of a factorial design allowed the testing of two interventions and patients were able to compare the differences between the Calming Hand and the hand-held fan. Triangulation of the methods and the assessment of consistent or convergent results was a strength of the mixed method design. This helped to increase confidence in the conclusions reached for outcome measures identified of potential important patient value and answer the research questions with regard to the effectiveness of the two interventions for breathlessness management in people with chronic breathlessness.

8.5 Limitations

It is acknowledged that there are several sources of bias associated with this mixed method study design that could limit the data synthesis and interpretation. The feasibility findings for the hand-held fan and Calming Hand relate to preliminary data in people with chronic breathlessness who have a diagnosis of COPD, IPF or asthma only. Reporting bias may be introduced from the methods, especially in light of myself, the researcher being the therapist, who provided the study interventions and the data collection for all of the outcome measurements, although any bias introduced in this way would be consistent across all four arms of the study. More importantly, this was a feasibility study therefore, the main aim was to assess the variability of change around the outcome measures to inform a phase III definitive RCT, rather than test the effectiveness of the two interventions.

The semi-structured interview is a subjective method open to bias, based on the social interaction between the researcher and participant. It relies on the researcher-led agenda, yet equally relies on what was said in answer by the participant (312, 324). It is possible that the patients and carers may have tried to inform what they think the researcher wanted to hear about the interventions in an attempt to please, or answer in a socially acceptable manner. Therefore, it is not clear if the views expressed at interview are necessarily representative, or indeed if other people with similar chronic breathlessness problems would experience worthwhile improvement, or no change from use of these interventions.

8.6 Implications for research and clinical practice

The data synthesis for the hand-held fan indicates a device ideally suited to speed recovery from the intensity of exertional breathlessness and help self-management during functional activities, although patients still felt reluctant to increase exercise capacity. These findings are relevant to clinical practice. Since the unpleasantness of breathlessness acts as a disincentive for to people to continue with exercise (86), as already outlined in chapter 2.2.2, these results suggest that clinicians and researchers should consider the use of the hand-held fan with a formal pulmonary rehabilitation exercise programme, rather than with exercise advice only. This could help to endorse the benefits of a faster recovery with exercise and promotes the knowledge of a tool suitable to use with activity related breathlessness.

The hand-held fan also represents an intervention that could tackle avoidance of breathlessness and help maintain pacing of everyday activities around the home. Both were key strategies for adaptation to breathlessness identified in the qualitative findings, as highlighted in Table 48 and Table 49. Avoidance deconditions a patient and they experience increased breathlessness perpetuated from a vicious cycle of doing less and less, as previously discussed in chapter 1.8.1. It therefore, may be an appropriate intervention to help break the deconditioning spiral if introduced to the patient earlier during the disease trajectory. Any reduction in the length of time a patient feels breathless after exertion could improve self-efficacy, confidence and potentially Life-space. This encourages the patient to continue activities, safe in the knowledge that there is a device to hand, which can quickly resolve their symptoms. This was reflected in the qualitative data findings, as displayed in Table 53 and 59. Therefore these findings endorse early clinical introduction of the hand-held

fan in any breathlessness management plan to negate the possibility of patients adopting a strategy of breathlessness avoidance.

The lack of signal from the synthesis of data for the Calming Hand suggests that exercise and functional activity are not suitable contexts for intervention use. A proposed Breathing, Thinking, Function classification for different non-pharmacological interventions, based on how each one affects breathlessness sensation, (168) indicates that the Calming Hand would be grouped as a "thinking" intervention. This type of self-management relaxation strategy targets the central perception of breathlessness, rather than the neuro-physiological central and peripheral pathways that are thought to operate with hand-held fan use.

Data synthesis also identifies the timing of a uni-dimensional breathlessness measure as an important future consideration. Prior study confirms that breathlessness "right now" and "average" are different constructs (288). This implicates a measurement of breathlessness intensity "right now" as opposed to "average over last 24 hours" for research projects that focus on exercise or activity related breathlessness.

8.1 Overall summary of thesis

The overall aim of this thesis was to investigate the effectiveness of two non-pharmacological interventions, which are currently used in clinical practice (cool facial airflow from the hand-held fan, and the Calming Hand) with regard to breathlessness management in people with chronic breathlessness.

The thesis study data provides initial evidence that the hand-held fan is an effective non-pharmacological intervention to relieve breathlessness intensity and support self-management of exertional breathlessness in people with chronic breathlessness in a variety of situations.

Airflow SR and meta-analysis data demonstrated significant relief of breathlessness intensity from hand-held fan use at rest in a mixed population of patients with mild or normoxaemia, Standardised Mean Difference [SMD] -8.5, 95% CI -12.9 to -4.1, $p<0.0001$. Similarly, synthesis of the feasibility data suggest worthwhile relief of breathlessness intensity when cool airflow from the hand-held fan is used with everyday activities or exertion-induced exercise in patients with COPD, IPF and asthma. Possible benefits are a faster recovery time

from exertion-induced breathlessness, which helps give patients a sense of control and self-mastery over their breathlessness and improves their confidence to perform functional duties.

Patients identified the hand-held fan as a helpful "medical" device that played a useful role as part of a complex intervention for breathlessness. The intervention was individualised to personal needs and integrated into everyday use. At rest, with activity or exercise, during the night, or even while eating were all identified as times when the device had helped to relieve breathlessness.

Conversely, there was little indication from quantitative or qualitative data to signal worthwhile benefit from the Calming Hand. A slower time to recovery from exertional breathlessness indicate that exercise and activity are not appropriate contexts for intervention use. Therefore, these data do not support the Calming Hand as an effective non-pharmacological intervention for the self-management of exertional breathlessness in people with chronic breathlessness.

The RCT was feasible in terms of recruitment, data completion and acceptable to patients and carers. The best primary outcome measures were judged to be recovery rate or recovery time from exertion-induced breathlessness. These are novel outcomes that may potentially reflect important patient improvements with exercise. Given the findings for the two interventions a future definitive phase III RCT would assess the benefits of the hand-held fan with exertion related breathlessness.

Key implications for research and clinical practice are early introduction of the hand-held fan in any breathlessness management plan, and use of the intervention with pulmonary rehabilitation programmes to help prevent patient fear of exertional breathlessness and provide knowledge of a device that is able to support a speedy recovery and promote self-mastery of breathlessness.

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10 Appendices

Appendix 1 Characteristics of excluded studies

Study	Reason
Ahmedzai et al (2004)	No repeat measures
Baltzan et al (2000)	No baseline measures
Bruera et al (1992)	Participants hypoxic
Bruera et al (1993)	Insufficient data reported, hypoxaemia
Breura et al (2003)	No repeated measures
Chua et al (1996)	No baseline measures
Currow et al (2009)	Cohort, no airflow arm
Davidson et al (1988)	No baseline measures
Dean et al (1992)	No repeat measures
Derry et al (2006)	No details on breathlessness scores
Dyer et al (2012)	No airflow
Eaton et al (2002)	No repeat measures
Emtner et al (2003)	No repeat measures
Evans et al (1986)	No follow up measures
Garrod et al (1999)	No follow up measures
Garrod et al (2000)	Participants hypoxic
Haidl et al (2003)	No airflow for control group
Killen & Corris (2000)	No repeat measures
Knebel et al (2000)	No repeat measures
Koskela et al (1988)	Sub-zero temperature -20°C

Lacasse et al (2005)	Participants hypoxic
Laude et al (2006)	No repeat measures
Leach et al (1992)	No repeat measures
Lewis et al (2003)	No repeat measures
Light et al (1989)	No repeat measures
Liss et al (1988)	Hypoxic
Maltais et al (2001)	No repeat measures
Marques-Magallanes (1988)	Hypoxic
McKeon et al (1988)	No repeat measures
Meecham Jones et al (1995)	No repeat measures
Moore et al (1992)	No baseline or repeat measures
Moore et al (2009)	Participants hypoxic
Nandi et al (2003)	No repeat measures
Nonoyama (2007)	No repeat measures
O'Driscoll et al (2011)	No repeat measures
Ozalevli et al (2007)	Room air, but not airflow
Quantrill et al (2007)	No repeat measures
Restrick et al (1992)	No repeat measures
Rooyackers et al (1997)	No airflow
Russell et al (1999)	No repeat measures
Sandland et al (2008)	Participants hypoxic
Sharma et al (2011)	Opinion piece
Somfay et al (2001)	No repeat measures

Spence et al, (1993)	Sub-zero temperature
Stevenson et al (2004)	No repeat measures
Swinburn et al (1991)	Participants hypoxic
Woodcock et al (1981)	No repeat measures

Appendix 2 References to excluded studies

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Appendix 3 Full Search strategy

The full search strategy was as follows:

1. *Exploded MeSH* lung diseases obstructive
2. *Exploded MeSH* pulmonary disease, chronic obstructive
3. COPD *key word*
4. *Exploded MeSH* neoplasms
5. *Exploded MeSH* lung diseases, interstitial
6. 1 OR 2 OR 3 OR 4 OR 5
7. *Exploded MeSH* heart failure, congestive
8. MotorADJ1neuroneADJ1disease *text word*
9. *Exploded* amyotrophic lateral sclerosis
10. Kyphoscoliosis *text word*
11. *Exploded MeSH* pulmonary fibrosis
12. 7 OR 8 OR 9 OR 10 OR 11 or / 1-5
13. Hand-held fan OR fan *text word*
14. Medical ADJ1 air *text word*
15. *Exploded MeSH* oxygen inhalation therapy
16. AirADJ1flow *text word*
17. Facial OR nasal AND cold OR cooling *text word*
18. 13 OR 14 OR 15 OR 16 OR 17
19. *Exploded MeSH* Dyspnea

20. dyspnoea *key word*

21. Difficulty OR short ADJ1 breath$ *text word*

22. *Exploded MeSH* Exercise

23. *Exploded MeSH* "Activities of Daily Living"

24. 19 OR 20 OR 21 OR 22 OR 23

25. 12 AND 18 AND 24

Appendix 4 Case Report Form

CHAFF study

(Initials and Study Number)

PATIENT TRIAL ID	
DATE OF INFORMED CONSENT	
PLANNED END DATE	
STUDY ARM	

Data entry reminder

- □ Check accuracy when entering data.
- □ Make sure your writing is legible.
- □ Always write in black.
- □ All fields must be completed.
- □ Not known (NK) only when all avenues are exhausted and need to explain why.
- □ Not done (ND) need to explain why
- □ Put a single line through any mistake
- □ Make the correct value clear
- □ Never occlude the original entry.
- □ Initial and date any alteration even if completing blank fields retrospectively.

Case notes reminder

- □ Stick study label on inside front cover of case notes.
- □ File patient information sheet, consent form, GP letter, copy of inclusion/exclusion Criteria in plastic wallet with GCP sticker in case notes.
- □ Record patient visit/telephone contacts in case notes.

