

Researching breathlessness in palliative care: consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup

S Dorman Poole Hospital NHS Foundation Trust, Longfleet Road, Poole, **C Jolley** King's College London, Division of Asthma, Allergy and Lung Biology, Denmark Hill, London, **A Abernethy** Division of Medical Oncology, Department of Medicine, Duke University Medical Center, United States, **D Currow** Department of Palliative and Supportive Services, Flinders University, Adelaide, Australia, **M Johnson** University of Hull and Honorary Consultant to St Catherine's Hospice, Scarborough, **M Farquhar** General Practice and Primary Care Research Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, **G Griffiths** Wales Cancer Trials Unit, Cardiff, **T Peel** North Tyneside General Hospital, Rake Lane, North Shields, Tyne & Wear, **S Moosavi** Airways Disease, Faculty of Medicine, National Heart and Lung Institute, Imperial College London, **A Byrne** Marie Curie Centre, Bridgeman Road, Penarth, Vale of Glamorgan and Wales Cancer Trials Unit, Cardiff, **A Wilcock** Hayward House Macmillan Specialist Palliative Cancer Care Unit, Nottingham University Hospitals NHS Trust, City Hospital Campus, Hucknall Road, Nottingham, **L Alloway** North Hampshire Palliative Care Service, Basingstoke, **C Bausewein**, **I Higginson** King's College London, London and **S Booth** Cambridge University Hospitals NHS Foundation Trust, Cambridge

Breathlessness is common in advanced disease and can have a devastating impact on patients and carers. Research on the management of breathlessness is challenging. There are relatively few studies, and many studies are limited by inadequate power or design. This paper represents a consensus statement of the National Cancer Research Institute Palliative Care Breathlessness Subgroup. The aims of this paper are to facilitate the design of adequately powered multi-centre interventional studies in breathlessness, to suggest a standardised, rational approach to breathlessness research and to aid future 'between study' comparisons. Discussion of the physiology of breathlessness is included. *Palliative Medicine* (2009); **00**: 1–15

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Background

Breathlessness can be a devastating symptom of advanced disease, including cancer,^{1,2} end-stage heart failure,³ severe chronic obstructive pulmonary disease (COPD),⁴ pulmonary fibrosis⁵ and end-stage renal failure.⁶ It is a multi-dimensional symptom with a profound impact on the lives of the patient and their carers.^{7,8} The American Thoracic Society (ATS) defines breathlessness as follows:

'...a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses'⁷

The management of breathlessness is unsatisfactory.⁹ Patients and their carers may have to cope with this frightening symptom for many years or, where the underlying cause is cancer, experience or observe an alarmingly rapid decline into severe breathlessness. Prevalence of breathlessness is high in patients with terminal disease: estimates vary from 29% to 74% of patients.⁷ The variation may relate to differently defined population groups, use of different measurement instruments and proxy measurements (health professionals tend to underreport patients' breathlessness).^{10,11}

Research on the management of breathlessness is difficult. There are relatively few studies, and many studies are limited by inadequate power or design flaws.^{12,13} To make progress, multi-centre trials are required to recruit and retain sufficient numbers of participants along with the use of standardised outcome measures¹²; this could also improve the utility of systematic reviews of interventions.¹³

To our knowledge, there are no guidelines on researching breathlessness. This paper represents a consensus statement

Correspondence to: Saskie Dorman, MRCP, MSc (Consultant in Palliative Medicine), Poole Hospital NHS Foundation Trust, Longfleet Road, Poole, BH15 2JB.
Email: saskie.dorman@poole.nhs.uk

of the National Cancer Research Institute (NCRI) Palliative Care Breathlessness Subgroup, whose members include researchers and clinicians with a range of expertise in palliative medicine, breathlessness, respiratory medicine, oncology, respiratory physiology, statistics, quantitative and qualitative research. The aims of this paper are

- to facilitate the design of adequately powered multi-centre interventional studies;
- to suggest a standardised, rational approach to breathlessness research; and
- to aid future ‘between study’ comparisons.

Physiology of breathlessness

Many comprehensive reviews on the physiology of breathlessness are available (e.g.^{7,14–17}) but, in this paper, an overview is presented.

The sensation of breathlessness is ultimately a result of activation of proprioceptive pathways during respiration¹⁶ and is closely related to the sensation of respiratory effort.¹⁸ A simple physiological model of breathlessness considers the relationship between the *capacity* of the respiratory muscles (muscle strength, fatigability), the *load* on the respiratory muscles (particularly mechanical load, but chemostimulation by hypercapnia, hypoxia and acidosis is also important) and the level of *neural respiratory drive* (NRD) necessary to maintain a balance between them.^{16,19}

Conscious awareness of the level of NRD is important in the perception of breathlessness, regardless of the nature of the stimulus exciting the respiratory controller.²⁰ Dissociation between the level and pattern of *efferent* neural drive to the respiratory muscles and *afferent* feedback (efferent–afferent mismatch) is important.^{7,21,22} In simple terms, the brain ‘expects’ a certain pattern of ventilation and afferent feedback in association with a given level of NRD, and any deviation causes or intensifies the sensation of breathlessness.

Afferent feedback is provided by a variety of lung and chest wall mechanoreceptors and chemoreceptors.⁷ Breathlessness is, therefore, frequently a feature of diseases in which there is uncoupling of NRD from the mechanical output of the respiratory muscles and ventilation (‘neuromechanical dissociation’).

The specific cortical and subcortical areas involved in integrating this information are not fully known. However, functional imaging studies implicate limbic areas, such as the insula, anterior and posterior cingulate cortex and amygdala, as well as the cerebellum.^{23,24} The involvement of limbic areas in processing the unpleasantness of breathlessness, in particular the anterior insula and amygdala, suggests a common cortical network for the perception of breathlessness, pain and other symptoms.^{25,26}

Research in palliative care

Undertaking research in palliative care is challenging due to practical, ethical, methodological and emotional issues for potential participants and their carers, including health professionals.^{27–33} Concerns regarding the vulnerability of this patient group may contribute to clinical teams and ethics committees acting as overprotective ‘gate-keepers’.³⁴ Patients themselves appreciate the opportunity to participate when given a choice.^{35–42} However, patients may find recruiting and consenting procedures exhausting, and even minor non-invasive study interventions and assessments may be burdensome. Generally, attrition rates are high, particularly in advanced disease.^{27,32,33,43–45} Some research groups anticipate that four patients have to be screened for every one that takes part and an attrition rate of 40% in trials lasting over 6 weeks (A Byrne, personal communication).

There has been little research on refractory breathlessness (breathlessness which persists despite optimum medical management of the conditions causing it). Measuring multi-dimensional symptom severity (or the impact of interventions for it) is more difficult than assessing absolute end points (such as death) or a physiological measurement (such as lung function). Thus, even in a condition like advanced COPD, for which there are few disease-altering treatment and patients remain highly symptomatic for many years, there is a paucity of evidence on symptom management and improving quality of life.

Standardising an approach to research into breathlessness in advanced disease

Study design

Researchers should carefully choose the most appropriate methodology which is most likely to give an accurate answer to the research question. Functional imaging and physiological studies can improve our understanding of the pathophysiology of breathlessness; qualitative studies allow us to explore the patients’ and carers’ experiences of breathlessness (see Section ‘Qualitative research’). Single-dose studies may be needed in feasibility studies of new drug therapy. However, a study investigating a drug therapy for refractory breathlessness should generally be based on multiple doses, over a period of time at least sufficient to reach steady state.

Randomised trials of interventions for breathlessness should be undertaken where appropriate. Randomised double-blind, placebo-controlled trials are frequently seen as the gold standard in evidence-based medicine. The control should be best-evidence practise, and in the absence of an evidence-based therapy, a placebo can be justified. Ideally, both participant and investigator will

be blind to the identity of the treatment used, but this may not always be possible⁴⁶ (particularly for non-pharmacological interventions, such as exercise or fan therapy). Difficulties with blinding introduce potential bias in the results.

Cross-over trials allow the testing of short-term interventions (such as oral morphine⁴⁷) in relatively stable patients but may lead to methodological difficulties in a population with a high anticipated attrition rate.

The phased approach of the Medical Research Council (MRC) evaluation of complex interventions^{48,49} is a useful method for health services research, particularly in palliative care in which interventions often combine medical and psycho-social components.

Qualitative methods may be most appropriate to explore the experience of breathlessness, whereas quantitative trials can assess the effectiveness of interventions; qualitative and quantitative methods can be usefully combined within the same study to measure effect size (for example) and explore potential barriers and enablers to the use of the intervention.

Quantitative interventional studies

Questions regarding the effectiveness of interventions can be formulated using the *Population, Intervention, Comparison and Outcome* (PICO) format.^{50,51} It is important to define each aspect clearly. The *Consolidated Standards of Reporting Trials* (CONSORT) statement describes in detail the standards which should be followed for reporting randomised controlled trials and highlights several issues relevant to other types of study design.^{52,53}

Population

The population should be clearly defined to allow others to assess the applicability and generalisability of the research findings (see Table 1). Sociodemographic data (such as age, gender, ethnicity) and diagnoses should be recorded. Many people with breathlessness due to advanced disease will have had to retire,^{54,55} so level of educational attainment and most recent occupation (rather than income level) may be helpful in trying to understand the social factors affecting the experience or concordance with treatments.