Minimum details to record are:

- Clearly written; date, brief study title/acronym and visit number.
- Date patient given patient information sheet (PIS)
- Date of consent
- Date of screening
- Medical history, concomitant diseases and medication including study medication, and any changes in concomitant diseases and medication at subsequent visits.
- Anything which is relevant to the ongoing care of the subject;
  - Relevant results and study medic's assessment of these results.
  - Brief description of any AEs with start & stop times/dates and any significant test results or a medical summary of events if more appropriate.
- Any other relevant details.

ELIGIBILITY CHECKLIST

ALL INCLUSION CRITERIA MUST BE ANSWERED "YES" FOR PATIENT TO BE SUITABLE FOR TRIAL ENTRY:

Tick boxes to confirm

Over 18 Yes ☐ No ☐

Able to provide written or verbal consent to take part in the study Yes ☐ No ☐

Level 3 + Medical Research Council (MRC) Dyspnoea scale Yes ☐ No ☐

Living in the community with or without a carer Yes ☐ No ☐

Intractable breathlessness from any cause Yes ☐ No ☐

Willingness to engage with breathlessness training and study measures Yes ☐ No ☐

Have not used the hand held fan or "Calming hand" for 2 weeks Yes ☐ No ☐

Medical Research Council (MRC) Dyspnoea Scale

- ○ 0 = Not troubled by breathlessness except on strenuous exercise
- ○ 1 = Short of breath when hurrying or walking up a slight hill
- ○ 2 = Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace
- ○ 3 = Stops for breath after about 100 m or after a few minutes on the level
- ○ 4 = Too breathless to leave the house, or breathless when dressing or undressing

ALL EXCLUSION CRITERIA MUST BE ANSWERED "NO" FOR PATIENT TO BE SUITABLE FOR TRIAL ENTRY: Tick boxes to confirm NONE apply

Cognitively impaired and unable to understand the study Yes ☐ No ☐

Trigeminal nerve damage/disease Yes ☐ No ☐

Too breathless to participate in study in the opinion of investigator and/or patient

Yes ☐ No ☐

HAVE ALL INCLUSION AND EXCLUSION CRITERIA BEEN SATISFIED?

Yes ☐ No ☐

HAS THE PATIENT READ AND UNDERSTOOD THE PIS? Yes ☐ No ☐

HAS THE PATIENT SIGNED AND DATED THE CONSENT FORM?

Yes ☐ No ☐

HAS THE PATIENT PROVIDED PERMISSION TO APPROACH CARER?

Yes ☐ No ☐

HAS THE CARER READ AND UNDERSTOOD THE CIS? Yes ☐ No ☐

HAS THE CARER SIGNED AND DATED THE CONSENT FORM?

Yes ☐ No ☐

<u>Decision:</u> ☐ Inclusion ☐ Exclusion

If excluded, specify reason ……

Name	Signature	Date

Section 1: Baseline Patient demographic data

- Age, sex, post-code
- Live in carer (relationship)
- Primary aetiology(ies)
- Hospital admissions (last 6/12)
- Medication, known allergies
- Home oxygen therapy
- Use of mobility aids
- Co-morbidities (grouped as for Charlson index)
- General question: "when you move about, what stops you? Breathlessness or leg weakness?"
- The Medical Research Council of Great Britain Dyspnoea (MRC) Scale (forms part of eligibility criteria)

Section 2: Baseline Patient assessment and data collection tools

- Intensity of breathlessness (0-10 numerical rating scale)
- Unpleasantness of breathlessness (0-10 numerical rating scale)
- Distress of breathlessness (0-10 numerical rating scale)
- Life-Space Assessment
- The General Self-efficacy Scale
- Patient Incremental Shuttle Walk Test (ISWT) measurements
- Intervention assessment

Section 3: Day One Patient ISWT with intervention use

- baseline (before exercise)
- maximal (after exercise)
- following 10 minutes of recovery with intervention(s) use
- Pre-SWT Clinical examination: SpO_2 HR
- Incremental Shuttle Walk Test (ISWT)
- Intensity of breathlessness (0-10 numerical rating scale)

Section 4: Day 14 Patient telephone assessment

- Intensity of breathlessness (0-10 numerical rating scale)
- Distress of breathlessness (0-10 numerical rating scale)
- Unpleasantness of breathlessness (0-10 numerical rating scale)
- Telephone assessment

Section 5: Day 28 Patient assessment and data collection tools

- Intensity of breathlessness (0-10 numerical rating scale)
- Unpleasantness of breathlessness (0-10 numerical rating scale)
- Distress of breathlessness (0-10 numerical rating scale)
- Life-Space Assessment over past 28 days
- The General Self-efficacy Scale
- Completion assessment

Section 6: Day 28 Patient ISWT assessment

- Pre-SWT Clinical examination: SpO_2 HR Ausc
- baseline (before exercise)
- maximal (after exercise)
- following 10 minutes of recovery with intervention(s) use
- Incremental Shuttle Walk Test (ISWT)
- Intensity of breathlessness (0-10 numerical rating scale)

Section 7: Baseline Carer assessment data collection tools

- Zarit care-giver burden short-form questionnaire
- The General Self-efficacy Scale

Section 8: Day 28 Carer assessment data collection tools

- Zarit care-giver burden short-form questionnaire
- The General Self-efficacy Scale

Section 9: Day 28 CRF completion form

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Section 1

Baseline Patient Demographic

Data collection tools

Completion of this form: Initials_____ Date__/___/____

DEMOGRAPHIC DETAILS:

Date of birth __/___/____

Age at screening ☐

Gender □ Male □ Female

Post code ☐

Live in carer (yes/no) □ Yes □ No

If yes, what relationship?

Spouse/partner□ Yes □ No

Parent □ Yes □ No

Child □ Yes □ No

Sibling □ Yes □ No

Friend □ Yes □ No

Other (specify) _____

MEDICAL REVIEW: Primary Aetiologies

1._____ **2.**_____

3._____ **4.**_____

Number of hospital admissions in the last 6 months? _____

Current medication:

Medication	Indication	Dose

Known drug insensitivity and allergy:

Home oxygen & mobility:

Home oxygen therapy? □ Yes □ No

Use of mobility aids? □Yes □ No

If yes what aids? 1._____

2._____

3._____

Charlson Comorbidity Index

Assigned weights for diseases	Conditions
1	Myocardial infarct Congestive cardiac failure Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS

Assign a number for each condition and the total equals the score.

SCORE_____

General question:

When you move about, what stops you?

Breathlessness □ Yes □ No

Leg weakness □ Yes □ No

Other – specify 1._____

2. _____

3._____

4. _____

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Section 2

Baseline Patient Assessment and data collection tools

NRS Breathlessness Scores

Please give the following a score from 0-10 by **circling the number** that best describes how you feel.

1. **How bad has your breathlessness felt *on average* over the past 24 hours?**

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

2. **What is *the worst* that your breathlessness has been over the past 24 hours?**

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

3. **How *unpleasant* has your breathlessness been *on average* over the past 24 hours?**

Not unpleasant at all	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant breathlessness

4. **How much *distress* has your breathlessness caused you *on average* over the past 24 hours?**

No distress at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable

5. What is *the* worst distress that your breathlessness has caused you over the past 24 hours?

No distress at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable

Life-space Assessment

Life-Space Validation Protocol: Example of scoring of the Life-Space Assessment. The subject travelled to all levels (levels 1-4) except for out of town (level5); travelled daily to levels 1 and 2, and travelled 1 to 3 times each week to levels 3 and 4; uses a cane at all times and requires assistance with driving.

Name: _____							Date: _____	
These questions refer to your activities just within *'the past month':*								
LIFE-SPACE LEVEL			FREQUENCY				INDEPENDENCE	SCORE
'During the past four weeks have you been to':			How often did you get there?				Did you use aids or equipment? Did you need help from another person?	Level X Frequency X Independence
Life-space Level 1... Other rooms of your home besides the room where you sleep?	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	
	1	0	1	2	3	4		
Score	___ X					_____ X		_____ _ *Level 1 Score*
Life-Space Level 2… An area outside your home such as your porch, deck or patio, hallway (of an apartment	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or	

building) or garage, in your own yard or driveway?	2	0	1	2	3	4	personal assistance	_____ _ *Level 2 Score*
Score	_____ X					_____ X		
Life-Space Level 3… Places in your neighbourhood, other than your own yard or apartment building?	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ _ *Level 3 Score*
	3	0	1	2	3	4		
Score	____ X					_____ X		
Life-Space Level 4…. *Places outside your neighbourhood, but within your town?*	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ _ *Level 4 Score*
	4	0	1	2	3	4		
Score	_____ X					_____ X		
Life-Space Level 5…. Places outside your town?	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ _ *Level 5 Score*
	5	0	1	2	3	4		
Score	_____ X					_____ X		

TOTAL SCORE (ADD)	_____ _ *Sum of Levels*

The General Self-efficacy Scale

- 1 = Not at all true
- 2 = Hardly true
- 3 = Moderately true
- 4 = Exactly true

	1 Not at all true	2 Hardly true	3 Moderately true	4 Exactly true
I can always manage to solve difficult problems if I try hard enough.				
If someone opposes me, I can find the means and ways to get what I want.				
It is easy for me to stick to my aims and accomplish my goals.				
I am confident that I could deal efficiently with unexpected events.				
Thanks to my resourcefulness, I know how to handle unforeseen situations.				
I can solve most problems if I invest the necessary effort.				
I can remain calm when facing difficulties because I can rely on my coping abilities.				
When I am confronted with a problem, I can usually find several solutions.				
If I am in trouble, I can usually think of a solution.				
I can usually handle whatever comes my way.				

Baseline Incremental Shuttle Walk Test (ISWT)

Pre-SWT Clinical examination/signs

Sp O_2: _____

HR: _____

Ausc: _____

Time of test: _____

Distance walked: _____

Number of shuttles: _____

Level / Speed of walking achieved: _____

Time (start to maximal breathlessness tolerance):_____

Mobility aids required: _____

Termination Criteria: _____

1. Any angina symptoms
2. Too breathless to continue – maximal perceived breathlessness
3. Leg pain limiting further exercise
4. Feeling faint or dizzy
5. Failure to meet the speed requirements of the test – patient more than half a metre from the cone when the bleep sounds
6. Other reason, please specify

Baseline ISWT NRS Breathlessness Scores

Please give the following a score from 0-10 by circling the number that best describes how you feel.

How bad is your breathlessness right now?

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

Baseline (before exercise), Maximal (after exercise) and following up to 10 minutes use of intervention(s)

Symptoms Breathlessness score	Baseline *(T0)*	Maximal *(Tmax)*	Recovery from exercise to baseline									
			(T1)	*(T2)*	*(T3)*	*(T4)*	*(T5)*	*(T6)*	*(T7)*	*(T8)*	*(T9)*	*(T10)*
NRS intensity												

Intervention assessment

Was the study intervention(s) given?

	Tick the appropriate box	If yes, specify type: Fan, Calming Hand, Usual Care If not, specify reason: e.g. unable to tolerate
Yes		
No		

Patient's status: ☐ On-going ☐ Withdrawn

If withdrawn, please specify reason: …….

Have there been any protocol deviations or violations?

If so, please specify and notify R&D monitor:

……

Completed by:

Name	**Signature**	**Date**

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Section 3

Day One Patient Incremental Shuttle Walk Test

WITH INTERVENTION(S) OPTIONAL

- **Baseline (before exercise)**
- **Maximal (after exercise)**
- **Following up to 10 minutes use of intervention(s)**

Day One Incremental Shuttle Walk Test (ISWT) with intervention use

Pre-SWT Clinical examination/signs

Sp O_2: _____

HR: _____

Ausc: _____

Time of test: _____

Distance walked: _____

Number of shuttles: _____

Level / Speed of walking achieved: _____

Time (start to maximal breathlessness tolerance):_____

Mobility aids required: _____

Termination Criteria: _____

1. Any angina symptoms
2. Too breathless to continue – maximal perceived breathlessness
3. Leg pain limiting further exercise
4. Feeling faint or dizzy
5. Failure to meet the speed requirements of the test – patient more than half a metre from the cone when the bleep sounds
6. Other reason, please specify

Day One ISWT NRS Breathlessness Scores

Please give the following a score from 0-10 by circling the number that best describes how you feel.

How bad is your breathlessness right now?

Not breathless at all

0	1	2	3	4	5	6	7	8	9	10

The worst imaginable breathlessness

Baseline (before exercise), Maximal (after exercise) and following up to 10 minutes use of intervention(s)

Symptoms Breathlessness score	Baseline (T0)	Maximal (Tmax)	Recovery from exercise to baseline									
			(T1)	(T2)	(T3)	(T4)	(T5)	(T6)	(T7)	(T8)	(T9)	(T10)
NRS intensity												

Section 4

Day 14 Patient Telephone Assessment

NRS Breathlessness Scores

Please give the following a score from 0-10 by **circling the number** that best describes how you feel.

1. How bad is your breathlessness right now?

Not breathless at all	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	The worst imaginable breathlessness

2. How much distress is your breathlessness causing you right now?

No distress at all	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	The worst imaginable

3. How *unpleasant* has your breathlessness been *on average* over the past 24 hours?

Not unpleasant at all	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	The most unpleasant breathlessness

Events since Day One

Telephone Assessment

Date of telephone call:

HAS THE PATIENT CONFIRMED WILLINGNESS TO CONTINUE IN THE STUDY AND HAS THIS BEEN

DOCUMENTED IN THE PATIENTS CASENOTES? Yes ☐ No ☐

Events since Day One

Any health problems or changes in current diseases since Day One visit

Additional treatment and changes to medication since Day One visit

Adverse events since Day One visit. AE form has to be completed for each AE. The form is provided by R&D.

Serious adverse events since previous visit. The Chief/Principal Investigator must report an SAE that is both related to the study treatment and unexpected for the study treatment to the Ethics Committee and R&D (as sponsor) within 15 days of the investigator learning of the event, using the NRES report form available from:

http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

Section 5

Day 28 Patient Assessment and data collection tools

NRS Breathlessness Scores

Please give the following a score from 0-10 by **circling the number** that best describes how you feel.

How bad has your breathlessness felt *on average* over the past 24 hours?

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

What is *the worst* that your breathlessness has been over the past 24 hours?

Not breathless at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable breathlessness

How *unpleasant* has your breathlessness been *on average* over the past 24 hours?

Not unpleasant at all	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant breathlessness

How much *distress* has your breathlessness caused you *on average* over the past 24 hours?

No distress at all	0	1	2	3	4	5	6	7	8	9	10	The worst imaginable

What is *the* worst distress that your breathlessness has caused you over the past 24 hours?

No distress at all

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

The worst imaginable

Life-space Assessment

Life-Space Validation Protocol: Example of scoring of the Life-Space Assessment. The subject travelled to all levels (levels 1-4) except for out of town (level5); travelled daily to levels 1 and 2, and travelled 1 to 3 times each week to levels 3 and 4; uses a cane at all times and requires assistance with driving.

<table>
<tr><td colspan="7">Name: _____</td><td colspan="3">Date: _____</td></tr>
<tr><td colspan="10">These questions refer to your activities just within ‘the past month’:</td></tr>
<tr><td colspan="2">LIFE-SPACE LEVEL</td><td colspan="4">FREQUENCY</td><td colspan="2">INDEPENDENCE</td><td>SCORE</td></tr>
<tr><td colspan="2">‘During the past four weeks have you been to’:</td><td colspan="4">How often did you get there?</td><td colspan="2">Did you use aids or equipment?
Did you need help from another person?</td><td>Level
X
Frequency
X
Independence</td></tr>
<tr><td rowspan="2">Life-space Level 1...
Other rooms of your home besides the room where you sleep?</td><td>Yes</td><td>No</td><td>Less than 1/week</td><td>1-3 times/ week</td><td>4-6 time/ week</td><td>Daily</td><td colspan="2" rowspan="2">1 = Personal assistance
1.5 = Equipment only
2 = No equipment or personal assistance</td><td rowspan="2"></td></tr>
<tr><td>1</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>Score</td><td colspan="6">___ X _____ X</td><td colspan="2">_____
Level 1 Score</td></tr>
</table>

Life-Space Level 2… An area outside your home such as your porch, deck or patio, hallway (of an apartment	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or	

building) or garage, in your own yard or driveway?	2	0	1	2	3	4	personal assistance	_____ *Level 2 Score*
Score	_____ X					_____	X	
Life-Space Level 3… Places in your neighbourhood, other than your own yard or apartment building?	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ *Level 3 Score*
	3	0	1	2	3	4		
Score	____ X					_____	X	
Life-Space Level 4…. *Places outside your neighbourhood, but within your town?*	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ *Level 4 Score*
	4	0	1	2	3	4		
Score	_____ X					_____	X	
Life-Space Level 5…. Places outside your town?	Yes	No	Less than 1/week	1-3 times/ week	4-6 time/ week	Daily	1 = Personal assistance 1.5 = Equipment only 2 = No equipment or personal assistance	_____ *Level 5 Score*
	5	0	1	2	3	4		
Score	_____ X					_____	X	
TOTAL SCORE (ADD)								_____ *Sum of Levels*

The General Self-efficacy Scale

- 1 = Not at all true
- 2 = Hardly true
- 3 = Moderately true
- 4 = Exactly true

	1 Not at all true	2 Hardly true	3 Moderately true	4 Exactly true
I can always manage to solve difficult problems if I try hard enough.				
If someone opposes me, I can find the means and ways to get what I want.				
It is easy for me to stick to my aims and accomplish my goals.				
I am confident that I could deal efficiently with unexpected events.				
Thanks to my resourcefulness, I know how to handle unforeseen situations.				
I can solve most problems if I invest the necessary effort.				
I can remain calm when facing difficulties because I can rely on my coping abilities.				
When I am confronted with a problem, I can usually find several solutions.				
If I am in trouble, I can usually think of a solution.				
I can usually handle whatever comes my way.				

COMPLETION ASSESSMENT

Date of last visit:

Events since Day 14

Any health problems or changes in current diseases since Day 14 telephone call

Additional treatment and changes to medication since Day 14 telephone call

Adverse events since Day 14 telephone call

AE form has to be completed for each AE. The form is provided by R&D.

Serious adverse events since previous visit. The Chief/Principal Investigator must report an SAE that is both related to the study treatment and unexpected for the study treatment to the

Ethics Committee and R&D (as sponsor) within 15 days of the investigator learning of the event, using the NRES report form available from:

http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

Have there been any protocol deviations or violations?

If so, please specify:

……

Completed by:

Name	**Signature**	**Date**

Section 6

Day 28 Patient Incremental Shuttle Walk Test (ISWT)

- **Baseline (before exercise)**
- **Maximal (after exercise)**
- **Following up to 10 minutes use of intervention(s)**

Day 28 Incremental Shuttle Walk Test (ISWT)

Pre-SWT Clinical examination/signs

Sp O_2: _____

HR: _____

Ausc: _____

Time of test: _____

Distance walked: _____

Number of shuttles: _____

Level / Speed of walking achieved: _____

Time (start to maximal breathlessness tolerance):_____

Mobility aids required: _____

Termination Criteria: _____

1. Any angina symptoms
2. Too breathless to continue – maximal perceived breathlessness
3. Leg pain limiting further exercise
4. Feeling faint or dizzy
5. Failure to meet the speed requirements of the test – patient more than half a metre from the cone when the bleep sounds
6. Other reason, please specify

Day 28 NRS Breathlessness Scores

Please give the following a score from 0-10 by <u>circling the number</u> that best describes how you feel.

How bad is your breathlessness right now?

Not breathless at all	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	The worst imaginable breathlessness

Baseline (before exercise), Maximal (after exercise) and following up to 10 minutes use of intervention(s

Symptoms Breathlessness score	Baseline *(T0)*	Maximal *(Tmax)*	Recovery from exercise to baseline									
			(T1)	*(T2)*	*(T3)*	*(T4)*	*(T5)*	*(T6)*	*(T7)*	*(T8)*	*(T9)*	*(T10)*
NRS intensity												

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Section 7

Baseline Carer data collection tools

Carer baseline Zarit care-giver burden short form questionnaire

Question Number	Question: Do you feel/wish….?	0 Never	1 Rarely	2 Sometimes	3 Quite frequently	4 Nearly Always
1	You don't have enough time for yourself?					
2	Stressed between caring and meeting other responsibilities?					
3	Your relative affects your relationship with others in a negative way?					
4	Strained when you are around your relative?					
5	Your health has suffered because of your involvement with your					
6	You have lost control of your life since your relative's illness?					

Carer baseline General Self-efficacy Scale

- 1 = Not at all true
- 2 = Hardly true
- 3 = Moderately true
- 4 = Exactly true

	1 Not at all true	2 Hardly true	3 Moderately true	4 Exactly true
I can always manage to solve difficult problems if I try hard enough.				
If someone opposes me, I can find the means and ways to get what I want.				
It is easy for me to stick to my aims and accomplish my goals.				
I am confident that I could deal efficiently with unexpected events.				
Thanks to my resourcefulness, I know how to handle unforeseen situations.				
I can solve most problems if I invest the necessary effort.				
I can remain calm when facing difficulties because I can rely on my coping abilities.				
When I am confronted with a problem, I can usually find several solutions.				
If I am in trouble, I can usually think of a solution.				
I can usually handle whatever comes my way.				