Efficacy trials establish the potential net clinical benefits of an intervention in a highly selected study population. These trials should be complemented with effectiveness studies that reflect real-world practice. For example, researchers should try not to exclude patients with significant co-morbidity in effectiveness studies as patients with lung cancer (for example) often also have significant COPD.⁸³ Use of a validated co-morbidity index⁵⁷ may help describe the study population.

The cause(s) of breathlessness, where known, should be recorded, to allow for comparison between studies and to identify the effectiveness of targeted therapy for specific conditions. More than one factor may be relevant,⁸⁴ and it is not always possible to identify the cause of breathlessness.

Current medications and other treatments, such as any recent cytotoxic chemotherapy, any therapy known to cause lung dysfunction (e.g. bleomycin) and radiotherapy, should also be recorded.

Initial functional status

Several measures of functional or performance status are in current use. The Eastern Cooperative Oncology Group performance status⁸⁵ is popular and is a useful discriminator in populations with a wide range of functional abilities. However, it is relatively crude and, in a palliative care population, all participants may fall into one category, that is, category 3 or 4. A recent modification of the Karnofsky Scale⁶³ has improved its face validity for palliative care patients.⁶⁴

Initial symptom severity

Patients should be categorised as breathless at rest or only on exertion, as different interventions will be appropriate for these two groups. Entry criteria may be set, for example, to include those with 'breathlessness at rest, with a Numerical Rating Scale (NRS) (Appendix 1) score of 4 or above' to clarify the population being studied. The MRC Breathlessness Scale (Appendix 2) and modified versions of this scale^{59–62} are widely used, although not well validated. For patients with advanced disease, most will fall into categories 4 or 5 and the scale does not specifically identify patients who are breathless at rest. The Dyspnoea Exertion Scale (DES)⁵⁸ (Appendix 3) has better face validity than the MRC Scale for individuals with advanced disease, who may be breathless on minimal exertion or at rest. The DES has not yet been fully validated.

Descriptors of breathlessness

Breathlessness consists of 'qualitatively distinct sensations',⁷ and patients use many different words to describe the experience of breathlessness, such as 'suffocating', 'choking' and 'tightness'.⁸⁶ There is currently insufficient evidence to determine the aetiology of an individual's breathlessness on the basis of the descriptors they use,⁸⁷ but researchers should consider collecting data on the quality of the sensations (using descriptors) so that data may be pooled from different studies to assess fully whether this will ever be possible. Simon and colleagues^{65,66} developed a list of 15 descriptors that are presented to patients in a random order and the patient is asked to choose the three most appropriate to describe their sensation of dyspnoea. This has been tested in experimental models of breathlessness on healthy volunteers, in patients

Table 1 Summary of recommended data collection

	Rationale	Possible tools
Population		
Age	Informs applicability of results in clinical practise	
Gender	Informs applicability of results in clinical practise	
Ethnicity	Different ethnicities report breathlessness in different ways ⁵⁶	
Diagnosis	Distinct pathophysiological processes and disease trajectory; informs applicability of results in clinical practise	
Co-morbidity	Several conditions may coincide and contribute to breathlessness; helps readers assess applicability to clinical practise	Charlson co-morbidity index ⁵⁷
Functional status	Interventions may be applicable at different stages in disease trajectory; assists translation to clinical practise; allows replication of study in different sites	DES ⁵⁸ or modified MRC – see text ^{59–62} Karnofsky ⁶³ or modified Karnofsky – see text ⁶⁴
Symptom descriptors	May help define symptom more clearly	Simon, <i>et al.</i> Questionnaire ^{65,66} Cancer Dyspnoea Scale ⁶⁷ DAQ ⁵⁸ DDQ ^{68,69}
Educational attainment	May help with understanding issues of symptom experience and compliance with treatments etc.	
Intervention and comparator		
Dose	Allow replication of study in different sites and translation into clinical practise	
Route		
Frequency		
Setting		
Duration of treatment		
Outcomes and other assessments		
Severity of breathlessness	Of importance to patients themselves	NRS, ^{70,71} modified Borg Scale ^{72–74}
Impact of breathlessness	Of importance to patients themselves	CRQ ⁷⁵
Health-related quality of life	Of importance to patients themselves	CRQ ⁷⁵ EuroQol ⁷⁶ , FACT-L ⁷⁷ , QLQ-C15-PAL ⁷⁸ , QLQ-LC13 ⁷⁹
Patient preference and comments	May identify additional data which current measurement tools are insufficiently sensitive to capture	Qualitative interviewing ⁸⁰
Reason therapy stopped		
Toxicity		National Cancer Institute Common Terminology Criteria for Adverse Events
Functional and physiological measures	May be relevant to identify cause of breathlessness and enhance understanding of pathophysiology, though not usually of prime importance to patients; proxy measures of outcome	Lung function Shuttle walk test ⁸¹ (see text) Reading numbers aloud ⁸² Respiratory rate Blood gas analysis and pulse oximetry (see text) Haemoglobin, BNP Chest radiology Functional neuroimaging (see text)
Survival		

DES, Dyspnoea Exertion Scale; DAQ, Dyspnoea Assessment Questionnaire; DDQ, Dyspnoea Descriptor Questionnaire; CRQ, Chronic Respiratory Questionnaire; FACT-L, Functional Assessment of Cancer Therapy-Lung; MRC, Medical Research Council; NRS, Numerical Rating Scale; BNP, Brain Natriuretic Peptide.

with chronic cardio-respiratory disease and those with lung cancer.⁸⁷ Unfortunately, it does not appear possible to determine the cause of breathlessness based on these descriptors⁸⁷ or the ideal intervention to help relieve the breathlessness.

The Cancer Dyspnoea Scale is a self-completed 12-item scale. The items describe sensations associated with breathlessness and map onto three factors (sense of effort, sense of anxiety and sense of discomfort).^{67,88}

Interventions for breathlessness

Interventions should be described clearly to allow replication of studies in different settings, sites and patient groups. This is crucial to taking breathlessness research forward and is a key recommendation of this group. It is particularly important in palliative care where many interventions may be described as complex, that is, ‘built up from a number of components, which may act both independently and interdependently’.⁸⁹

Examples of interventions which have been studied include opioids, oxygen and breathlessness clinics for patients with lung cancer. Examples of the minimum data about each intervention are shown in Table 2.

Comparators

It is essential to describe whichever comparator is chosen in sufficient detail to allow replication in different sites. When an accepted standard treatment of known effectiveness exists, this should act as the comparator rather than a placebo.⁴⁶

Outcome assessment

Appropriate outcome measures should be used which are valid, reliable and responsive.⁹⁴ Recommendations are set out in Table 3.

Important considerations include

- relevance to people with advanced disease (face validity);
- construct validity (extent to which the instrument measures breathlessness rather than some other construct);
- responsiveness to changes in breathlessness;
- test-retest reliability;
- feasibility for patients with advanced disease, for example, ease of completion for frail, fatigued patients and carers; ease of understanding,¹⁰³ number of other measures to complete (time and complexity of completion), suitability for repeated administration (where required);
- requiring no extra travel where possible (this makes some specialised measurements available only to sub-groups of patients);
- feasibility for researcher, for example, number of administrations of each instrument per researcher across study period (maintenance of inter-rater reliability);
- assessment of toxicity;

- disease trajectory.

Suitable measures will demonstrate test-retest reliability and responsiveness and therefore the sample size required to show the effectiveness of an intervention will be minimised and resources will be used as effectively as possible. Using outcome measures which fail to show responsiveness means that potentially effective interventions may be missed.⁹⁴

The likely prognosis and disease trajectory of the patients are key in the selection of an appropriate scale and timing of participant assessments. For instance, patients with breathlessness due to lung cancer are likely to deteriorate more quickly than those with COPD, where symptom severity may only change over months or years.

Outcome measures can be divided broadly into *subjective* reports of breathlessness severity and impact, and *functional* and *physiological* measures of the respiratory system (see Section ‘Physiological and functional assessments in breathlessness research’). Breathlessness should not be viewed in isolation; it often co-exists with other symptoms, such as fatigue and anxiety.^{104,105} For patients who are breathless on exertion, activities may be limited by muscle fatigue rather than breathlessness¹⁰⁶ and researchers should consider including a measure of fatigue. We also recommend a *measure of the sense of mastery* or control that the participant has over their breathlessness¹⁰⁷ and a *measure of their emotional or psychological state*.^{107,108} Researchers should also consider measuring sleep disturbance due to breathlessness.¹⁰⁹

It is important to measure symptoms as well as functional status. Whilst a reduction in breathlessness or an increased sense of mastery may not be translated into a measurable improvement in functional status, even a small change in symptom perception may have a significant effect on the patient’s ability to manage their condition. This in turn may make the difference to important outcomes, such as the patient and carer’s ability to be treated at home, the amount of professional support

Table 2 Examples of interventions that have been tested in breathlessness clinical trials

Intervention			
Morphine ⁴⁷ Oxygen ^{90,91}	Dose and frequency Concentration	Route of delivery Route of delivery (e.g. inhaled via nasal cannulae and inhaled by Venturi 28% mask etc.)	Total duration of treatment Total duration of treatment
Breathlessness clinic ^{92,93}	Components of clinic, e.g. exercise program (duration and intensity of exercise), anxiety management, relaxation techniques, crisis management; duration of clinic visits; frequency of clinic	Setting (e.g. home, hospice, hospital, day care); individual or group treatments	Total duration of clinic course

Table 3 Measures of symptom severity, impact of breathlessness and health-related quality of life