Section 8

Day 28 Carer data collection tools

Carer baseline Zarit care-giver burden short form questionnaire

Question Number	Question: Do you feel/wish….?	0 Never	1 Rarely	2 Sometimes	3 Quite frequently	4 Nearly Always
1	You don't have enough time for yourself?					
2	Stressed between caring and meeting other responsibilities?					
3	Your relative affects your relationship with others in a negative way?					
4	Strained when you are around your relative?					
5	Your health has suffered because of your involvement with your					
6	You have lost control of your life since your relative's illness?					

Carer baseline General Self-efficacy Scale

- 1 = Not at all true
- 2 = Hardly true
- 3 = Moderately true
- 4 = Exactly true

	1 Not at all true	2 Hardly true	3 Moderately true	4 Exactly true
I can always manage to solve difficult problems if I try hard enough.				
If someone opposes me, I can find the means and ways to get what I want.				
It is easy for me to stick to my aims and accomplish my goals.				
I am confident that I could deal efficiently with unexpected events.				
Thanks to my resourcefulness, I know how to handle unforeseen situations.				
I can solve most problems if I invest the necessary effort.				
I can remain calm when facing difficulties because I can rely on my coping abilities.				
When I am confronted with a problem, I can usually find several solutions.				
If I am in trouble, I can usually think of a solution.				
I can usually handle whatever comes my way.				

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Section 9

Day 28 CRF completion form

Principal or Co-investigator

Patient`s status: ☐ Completed ☐ Withdrawn

If withdrawn, please specify reason: **……**

"I confirm that the contents of this CRF are

accurate and complete"

Name **Signature** **Date**

……

Appendix 5 Patient Study Information Sheet

Hull and East Yorkshire Hospitals NHS
NHS Trust

Short Title of Project: CHAFF study: Calming Hand and Fan Feasibility

Full Title: The "Calming hand" and the hand held fan as self-management strategies: assessing how these options help patients cope with breathlessness from activity or anxiety and assist their carer's.

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Many people live with the continuing distress and difficulties arising from breathlessness despite treatment of the underlying disease which is causing it.

Exercise is known to be important and helpful for breathlessness. People with breathing difficulties are often reluctant to exercise as it inevitably increases their breathlessness. There are a number of simple measures that ease breathlessness such as directing cool air flow to the face from a hand held battery operated fan. Alternatively, some people find the "Calming hand", a coping strategy to help with breathing and anxiety useful. These options are cheap, easy to use and portable providing something that both the patient and their carer can manage. But will such simple options enable people who are breathless from exercise recover faster and help them be confident with managing more activity as part of their daily routine? In order to answer this question, we will need a big study with several breathlessness research teams in different sites working on this issue.

This study is the first step in the planning stage of a larger study involving other sites. We aim to study approximately 40 patients from 1 centre – Castle Hill hospital, Hull.

Why have I been chosen?

Patients with persistent daily breathlessness due to any heart or lung disease are being asked if they would like to participate. You will have been approached by one of the research team at clinic and given this leaflet. We will also request your permission to approach your carer to see if they wish to take part in the study as well. The research team will contact you by telephone to discuss, answer any questions and see if you would like a chance to take part in this study or not. They will request your verbal consent to check your notes so they can see if you are eligible to take part.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will also be asked to sign a written patient consent form. If you decide not to participate or you do not wish your carer to take part, it will not affect the treatment you receive now or in the future.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason and this will not compromise the quality of care you receive in any way.

Your study doctor may withdraw you from the study if he/she does not think it is in your best interests to continue or if you are unable to complete the study questionnaires.

What do I have to do?

You will be required to do the following:

- Attend the Breathlessness clinic at Castle Hill hospital at least once to meet the study investigator. The follow-up appointment at the end of the study can be a home visit if you prefer.
- Learn how to use the fan and the usual care (if in the fan group), the Calming hand and the usual care (if in the Calming hand group), both of these and the usual care (if in the both Group), or the usual breathlessness care only (if in the usual care group).
- Learn how to use the practical information and advice sheets given to you on managing breathlessness and exercise.
- Complete the study questionnaires at the relevant times throughout the study (the investigator will help you with this)
- Continue with your usual care from your medical team. This study will not prevent you receiving any treatment your usual medical team think you need.

What will happen to me if I take part?

The study will last for 28 days.

- On Day 1 at a Breathlessness clinic appointment you will be asked to complete a walking test and some questionnaires including baseline assessments about your breathlessness and general health. You will also be asked to sign the written consent form. The study investigator will help you complete all of these.

There will be 4 groups in the study – (randomised trial – see next section).

1. One group of patients and their carers will be given a hand held fan, the usual breathing control exercises, and receive simple advice regarding the importance of exercise.

2. One group of patients and their carers will be given the Calming hand, the usual breathing care exercises, and receive simple advice regarding the importance of exercise.
3. One group of patients and their carers will be given both a hand held fan, the Calming hand, and the usual breathing care exercises, and receive simple advice regarding the importance of exercise.
4. One group of patients and their carers will be given the usual breathing care exercises and simple advice regarding the importance of exercise without the fan or Calming hand.

The groups of patients and their carers that are given the hand held fan and/or the Calming hand will be invited to participate in an optional interview on Day 28 at the end of the study.

The study investigator will teach, explain and demonstrate to you:

- how to do the walking test on day 1 and day 28
- how to sit comfortably forward, leaning on to the elbows, when feeling your maximal or worst breathless from walking
- how to score your breathlessness during your recovery using the numbered scale

You will be asked to walk at your usual pace on a flat surface, up and down a 10 metre course using a walking aid if needed, until you feel your worst or maximal breathlessness tolerance from exercise. The study investigator will monitor you closely when walking and chairs will be positioned alongside the 10 metre walking line. At the point you feel maximal breathlessness you will sit down and adopt a comfortable recovery position. We will ask you for your breathless scores before, after and during the recovery period from exercise.

After the first walking test you will be randomised to one of the four groups and the study investigator will teach, explain and demonstrate to you:

- how to use the fan at the right distance from the face
- how to use the “Calming hand” exercises
- how to use the breathing control exercises

- how to use you're group intervention(s) for up to 10 minutes or until you feel your breathlessness has recovered.

At this point you will have the option of repeating the walking test using your group intervention(s) to recover when you feel your maximal breathlessness.

After this you will take home you're group intervention(s) and you will be encouraged to use them when you feel breathless from anxiety, exercise or other daily activities for the next 28 days. The study investigator will telephone you on Day 14 to see how you are managing and asked some questions about your breathlessness.

On Day 28, at the end of the study you will be asked to attend Breathlessness clinic again to repeat the walking test using your intervention(s) to help you recover from breathlessness. You will also be asked to complete the follow-up questionnaires and assessments about your breathlessness. This can also be done through a home visit if preferred.

Randomised trial: Sometimes it is not known which way is the best treatment for patients with a particular condition, so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better than the other. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the lead investigator nor the study participant can decide which treatment the participant and their carer receives.

After the study

You may be able to keep continue using the hand-held fan and /or the Calming hand following completion of this study if you and your doctor found it benefited you. If you did not have the fan and/or the Calming hand during the study, you will have an opportunity to try both of these at the end of the study.

At the end of the study period, participants who have used the fan or the Calming hand, and their carer's, will be invited to participate in an optional interview with a member of the research team. This meeting will provide feedback to the research team about their

experiences using the fan and/or the Calming hand and they can make any suggestions that may help improve the study from the participant perspective. If this is something you wish to help with, further information will be given at the time.

Are there alternatives to being part of this study for managing my breathlessness?

You could attend breathlessness clinic/service in the area, but not take part in the study. Alternatively, if you did not wish to attend a clinic, your usual medical team will be able to give general advice about how to try to control your breathlessness.

What are the possible disadvantages of taking part in the study?

The following should be taken into account:

- you may find attendance at clinic, or having the therapist attend at home, and the questionnaires or the walking test tiring and time consuming – if so, you are free to withdraw from the study at any time if you wish
- you may be allocated to the "no fan" and/or "no Calming hand" group and feel you would like to try one of these before the end of the study. If you do not wish to wait until the end then you would be free to withdraw from the study at any time.

What are the possible benefits of taking part in the study?

Although this study may not directly benefit you it aims to further medical knowledge and may improve future treatment of breathlessness.

Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything and there will not be any payment for taking part in the study.

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment being studied. If this happens, your research doctor will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your continued care outside of the study. If you do decide to continue in the study, you will be asked to sign an up-dated consent form.

What will happen to the information already gathered if I don't want to carry on with the study?

If you withdraw from the study, we will ask your permission to use the data collected up to your withdrawal.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible problem you might experience will be addressed.

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer all your questions

Contact Ms Flavia Swan mob 07794 297206 or Ms Anne English on 07772 630804

If you have any concerns or complaints about the way the researcher has carried out this study, or any other aspects of your care, you may contact:

The Patient Advice and Liaison Service (PALS), Hull and East Yorkshire NHS Trust, Telephone: 01482 623065, email: pals@hey.nhs.uk

In the unlikely event that something does go wrong and you are harmed as a result of the research study the normal NHS complaints mechanism will still be available to you if appropriate as detailed in the above paragraph.

Will my taking part in the study be kept confidential?

The researchers would like to have access to your medical record to obtain information about the underlying causes of your breathlessness.

- Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law.
- Only the researchers involved with the study will have access to your details that will be held securely on a database at Hull York Medical School (HYMS) Research Office. Your name will not appear on any materials produced from this study and only non-identifiable information will be sent off site. However access to your medical records may be required by other agencies such as regulatory bodies and Ethics Committees, this will only occur when necessary and the provisions of law will be complied with.

Anonymised data only will be entered onto the secure database. Passwords will only be known by members of the research team. All data will be managed and held in accordance with the Data Protection Act.

The research team will need to have access to your medical record to confirm that correct study treatments have been given and that information in the study data is correct.

Will my GP be notified of my participation in this study?

Your GP will be notified of your participation but if, however, you do not wish this, please inform the researcher; you do not need to give a reason.

What will happen to the results of the study?

The results of this study may be published or presented at scientific meetings and in journals. In any publication, information will be provided in such a way that you cannot be identified. The results of this study will be used to inform the development of a larger study.

Let us know if you would like the results of the study and we will contact you.

Who is organising and funding the research?

The Hull and East Yorkshire Hospitals NHS Trust is sponsoring the research (that is, taking overall responsibility for its conduct) and the study is funded by a grant from the Hull York Medical School, Centre for Health and Population Studies PhD Studentship.

The research team comprises:

- Ms Flavia Swan, Lead Investigator, PhD Student, HYMS PGTS Physiotherapy clinical specialist in palliative care
- Ms Anne English, Co-investigator, Physiotherapy Clinical Specialist in palliative care, Queen's Oncology Centre, Castle Hill Hospital
- Prof Miriam Johnson, Lead academic supervisor, Reader in Palliative Medicine at Hull-York Medical School (University of Hull) – academic and palliative care researcher
- Dr Rachael Barton, Consultant Oncologist at Castle Hill Hospital with a special interest in lung cancer – research oncologist
- Dr Simon Hart, Honorary consultant in Respiratory Medicine at Castle Hill hospital with a special interest in pulmonary fibrosis

Who has reviewed the study?

This study has been reviewed and approved by the Yorkshire & the Humber Research Ethics Committee - Leeds East, and the Supportive care Early Diagnosis, Advanced disease (SEDA) research group of the Hull York Medical School (HYMS) Centre for Health and Population Studies. The study was submitted and received a high mark as part of the PhD research training, (RCT module) undertaken by the principal investigator at Department of Health Sciences, University of York.

Contact details: If you require further information about this study, please contact:

Ms Flavia Swan, Lead study investigator on mob 07794 297206

Ms Anne English, Study co-investigator on mob 07772 630804

Thank you for taking the time to consider this study. This information sheet is for you to keep.

Appendix 6 Patient Consent Form

Hull and East Yorkshire Hospitals NHS
NHS Trust

CONSENT FORM: Participant **Study Number:** R1369

Title of Project: CHAFF study: Calming Hand and Fan Feasibility

Name of Researcher: Flavia swan

Please initial box

1. I confirm that I have read and understood the information sheet dated 20th Oct 2013, version 3, for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during this study may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP/hospital consultant being informed of my participation in the study. ☐

5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified. ☐

6. I agree to take part in the above study only ☐

7. I agree to take part in the above study *and* the optional sub-study interview. ☐

8. I agree to give my permission for the research team to approach my carer about taking part in both, the study *and* the optional sub-study interview. ☐

9. I agree to give my permission to audio-record the sub-study interview and use only anonymised direct quotes in publication. ☐

Name of participant Date Signature

_____

Verbal consent witness Date Signature

_____

Name of person taking consent Date Signature

(if different from researcher)

_____

Researcher Date Signature

_____

When completed, 1 for patient; 1 for researcher file; 1 (original) to be kept in patient notes

Appendix 7 Carer Study Information Sheet

Hull and East Yorkshire Hospitals NHS
NHS Trust

Short title of project: CHAFF study: Calming Hand and Fan Feasibility

Full title: The "Calming hand" and the hand held fan as self-management strategies: assessing how these options help patients cope with breathlessness from activity or anxiety and assist their caregivers.

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Many people live with the continuing distress and difficulties arising from breathlessness despite treatment of the underlying disease which is causing it.

Exercise is known to be important and helpful for breathlessness. But, people with breathing difficulties are often reluctant to exercise as it inevitably increases their breathlessness. There are a number of simple measures that ease breathlessness such as directing cool air flow to the face from a hand held battery operated fan. Alternatively, some people find the "Calming hand", a coping strategy to help with breathing and anxiety useful. These options are cheap, easy to use and portable providing something that both the caregiver and patient can manage. But will such simple options help the carer to manage the burden of caring for a breathless person more effectively and will these improve how they feel about coping and assisting with any unexpected breathless episode. The study at one centre is the first step in the planning stage of a larger study involving other sites in the UK.

Why have I been chosen?

You have been selected to participate in this study because you are a carer for someone who experiences breathlessness due to heart or lung disease. The person you normally care for will have been approached by one of the research team at clinic and given a patient study information leaflet. You will also be approached at the same time and given the carer study information leaflet.

The research team will contact you and the person you care for by telephone to discuss, answer any questions and see if you would like a chance to take part in the carer study or not.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this carer information sheet to keep and be asked to sign a written carer consent form. Whatever your decision, it will not affect your relationship with the staff treating the person in your care.

If you decide not to participate, it will not affect the treatment given to you as the carer or the person you care for now or in the future. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

The study investigator may withdraw you from the study if he/she does not think it is in your best interests to continue or if you are unable to complete the study questionnaires.

What do I have to do?

You will be asked to:

- Attend the Breathlessness clinic at Castle Hill hospital at least once to meet the study investigator. The follow-up appointment at the end of the study can be a home visit if you prefer.
- Learn how to help the patient use the practical information and advice sheets given to them on using the different treatments and managing breathlessness with exercise during the 28 days of the study.
- Complete 2 questionnaires regarding your experience as a caregiver at the beginning of the study and also at the end of the study which will be 28 days later (the study investigators will help you with this)

The questionnaire will ask you about your quality of life and any strain or burden you may experience in your role as a carer. The questionnaires will take about 15 minutes to complete.

After the study

- Participate in an interview meeting with a member of the research team.

This meeting will be optional to provide feedback to the research team about the carer experiences and how they felt about the patient or their own use of the fan and/or the Calming hand. They can make any suggestions that may help improve a future study from the participant or carer perspective. If this is something you wish to help with, further information will be given at the time.

What will happen to me if I take part?

The study will last for 28 days.

- On Day 1 at a Breathlessness clinic appointment you will be asked to complete 2 questionnaires about how caring for a breathless person affects your general health

and quality of life and you will be asked to sign the written consent form. The study investigator will help you complete all of these.

There will be 4 groups in the study – (randomised trial – see next section).

One group of patients and their carers will be given a hand held fan, the usual breathing control exercises, and receive simple advice regarding the importance of exercise.

One group of patients and their carers will be given the Calming hand, the usual breathing care exercises, and receive simple advice regarding the importance of exercise.

One group of patients and their carers will be given both a hand held fan, the Calming hand, and the usual breathing care exercises, and receive simple advice regarding the importance of exercise.

One group of patients and their carers will be given the usual breathing care exercises and simple advice regarding the importance of exercise without the fan or Calming hand.

- On Day 28 the carer will be asked to fill in the same 2 questionnaires that they completed on Day 1.
- The groups of patients and their carers that are given the hand held fan and/or the Calming hand will also be invited to participate in an optional interview on Day 28 at the end of the study.

Randomised trial

Sometimes it is not known which way is the best treatment for patients with a particular condition, so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better than the other. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the lead investigator nor the study participant can decide which treatment the participant and their carer receives.

What are the possible disadvantages of taking part in the study?

- We will ask you to complete a questionnaire about quality of life and the strain you may experience in your role as a caregiver. If these questions bring to mind concerns, you will be able to speak about them with the study nurse or team treating the person you care for. The research nurse will provide you the contact details of the support services and health professionals available to you.

What are the possible benefits of taking part in the study?

This study aims to further medical knowledge and may improve future treatment of breathlessness however it may not directly benefit you.

Will taking part in this study cost me anything, and will I be paid?

Participation in this study will not cost you anything and there will not be any payment for taking part in the study.

What will happen to the information already gathered if I don't want to carry on with the study?

If you withdraw from the study, we will ask your permission to use the data collected up to your withdrawal.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible problem you might experience will be addressed. If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer all your questions

Contact Ms Flavia Swan mob 07794 297206 or Ms Anne English on 07772 630804

If you have any concerns or complaints about the way the researcher has carried out this study, or any other aspects of your care, you may contact:

The Patient Advice and Liaison Service (PALS), Hull and East Yorkshire NHS Trust, Telephone: 01482 623065, email: pals@hey.nhs.uk

In the unlikely event that something does go wrong and you are harmed as a result of the research study the normal NHS complaints mechanism will still be available to you if appropriate as detailed in the above paragraph.

What will happen to the results of the study?

The results of this study may be published or presented at scientific meetings and in journals. In any publication, information will be provided in such a way that you cannot be identified. The results of this study will be used to inform the development of a larger study.

Let us know if you would like the results of the study and we will contact you.

Who is organising and funding the research?

The Hull and East Yorkshire Hospitals NHS Trust is sponsoring the research (that is, taking overall responsibility for its conduct) and the study is funded by a grant from the Hull York Medical School, Centre for Health and Population Studies PhD Studentship.

The research team comprises:

- Ms Flavia Swan, Lead Investigator, PhD Student, HYMS PGTS Physiotherapy clinical specialist in palliative care
- Ms Anne English, Co-investigator, Physiotherapy Clinical Specialist in palliative care, Queen's Oncology Centre, Castle Hill Hospital
- Prof Miriam Johnson, Lead academic supervisor, Reader in Palliative Medicine at Hull-York Medical School (University of Hull) – academic and palliative care researcher
- Dr Rachael Barton, Consultant Oncologist at Castle Hill Hospital with a special interest in lung cancer – research oncologist
- Dr Simon Hart, Honorary consultant in Respiratory Medicine at Castle Hill hospital with a special interest in pulmonary fibrosis

Will my taking part in the study be kept confidential?

- Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law.
- Only the researchers involved with the study at your site will have access to your details that will be held securely at the site. Your name will not appear on any materials produced from this study and only non-identifiable information will be sent off site.
- Anonymised data will be collected and then input by the investigator onto a secure database at Hull York Medical School Research Office (HYMS). All data will be managed and held in accordance with the Data Protection Act.

Who has reviewed the study?

This study has been reviewed and approved by the Yorkshire and Humber Research Ethics Committee – Leeds East, the Supportive care, Early diagnosis, Advanced disease (SEDA) research group of the Hull York Medical School (HYMS) Centre for Health and Population Studies. The study was submitted and received a high mark as part of the PhD research training, (RCT module) undertaken by the principal investigator at Department of Health Sciences, University of York.

Contact details

If you require further information about this study, please contact:

- Ms Flavia Swan, Lead study investigator on mob 07794 297206
- Ms Anne English, Study co-investigator on mob 07772 630804

Thank you for taking the time to consider this study. This information sheet is for you to keep.