Breathlessness severity		
NRS ^{70,71}	Numerical Rating Scale	0 to 10. Usually verbal anchors are provided for 0 (for example, 'no breathlessness') and 10 ('shortness of breath as bad as can be').
Modified Borg Scale ^{72,73}		The original Borg Scale had 21 points, labelled with verbal descriptors. ⁹⁵ Borg subsequently modified the scale to range from 6 to 20, so the pulse rate during exercise would be 'fairly close to 10 times the ratings of perceived exertion (RPE) values'. ⁹⁵ Verbal anchors range from 'very, very light' to 'very, very hard'; the modified scale ranges from 0 to 10 ^{72,73} . This is a ratio scale: '6' denotes a perception twice as intense as '3', and so on. There are several modifications of the scale. The version used in ⁹⁶ is recommended for use.
Impact of breathlessness		
CRQ ⁷⁵	Chronic Respiratory Disease Questionnaire	The CRQ includes 20 items covering areas identified by patients and experts as important to the quality of life of patients with chronic airflow limitation and supersedes the CDQ. CRQ domains include dyspnoea (5 items), fatigue (4), emotional function (7) and mastery (the feeling of control over the disease and its effects; 4 items). Individuals choose the five activities most important to them and rate the associated breathlessness over the last 2 weeks on a Likert-like scale (1 to 7). Important activities which are no longer done (perhaps because of breathlessness) are not identified. The CRQ has been translated into several languages. ⁹⁷ Initially, it was developed as an interviewer-administered questionnaire, ⁷⁵ but a self-administered version is now available. ^{98–100} A standardised version is available with five listed activities. ¹⁰¹ Activities include feeling emotional, basic care (bathing, showering, eating or dressing), walking, chores (such as housework) and social activities.
MDRS ¹⁰²	Motor Neurone Disease Dyspnoea Rating Scale	The MDRS is similar to CRQ, with a shorter list of activities (to suit patients with 'exercise-limiting limb weakness' ¹⁰²), and breathlessness is graded from 0 to 4 rather than from 1 to 7. There are also subscales for fatigue, emotion and mastery, as in the CRQ. ⁷⁵
Health-related quality of life		
EuroQol 5D ⁷⁶		Self-administered, validated, measure of health-related quality of life; consists of a 5-question multi-attribute questionnaire and a VAS self-rating scale. Respondents are asked to rate severity of their current problems (level 1 = no. problems, level 2 = some/moderate problems, level 3 = severe/extreme problems) for five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. ⁷⁶

needed and levels of carer exhaustion. These aspects of breathlessness are hard to measure quantitatively at present, although qualitative data may be needed to explore their significance.

Self-report measures of symptom severity and impact

The available outcome measures for assessing the severity and impact of breathlessness have recently been systematically reviewed.^{110,111} Although none has been well validated¹¹² specifically for use in palliative care, evaluation in this population is in progress. We list here the outcome measures that we consider to be the most suitable.

We recommend that assessment of breathlessness severity should be recorded using for instance the NRS or modified Borg Scale:

- 'right now',
- 'average over past 24 h' and
- 'worst over past 24 h'.

The minimal clinically important difference is reported as 1 unit for the modified Borg Scale used during exercise, although Ries¹¹³ noted that its design as a ratio scale

means it is possible that larger changes may be more commonly seen at the higher end of the scale.

Measuring the degree of relief of breathlessness may also be useful (for instance, using a NRS) (Appendix 1). The Chronic Respiratory Questionnaire (CRQ), measuring symptoms over the previous 2 weeks, has been validated for use in many conditions⁹⁷ (COPD,^{75,107,114–117} interstitial lung disease¹¹⁸ and cystic fibrosis,¹¹⁹ with less satisfactory evaluation in α_1 -antitrypsin deficiency¹²⁰; the very similar Chronic Heart Failure Questionnaire has been validated in heart failure¹²¹). It is appropriate for measuring the impact of breathlessness on *activity*, as well as emotions, fatigue and the sense of mastery.⁷⁵ The minimal important difference (defined by Schunemann, *et al.* as 'the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management') is reported as 0.5 per domain.¹²² The Motor Neurone Disease Dyspnoea Rating Scale is similar to the CRQ; it was developed for patients whose activities are limited by limb weakness¹⁰² (Table 3).

Quality of life and health-related quality of life

Quality of life is difficult to measure as the relevant domains vary according to each individual and may alter over time.¹²³ Health-related quality of life measures have been reviewed previously.¹²⁴ Standardised measures (using a pre-determined value system) include generic and disease-specific instruments, such as FACT-L⁷⁷ and the European Organisation for Research and Treatment of Cancer (core QLQ-C30¹²⁵, QLQ-C15-PAL⁷⁸ or QLQ-LC-13 module⁷⁹). An attempt to capture the uniqueness of individuals through patient-generated quality of life measures is appealing in theory¹²³ but in practice may be too complex for patients with advanced disease, particularly where a battery of instruments is required.¹²⁶ The EuroQOL 5D⁷⁶ is a widely used standardised generic health-status measure (see Table 3).

Timing of outcome assessment

Symptoms should be assessed consistently at specified times following an intervention.¹²⁷ The optimal timing for breathlessness assessment is not currently well defined and is an important area for future research.

Pharmacokinetics and pharmacodynamics must be taken into account when deciding on the appropriate timing of outcome assessments. For long-term interventions, the timing of assessments is more complex: there is often a high attrition rate, so outcome assessments which are too widely spaced will risk a high proportion of missing data. Appropriate methods for handling missing data should be defined before data collection begins, with advice from a statistician.

Physiological and functional assessments in breathlessness research

Overall, there appears to be poor correlation of physiological measures of lung function with patients' reports of breathlessness.^{105,128,129} However, physiological assessment can assist in defining the patient population and may provide insight into the mechanisms and causes of breathlessness.^{83,84}

Reflecting the physiological mechanisms of breathlessness (see Section 'Physiology of breathlessness'), it is useful to consider measurements in terms of ventilatory load and capacity.

Assessment of ventilatory load

Mechanical load

Simple spirometry is recommended in the clinical assessment of patients with COPD¹³⁰ as an indication of disease severity and can be performed on portable equipment in the home or at the bedside without specialist training.

However, it does not correlate in a simple way with breathlessness severity.^{128,131} Patient-reported breathlessness measures appear to predict performance at the 6-minute walk test (6MWT) better than spirometry.¹²⁹

The degree of static (at rest) and dynamic (on exercise) lung hyperinflation correlates better with breathlessness than forced expiratory volume in one second and can be assessed by measuring lung volumes (particularly end expiratory lung volume^{132,133}), inspiratory capacity^{133–135} or reserve volume.¹³⁶

Chemoreceptor drive

Chemoreceptor drive can be measured directly (blood gas analysis, pulse oximetry, transcutaneous capnography and lactate measurement) or indirectly (assessment of pulmonary diffusion and peripheral muscle function). Currently, measures of peripheral muscle function are only available at specialist centres and collaboration with respiratory physiologists will be crucial to gain a fuller understanding of the pathophysiological processes relevant to breathlessness.

Measurement of ventilatory capacity

These can be subdivided into inspiratory muscle tests and expiratory muscle tests, which may be volitional or non-volitional.^{137,138}

Volitional investigations

Sniff nasal pressure is more comfortable for patients to perform and more reliable than $P_{I_{max}}$ manoeuvres¹³⁹; this has been measured in patients with cancer.^{140,141}

Non-volitional investigations

Non-volitional tests involve stimulation of the peripheral nerves responsible for respiratory muscle activation¹³⁷ and are only available in some respiratory departments. These assessments have yet to be carried out in patients with cancer.

Assessment of NRD

Indirect assessments of NRD include respiratory rate, minute ventilation (VE) and mouth occlusion pressure ($P_{0.1}$). Respiratory rate is a simple bedside measurement. There is a linear relationship between breathlessness and VE in healthy subjects.¹⁴² Although $P_{0.1}$ has been shown to correlate with breathlessness during exercise in COPD,¹⁴³ mechanical measures of NRD underestimate NRD in patients with neuromechanical dissociation, such as severe COPD.¹⁴⁴

Respiratory muscle electromyogram activity (EMG) can be used to measure NRD.^{137,145} Rib cage muscle and sternocleidomastoid EMG activity have been shown to relate to the sensation of respiratory effort in healthy subjects.¹⁴⁶

Assessment of central integration and processing

Functional imaging, such as functional magnetic resonance imaging and positron emission tomography, has enhanced understanding of the neurophysiology of breathlessness,^{23,25,26} but studies have thus far involved healthy participants (using more or less artificial measures to evoke breathlessness, such as breath holding or external respiratory loading). Studies have not been carried out with patients with advanced disease. Magnetoencephalography (MEG) scanning may be helpful in this regard, as patients will be able to sit up during scanning.¹⁴⁷

Functional measures: which test?

Exercise testing may be used to stimulate breathlessness or as a means of assessing ventilatory limitation of exercise capacity. These tests range from simple field exercise tests, which should be possible in every clinical setting, to full cardiopulmonary exercise tests, which may only be available in specialist units.¹⁴⁸

It is important to choose tests appropriate to the clinical scenario and research question. Different tests produce different symptoms: leg fatigue is more frequently cited than breathlessness as the reason for stopping cycle ergometry in COPD¹⁴⁹; arm fatigue is more common than breathlessness in upper limb exercise in patients with cancer,¹⁵⁰ whereas breathlessness is cited more commonly than leg fatigue in treadmill exercise. Collaboration with established researchers familiar with such outcome measures is encouraged.