Appendix 8 Carer Consent Form

Hull and East Yorkshire Hospitals NHS
NHS Trust

CONSENT FORM: Carer **Study Number:** R1369

Title of Project: CHAFF study: Calming Hand and Fan Feasibility

Name of Researcher: Flavia Swan

Please initial boxes

1. I confirm that I have read and understood the information sheet dated 6th May 2012, version 1.0, for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights or medical care of the person for whom I am a caregiver being affected. ☐

3. I understand that data collected during this study, may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my study records. ☐

4. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified. ☐

5. I agree to take part in the above study only ☐

6. I agree to take part in the above study *and* the optional sub- study interview. ☐

7. I agree to give my permission to audio-record the sub-study interview and use anonymised direct quotes in publication. ☐

Name of carer Date Signature

_____

Verbal consent witness Date Signature

_____

Name of person taking consent Date Signature

(if different from researcher)

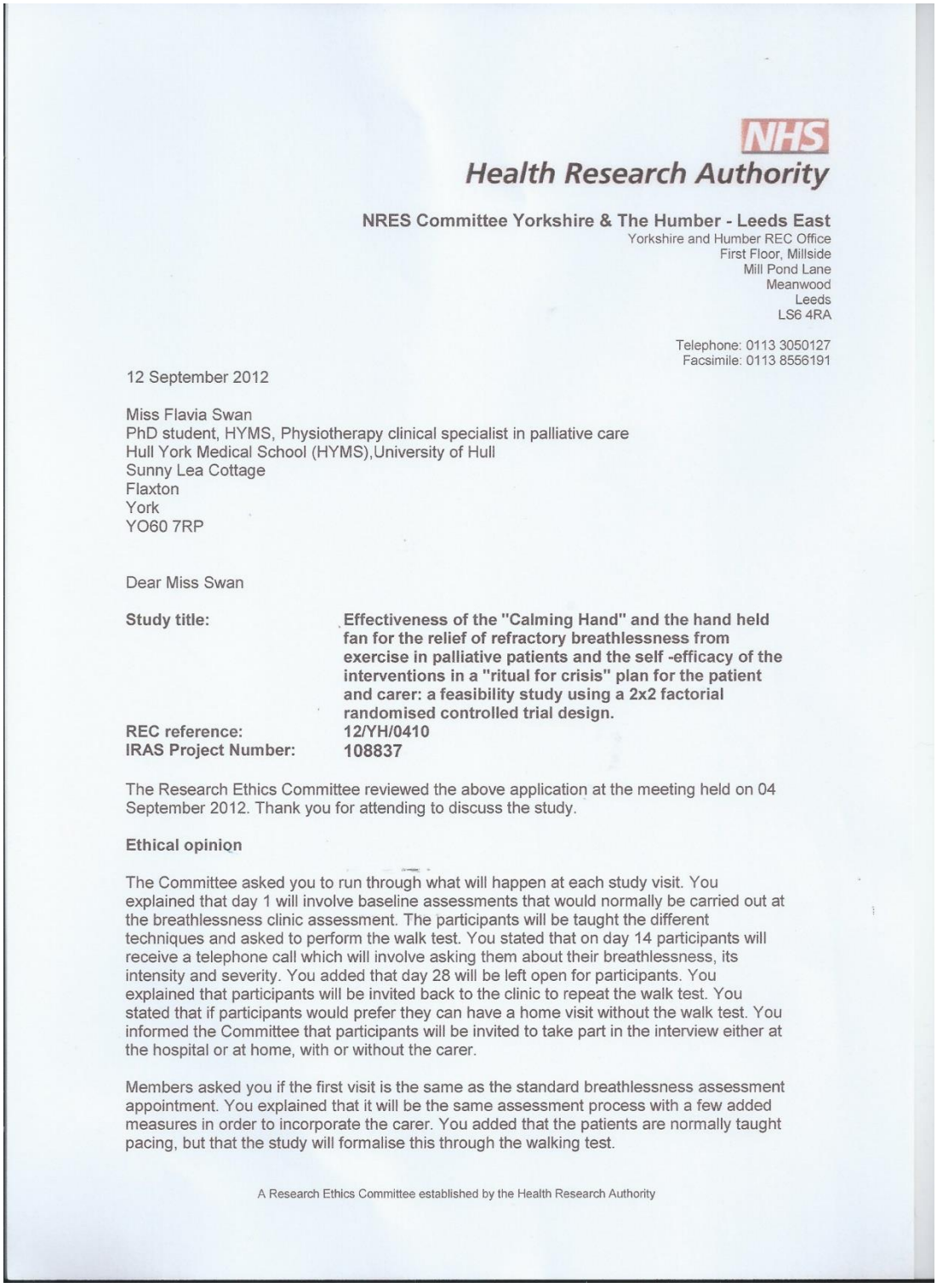
_____

Researcher Date Signature

_____

When completed, 1 for patient; 1 for researcher file; 1 (original) to be kept in patient notes

Appendix 9 Ethics permission



NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds East
Yorkshire and Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050127
Facsimile: 0113 8556191

12 September 2012

Miss Flavia Swan
PhD student, HYMS, Physiotherapy clinical specialist in palliative care
Hull York Medical School (HYMS),University of Hull
Sunny Lea Cottage
Flaxton
York
YO60 7RP

Dear Miss Swan

Study title: **Effectiveness of the "Calming Hand" and the hand held fan for the relief of refractory breathlessness from exercise in palliative patients and the self -efficacy of the interventions in a "ritual for crisis" plan for the patient and carer: a feasibility study using a 2x2 factorial randomised controlled trial design.**
REC reference: **12/YH/0410**
IRAS Project Number: **108837**

The Research Ethics Committee reviewed the above application at the meeting held on 04 September 2012. Thank you for attending to discuss the study.

Ethical opinion

The Committee asked you to run through what will happen at each study visit. You explained that day 1 will involve baseline assessments that would normally be carried out at the breathlessness clinic assessment. The participants will be taught the different techniques and asked to perform the walk test. You stated that on day 14 participants will receive a telephone call which will involve asking them about their breathlessness, its intensity and severity. You added that day 28 will be left open for participants. You explained that participants will be invited back to the clinic to repeat the walk test. You stated that if participants would prefer they can have a home visit without the walk test. You informed the Committee that participants will be invited to take part in the interview either at the hospital or at home, with or without the carer.

Members asked you if the first visit is the same as the standard breathlessness assessment appointment. You explained that it will be the same assessment process with a few added measures in order to incorporate the carer. You added that the patients are normally taught pacing, but that the study will formalise this through the walking test.

A Research Ethics Committee established by the Health Research Authority

The Committee asked you if the study will involve actively encouraging exercise or whether it will look at managing patient's usual breathlessness. You confirmed that exercise will be encouraged. Members asked you about those participants who choose not to exercise between study visits. You stated that participants may choose not to exercise, but that as a feasibility study you intend to look at whether the techniques allowed the participants to exercise, if they chose to exercise during the study.

The Committee asked you how carers will be approached to take part in the study. You explained that a patient normally attends the breathlessness clinic with a carer. You added that you will approach the patient about taking part in the study and then with the patient's permission you will approach the carer.

Members asked you how you will link the carer quality of life questionnaire to the interventions. You stated that carers will be asked to complete the questionnaire at the start of the study and then again at the end. You explained that you will tie the results in with the qualitative interview to ascertain whether they are coping and if the interventions have helped the patient. Members asked if you require both patient and carer to take part in the study. You stated that you do not require pairs and that it is optional for carers to take part in the study.

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.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites 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).

Non NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System 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 approvals from host organisations

1. The consent form requires the following information:

- A sentence requesting permission to audio-record the interview
- A sentence requesting permission to use anonymised direct quotes in publication.
- A sentence requesting permission to approach the participant's carer about taking part in the research.

2. The participant information sheet should explain that with the participants permission you will approach their carer about taking part in the study.

It is 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).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of insurance or indemnity		14 October 2011
Evidence of insurance or indemnity		09 July 2012
Evidence of insurance or indemnity		09 July 2012
GP/Consultant Information Sheets	1	06 May 2012
Investigator CV	1	06 May 2012
Other: CV- Miriam Johnson		10 August 2012
Other: Fan Group Advice Leaflet	1	06 May 2012
Other: Calming Hand Group Advice Leaflet	1	06 May 2012
Other: Control Group Advice Leaflet	1	06 May 2012
Other: Study Assessment Toolkit	1.0	06 May 2012
Participant Consent Form: Patient Consent Form	1	06 May 2012
Participant Consent Form: Carer Consent Form	1	06 May 2012
Participant Information Sheet: Patient Study Information Sheet	1.0	06 May 2012
Participant Information Sheet: Carer Study Information Sheet	1.0	06 May 2012
Protocol	1	06 May 2012
REC application		09 August 2012
Referees or other scientific critique report		11 January 2012

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

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 NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0410	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp
Dr Carol Chu
Chair

Email: nicola.mallender-ward@nhs.net

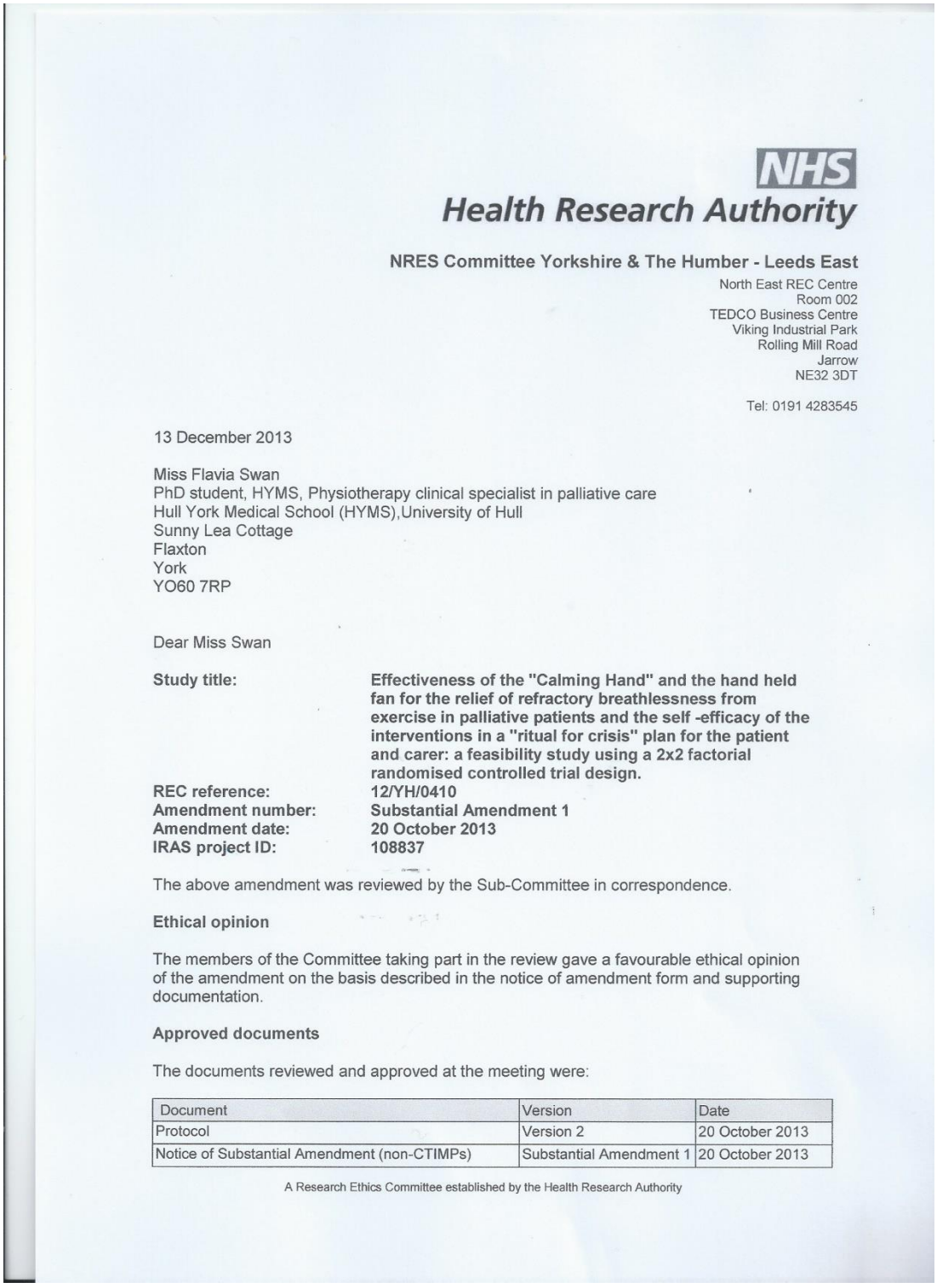
Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Dr Miriam Johnson, St Catherine's Hospice*