Various walking tests have been used extensively in studies of patients with cardiorespiratory disease. These measures have been systematically reviewed.¹⁵¹

The incremental shuttle walk test has evidence of reliability in patients with COPD¹⁵² and those with cancer.⁸¹ An endurance shuttle walk test is also available.¹⁵³ The 6MWT has been widely used in studies of patients with COPD. It has evidence of test-retest reliability and responsiveness in elderly patients with heart failure.^{154,155} The ATS has set out recommendations for standard practise in the 6MWT.¹⁵⁶ There is a learning effect (generally greatest between first and second tests)¹⁵⁶ and motivation and encouragement also have an effect on performance¹⁵⁷; the shuttle walk tests may, therefore, be preferable¹⁵⁸ as they are externally paced.

Cycle ergometry which is widely used in respiratory medicine is rarely used in patients with cancer as those with advanced disease will often have other conditions that make it particularly uncomfortable.

An alternative form of exercise testing is upper limb exercise (e.g. the one-arm or two-arm tests) which has been evaluated in patients with primary or secondary lung cancer.¹⁵⁰ Exercise testing is frequently limited by limb fatigue rather than by breathlessness, and further evaluation of responsiveness is needed.¹⁵⁰

Ultimately, exercise tests are an artificial representation of day to day activity levels. Lightweight physical

activity monitors, for example, worn on the thigh for a week or more, are currently being explored as a more meaningful outcome measure (Wilcock, personal communication 2008).

Some patients may not be breathless at rest but become so on minimum exertion, even on talking. For this group of patients, a test has been developed which involves reading numbers aloud, as a means of assessing the limiting effect of breathlessness.⁸² The test, discriminates between healthy volunteers and patients with cancer, is reliable and responsive to improvements seen after drainage of a pleural effusion.⁸²

Qualitative research

Qualitative methods including unstructured and semi-structured interviews and focus groups can allow exploration of the subjective experience of breathlessness and interventions for it. This can augment the findings from quantitative research and offer an extra dimension of understanding of the patients' and carers' experience. Insights into clinicians' understanding of the symptom and its management may also be gained; this is information which is not readily obtainable by quantitative methods.^{8,80,159} A full review of qualitative methods is beyond the scope of this paper but several useful texts are available.^{160,161}

Practical aspects of conducting multi-centre palliative care clinical trials in dyspnoea

The study of breathlessness demands a multi-disciplinary approach which includes respiratory scientists, respiratory physicians, palliative medicine physicians, oncologists or other appropriate specialists, social scientists, clinical pharmacologists, physical therapists, nurses, biometricians and biostatisticians. Such an approach leads to robust design in what is a complex somato-psychic experience. Phase I and II studies can be usefully carried out at a single centre, but for interventional studies, such as randomised controlled trials of drug therapies, multi-centre research is crucial.¹⁶²

The particular problems, outlined already, of researching in palliative care make multi-centre collaboration particularly important to recruit sufficient patients for adequately powered trials that can give definitive answers to clinical questions. Web-based entry can facilitate international collaboration.¹⁶² Multi-centre research must be rigorously conducted with carefully operationalised study protocols, staff with dedicated research time, and continuing quality assurance to ensure that results are meaningful. Adherence to Good Clinical Practice guidelines (GCP Directive 2005/28/EC)¹⁶³ is essential. Clinical

trials investigating medicinal products must adhere to the strict regulatory requirements for trial management. Multi-centre collaboration in palliative care is in its infancy and there have been few such international trials. One randomised controlled trial currently underway by Currow in Australia and Abernethy in the United States is evaluating oxygen in the palliation of breathlessness (ISRCTN67448752); this study is important both for the assessment of efficacy of palliative oxygen and for the demonstration that rigorous international multi-centre trials in palliative care and breathlessness are possible.

To ensure smooth day to day running of the trial, a Trial Management Group should be established. This will include the chief investigator, clinical co-investigator, trial and data management staffs, statistician, patient representative, trials nurse, pharmacist and other experts as appropriate.

Unlike oncology trials, breathlessness trials will frequently be carried out in several different departments of different hospitals, the community and in hospices at the same time. It is essential for smooth running of such trials that excellent communication and a sense of cohesion is established and maintained between all these different teams. Study newsletters, routine mass e-mails and staff teleconferences are helpful. Individual responsibilities should be well delineated. Face-to-face training and monitoring are also crucial.