A Research Ethics Committee established by the Health Research Authority

Appendix 10 Ethics Amendment Approval



NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds East

North East REC Centre
Room 002
TEDCO Business Centre
Viking Industrial Park
Rolling Mill Road
Jarrow
NE32 3DT

Tel: 0191 4283545

13 December 2013

Miss Flavia Swan
PhD student, HYMS, Physiotherapy clinical specialist in palliative care
Hull York Medical School (HYMS),University of Hull
Sunny Lea Cottage
Flaxton
York
YO60 7RP

Dear Miss Swan

Study title:	**Effectiveness of the "Calming Hand" and the hand held fan for the relief of refractory breathlessness from exercise in palliative patients and the self -efficacy of the interventions in a "ritual for crisis" plan for the patient and carer: a feasibility study using a 2x2 factorial randomised controlled trial design.**
REC reference:	**12/YH/0410**
Amendment number:	**Substantial Amendment 1**
Amendment date:	**20 October 2013**
IRAS project ID:	**108837**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	Version 2	20 October 2013
Notice of Substantial Amendment (non-CTIMPs)	Substantial Amendment 1	20 October 2013

A Research Ethics Committee established by the Health Research Authority

Participant Information Sheet	Version 3.0	20 October 2013
Covering Letter	Email from Flavia Swan	26 November 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/YH/0410:	**Please quote this number on all correspondence**

Yours sincerely

pp
Alan Ebbutt
Alternate Vice Chair

E-mail: hayley.jeffries@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr James Illingworth, Hull and East Yorkshire Hospitals NHS Trust*
Dr Miriam Johnson, St Catherine's Hospice

Appendix 11 Patient Intervention Information Sheets

Usual Care Group Leaflet

Practical Advice on Managing Breathlessness

This leaflet describes some everyday things you can try to help manage your breathlessness.

Breathing Control

The breathing control method below can help speed breathlessness recovery.

Preparation

- While sitting place one hand on your tummy, just above your belly button.
- Relax your shoulders and upper chest.
- Rest your elbows in by your side.

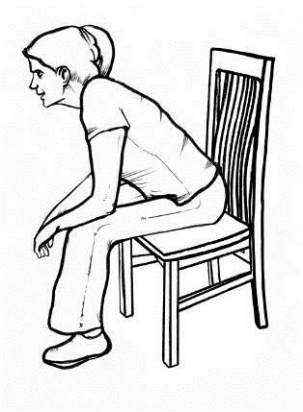
Spend as long as you need on each of the following points:

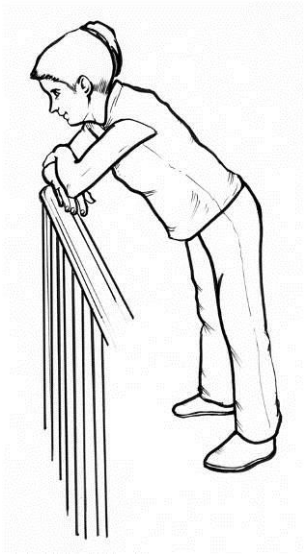
- Feel the breathing movement under your hand.
- Breathe in smoothly, allow your tummy to swell.
- Take in only the air you need.
- Breathe out, relax and let your tummy fall.
- Release each out breath until it comes to its natural end.
- Each time you breathe out, relax your upper chest a little more.

Breathing from your tummy in this way often does not come naturally. You should therefore practice breathing control when you are not breathless for 10-15 minutes at a time, at least twice a day. This will help you master the technique. Breathe gently when practising; there should only be a slight movement of your tummy at rest.

The 'forward lean' position

The pictures below show the ‘forward lean’ position. These are positions that may help you to recover from breathlessness.





Additional advice

- Avoid breath holding during activities i.e. climbing stairs or bending.
- ‘Blow as you go’, breathe out on effort i.e. blow out when bending, lifting, reaching or standing up from a chair.
- Avoid rushing. Breathless people sometimes rush as they wrongly believe if they move quicker they will be less breathless when they get there.
- Paced breathing i.e. take a breath in and out on each step when climbing the stairs.

The importance of keeping active

It is common for people to avoid activity that makes them breathless. Over time a person may become less fit as they become less active in their day to day life. Being less fit will make breathlessness come on more easily. It is therefore very important to keep as fit and active as possible.

Remember that breathlessness is not harmful and your breathing will recover with rest. In fact you need to become moderately breathless when exercising in order to improve your fitness. Try to exercise every day. Consider joining local exercise or walking for health groups.

Below are some suggested exercises to help keep you fit. Use the breathing methods and positions described in this leaflet to help you to control your breathlessness during and after activity.

Sit to Stand

Repeatedly stand up and sit down from a chair. See how many times you can repeat this in a row before needing to rest. Perhaps do this while waiting for the kettle to boil or during every advert break when watching the TV or even every hour. Remember to pace your breathing; breathe out as you stand up, breathe in as you sit down. This is a great exercise to strengthen your legs.

Walking

Walking is a fantastic way to keep fit. Try to go for a walk every day. If you don't feel you can walk very far just walk lengths of the garden or living room or laps around the house, little and often throughout the day. Start off with short distances and build up as able. The further you walk the fitter you will become. Consider taking a friend or relative with you for walks outdoors for moral support.

Do not to exercise if you feel unwell, feel faint or dizzy, are much more breathless than normal, develop chest pain or if the exercise worsens or causes pain any where in the body. If you experience any of the above contact your healthcare professional for advice.

Calming Hand and Usual Care Group Leaflet

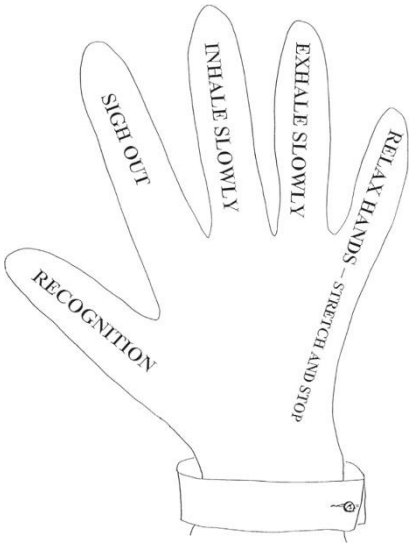
Practical Advice on Managing Breathlessness

This leaflet describes some practical things you try to help manage your breathlessness day to day.

The Calming Hand

This is a tool to help you cope with your breathlessness when feeling anxious or panicky. It is simple to remember and you can use it in any situation to try and distract yourself from breathlessness and panic.

Count the steps out on your fingers as an aide to memoire:



Using the Calming Hand

1. Acceptance – Squeeze thumb and recognise that you are starting a breathless or panic attack.
2. Sigh out. Flop and Drop – relax shoulders
3. Breathe in and out slowly, gently and focus on the breath out.
4. Stretch hands fully and then let them go

Breathing Control

The breathing control method below can help speed breathlessness recovery. Use the handheld fan with this breathing method.

Preparation

- While sitting place one hand on your tummy, just above your belly button.
- Relax your shoulders and upper chest.
- Rest your elbows in by your side.

Spend as long as you need on each of the following points:

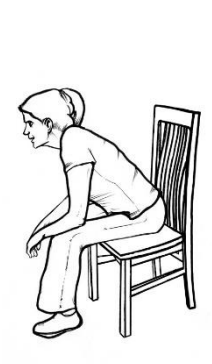
- Feel the breathing movement under your hand.
- Breathe in smoothly, allow your tummy to swell.
- Take in only the air you need.
- Breathe out, relax and let your tummy fall
- Release each out breath until it comes to its natural end.
- Each time you breathe out, relax your upper chest a little more.

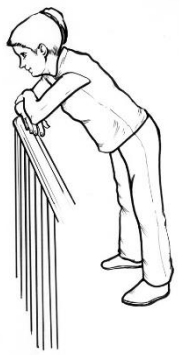
Breathing from your tummy in this way often does not come naturally.

You should therefore practice breathing control when you are not breathless for 10-15 minutes at a time, at least twice a day. This will help you master the technique. Breathe gently when practising; there should only be a slight movement of your tummy at rest.

Forward lean position

The following positions may help you to recover from breathlessness. The handheld fan can be used with these positions.





Managing severe breathlessness or panic

If you feel severely breathless or even 'panicky' try using the Recovery Breathing method described below.

- Take up a 'forward lean' position as shown in the picture
- Use the Calming Hand.
- Focus on the *out* breath.
- Don't worry about the in breath; it will take care of itself
- When you feel ready, blow out for longer until your breathing has eased.

Additional advice

- Avoid breath holding during activities i.e. climbing stairs or bending.
- 'Blow as you go', breathe out on effort i.e. blow out when bending, lifting, reaching or standing up from a chair.
- Avoid rushing. Breathless people sometimes rush as they wrongly believe if they move quicker they will be less breathless when they get there.
- Paced breathing i.e. take a breath in and out on each step when climbing the stairs.

The importance of keeping active

It is common for people to avoid activity that makes them breathless. Over time a person may become less fit as they become less active in their day to day life. Being less fit will make breathlessness come on more easily. It is therefore very important to keep as fit and active as possible.

Remember that breathlessness is not harmful and your breathing will recover with rest. In fact you need to become moderately breathless when exercising in order to improve your fitness. Try to exercise every day. Consider joining local exercise or 'walking for health' groups.

Below are some suggested exercises to help keep you fit. Use the handheld fan, breathing methods and positions described in this leaflet to help you to control your breathlessness during and after activity.

Sit to Stand

Repeatedly stand up and sit down from a chair. See how many times you can repeat this in a row before needing to rest. Perhaps do this while waiting for the kettle to boil or during every advert break when watching the TV or even every hour. Remember to pace your breathing; breathe out as you stand up, breathe in as you sit down. This is a great exercise to strengthen your legs.

Walking

Walking is a fantastic way to keep fit. Try to go for a walk every day. If you don't feel you can walk very far just walk lengths of the garden or living room or laps around the house, little and often throughout the day. Start off with short distances and build up as able. The further you walk the fitter you will become. Consider taking a friend or relative with you for walks outdoors for moral support.

Do not exercise if you feel unwell, feel faint or dizzy, are much more breathless than normal, develop chest pain or if the exercise worsens or causes pain any where in the body. If you experience any of the above contact your healthcare professional for advice.

Hand-held Fan and Usual Care Group Leaflet

Practical Advice on Managing Breathlessness

This leaflet describes some practical things you try to help manage your breathlessness day to day.

The hand-held fan

Breathlessness can be reduced by a draught of cool air from a handheld fan directed at the face. Keep the fan with you at all times so that you have it ready in times of need.

Using the hand-held fan

- Hold the fan about 6 inches (15cm) from your face or the distance you find most helpful.
- Aim the cool air at your nose and mouth.
- Either hold the fan still or move it around slightly, whatever you find most helpful.

Breathing Control

The breathing control method below can help speed breathlessness recovery. Use the hand-held fan with this breathing method.

Preparation

- While sitting place one hand on your tummy, just above your belly button.
- Relax your shoulders and upper chest.
- Rest your elbows in by your side.

Spend as long as you need on each of the following points:

- Feel the breathing movement under your hand.
- Breathe in smoothly, allow your tummy to swell.

- Take in only the air you need.
- Breathe out, relax and let your tummy fall
- Release each out breath until it comes to its natural end.
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Forward lean position The following positions may help you to recover from breathlessness. The handheld fan can be used with these positions.

Managing severe breathlessness or panic

If you feel severely breathless or even 'panicky' try using the Recovery Breathing method described below.

- Take up a 'forward lean' position as shown in the picture
- Use your hand-held fan.
- Focus on the *out* breath, blow onto the fan.
- Don't worry about the in breath; it will take care of itself
- When you feel ready, blow out for longer until your breathing has eased.

Additional advice

- Avoid breath holding during activities i.e. climbing stairs or bending.
- 'Blow as you go', breathe out on effort i.e. blow out when bending, lifting, reaching or standing up from a chair.
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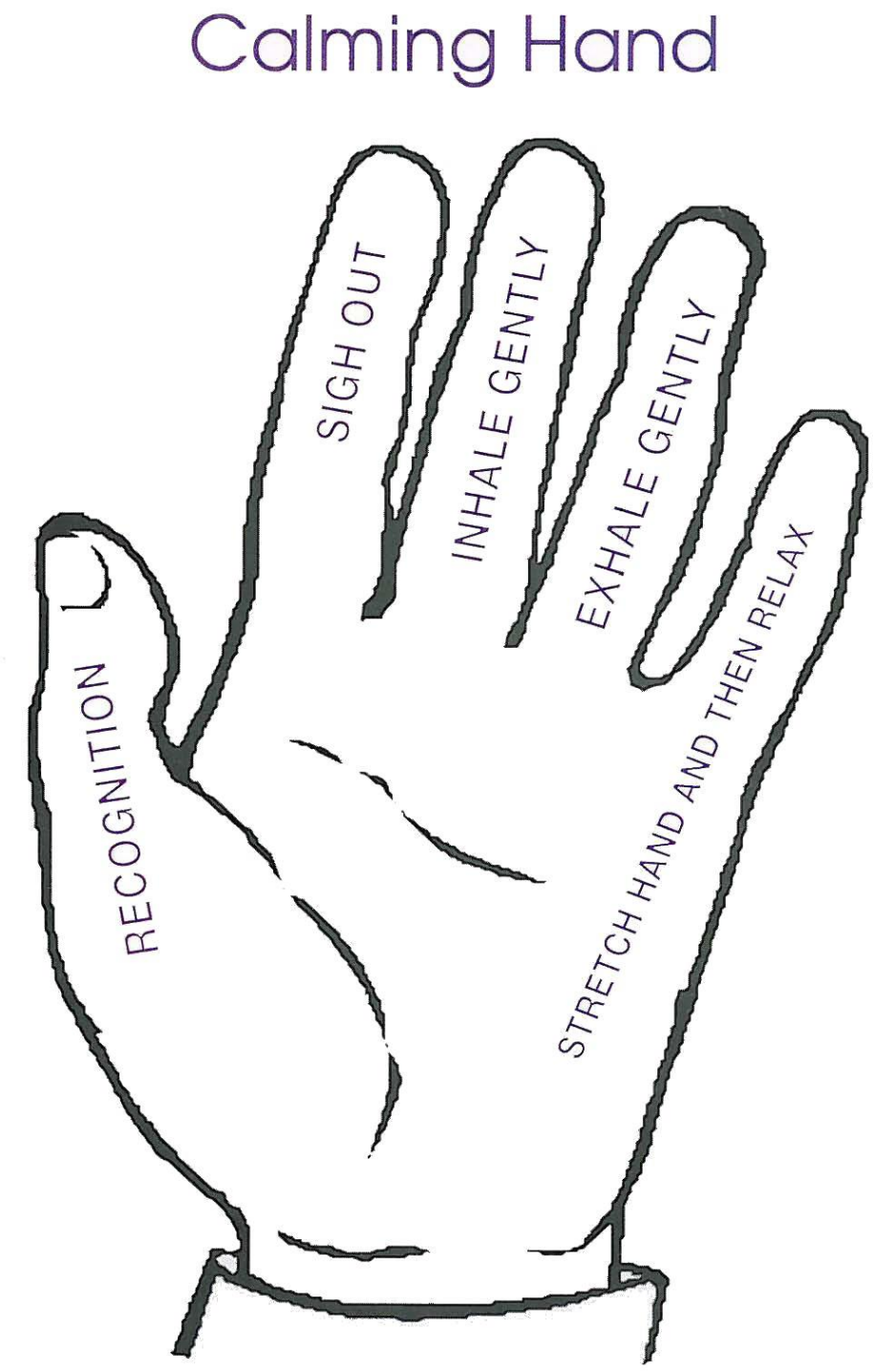
Do not exercise if you feel unwell, feel faint or dizzy, are much more breathless than normal, develop chest pain or if the exercise worsens or causes pain any where in the body. If you experience any of the above contact your healthcare professional for advice.

Appendix 12 Calming Hand Diagram and Information



Calming Hand Information for Patients

The Calming Hand is a tool used for teaching control of panic attacks. It also works well with episodes of breathlessness. Its simplicity makes it useful in helping you to remember the main points of your coping strategy when actually experiencing an episode of panic or breathlessness.

Acceptance Recognise the signs of panic and that they are not sinister. Hold your thumb firmly whilst reminding yourself of what to do next. This will help to calm your breathing.

Sigh out This enables you to relax your shoulders and upper chest (remember to flop and drop). If possible, try to breathe out for longer than you breathe in.

Inhale Take a slow and gentle relaxed breath – SLOWLY in, followed by....

Exhale .... a gentle breath out. Relaxed breathing helps to relieve the sensation of breathlessness.

Stretch hands, relax and stop Hand stretching is helpful when having an acute episode of panic; it is also acceptable to do in a public place.

After completing the Calming Hand, your feelings of panic/breathlessness may not go away instantly. You may need to follow steps 1-5 again. Sometimes, it may take longer for the panic to subside. When the panic settles, it is advisable to practise breathing control/diaphragmatic breathing as previously shown by your health care professional.

Appendix 13 Interview Topic guide

Introduction: hello my name is Flavia Swan, PhD student, HYMS

Who for? Interview for CHAFF feasibility study

Why? Purpose is follow-up interview with participants and/or carers to gain further information on the perception and experience of the hand-held fan and the "Calming hand" for the management of chronic refractory breathlessness.

Consent: signed, re-iterate confidentiality and use of anonymised quotes only

Factual questions:

- How old are you?
- Social circumstances? Carer?

Characteristics of breathlessness:

- What is it like?
- How long? What happened?
- When?

Management of breathlessness

- What helps?
- ADL?
- How do you manage?
- Recovery?
- Medical treatment?

Interventions and study design

- Hand-held fan?
- Calming hand?
- Usual care
- Outcome measurements used?

Personal preference and beliefs

- Why do you think?
- How would you improve care?
- What advice would you give?

11 Glossary

Abbreviation	Term in full
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACCP	American College of Chest Physicians
AMED	Allied and Complementary Medicine
ATS	American Thoracic Society
BIS	Breathlessness Intervention Service
BSS	Breathlessness Support Service
BTF	Breathing, Thinking, Functioning model
CB	Continuous Breathlessness
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of controlled trials
CI	Confidence Interval
CHF	Congestive Heart Failure
CONSORT	CONsolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRQ	Chronic Respiratory Questionnaire
CSES	COPD Self-efficacy Scale
CTU	Clinical Trails Unit
DAS	Distractive Auditory Stimuli
dACC	Dorsal Anterior Cingulate Cortex
DB	Diaphragmatic Breathing
EB	Episodic Breathlessness
ED	Emergency Department
ERS	European Respiratory Society
FEV^1	Forced Expiratory Volume in one second
fMRI	Functional Magnetic Resonance Imaging
FVC	Forced Vital Capacity

GCP	Good Clinical Practice
GRAMMS	Good Reporting of A Mixed Methods Study
GSES	General Self-efficacy Scale
HADS	Hospital Anxiety and Depression Scale
HCP	Health care Professionals
HF	Heart Failure
HSE	Health Survey for England
ICH GCP	International Conference for Harmonisation of Good Clinical Practice
ILD	Interstitial Lung Disease
IPF	Idiopathic Pulmonary Fibrosis
IRQ	Interquartile range
ISWT	Incremental Shuttle Walk Test
LTOT	Long-Term Oxygen Therapy
MCID	Minimal Clinically Important Difference
MDP	Multi-dimensional Dyspnoea Profile
MEG	magnetoencephalography
MD	Missing Data
MHRA	Medicines and Healthcare products Regulatory Agency
MND	Motor Neuron Disease
MRC	Medical Research Council
MSAS-SF	Memorial Symptom Assessment Scale – Short Form
6MWT	six Minute Walk Test
NHS	National Health service
NICE	National Institute for Clinical Excellence
NIPPV	Non Invasive Partial Pressure Ventilation
NMES	Neuro-muscular Electrical Stimulation
NOT	Nocturnal Oxygen Therapy
NRS	Numerical Rating Scale
NYHA	New York Heart Association (classification of heart failure based on severity of symptoms I-IV

OR	Odds Ratio
PET	Position Emission Tomography
PLB	Pursed-lip breathing
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SBOT	Short-Burst Oxygen Therapy
SGRQ	St Georges Respiratory Questionnaire
SMD	Standardised Mean Difference
SD	Standard Deviation
SE	Standard Error
SR	Systematic Review
UCSD (SOBQ)	University of California, San Diego Shortness of Breath Questionnaire
UK	United Kingdom
VAS	Visual Analogue Scale
WHO	World Health Organisation
ZBI	Zarit Caregivers Burden Interview