Study procedures must be completely described in a study manual distributed to all sites. Standard operating procedures should be housed with the manual, as well as other important documents, such as a schedule of events, fax cover sheets, sample consent form and recruitment script. Processes critical to the conduct of the trial must be standardised so that the intervention is exactly the same at each site. Equipment, such as pulse oximeters, should be calibrated with details recorded in a log in the manual. Procedures for use of breathlessness scales and for conducting 6MWT or shuttle test should be detailed, with relevant sign-off logs demonstrating site-level training. Site training should be conducted using the manual and operating procedures, and site performance should be measured against the site's ability to adhere to each of the standards.

Central co-ordination of randomisation and of data collation, cleaning and analysis are equally crucial and are relatively new to palliative care. Data queries and data cleaning should be timely, so that sites will still have easy access to case notes and other medical records to reply to data queries. The data co-ordinating centre should monitor missing data and seek to ensure that the study data are as complete as possible (recognising that missing data may be more common in the palliative care setting).

Adverse event monitoring should be a separate standardised procedure. An independent data safety review board should be formed for periodic outside review of adverse events for interventional studies to determine

whether they are related to the study intervention. This review board may or may not be responsible for interim efficacy review of the study.

An independent Trial Steering Committee should be set up to oversee the trial. This will meet regularly to consider the data safety review board recommendations and determine whether the trial should continue recruitment or close early (e.g. because of poor recruitment, safety reasons or treatment effect).

Analysis should be conducted by, or with the input of, trained biostatisticians who understand the nuances of multi-centre clinical research involving individuals with advanced life-limiting illness. 'Intention to treat' analyses are paramount, especially in palliative care. There is an ethical responsibility to the study participants who selflessly contributed their time and data to the study that results are published, and that there is an enduring record of their personal commitment to this research.

Summary of recommendations

At times, data collected in studies examining palliative care interventions for breathless patients are of limited use because of methodological flaws in the studies or incomplete recruitment. The conclusions and recommendations of the NCRI Palliative Care Breathlessness Research Subgroup are as follows:

- 1) Multi-centre trials are needed to answer the key clinical questions. International collaboration is now feasible.
- 2) Statisticians expert in the design and conduct of clinical studies should be involved at an early stage of trial planning.
- 3) Feasibility studies and a calculation of anticipated recruitment (calculating attrition rates from properly conducted pilot studies) are important in the planning stages.
- 4) A mixed methods approach (quantitative and qualitative) and the MRC complex interventions framework may be most appropriate for evaluating service interventions or multi-faceted treatments.
- 5) Populations should be accurately defined; co-morbidity indices, such as the Charlson Co-morbidity Scale, and performance status measures, such as the modified Karnofsky Scale, are recommended. The cause of breathlessness should be identified, where possible.
- 6) Interventions should be described clearly to allow replication of studies in different settings, sites and patient groups.
- 7) Validated outcome measures (e.g. NRS or modified Borg Scale) (Appendix 4) should be used to assess the severity of breathlessness 'right now', 'on average over the last 24 h' and 'at worst over the last 24 h'; it may

also be helpful to assess the degree of relief from breathlessness.

- 8) For long-term studies, a scale, such as the CRQ (which includes a 'mastery' subscale), should be used.
- 9) Research is urgently needed to explore the validity of outcome measures in the palliative care population, as there is not yet a gold standard outcome measure in this setting.
- 10) We encourage collaboration with investigators familiar with physiological measurements, to increase understanding of the pathophysiology of breathlessness, bringing forward the possibility of targeted interventions.

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Appendix 1

Numerical Rating Scale (NRS)

‘On a scale from 0 to 10
Indicate how much shortness of breath you are having right now
With 0 = no shortness of breath
And 10 = shortness of breath as bad as can be
Circle the number:
0 1 2 3 4 5 6 7 8 9 10’⁷⁰

Appendix 2

Medical Research Council (MRC) Respiratory Symptoms Questionnaire (breathlessness subscale)^{61,62}

Grade 1	Are you ever troubled by breathlessness except on strenuous exertion?	(No disability)
Grade 2	Are you short of breath when hurrying on the level or walking up a slight hill?	(Slight disability)
Grade 3	Do you have to walk slower than most people on the level? Do you have to stop after a mile or so (or after ¼ hour) on the level at your own pace?	(Moderate disability)
Grade 4	Do you have to stop for breath after walking about 100 yards (or after a few minutes) on the level?	(Severe disability)
Grade 5	Are you too breathless to leave the house or breathless after undressing?	(Total disability)

Appendix 3

Dyspnoea Exertion Scale (DES)⁵⁸

‘Which is the furthest statement down the list that applies to you?’

0	I am able to walk at my own pace the on the level without getting breathless over any distance
1	I become breathless if I walk more than 100 yards on the level at my own pace
2	I become breathless if I walk around the house or on the ward on the level at my own pace
3	I become breathless if I move around in bed or get out of bed
4	I become breathless on talking
5	I am breathless at rest

Appendix 4

Modified Borg Scale⁹⁶

Indicate how much shortness of breath you are having right now:

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal