

**TITLE: Towards an expert consensus to delineate a clinical syndrome of chronic breathlessness**

**Running title: Towards consensus: chronic breathlessness syndrome**

**Authors:**

Miriam J Johnson, MD. Hull York Medical School, University of Hull, Hull, UK.

Janelle Yorke, PhD. School of Nursing, Midwifery and Social Work, University of Manchester,  
Manchester, UK

John Hansen-Flaschen, MD. Perelman School of Medicine, Hospital of the University of Pennsylvania,  
Philadelphia. USA

Robert Lansing, PhD. Research Scientist at Beth Israel Hospital Harvard Medical School, Boston, Ma.  
USA.

Magnus Ekström, PhD. Department of Clinical Sciences, Division of Respiratory Medicine &  
Allergology, Lund University, Lund, Sweden.

Thomas Similowski, MD. Service de Pneumologie et Reanimation Medicale, Groupe Hospitalier Pitie-  
Salpetriere Charles Foix, Paris, France

David C Currow, PhD. Discipline, Palliative and Supportive Services,

Flinders Centre for Clinical Change, Flinders University, Adelaide, Australia

**Author for correspondence:**

Miriam J Johnson, Hertford Building, Hull York Medical School, University of Hull, Hull, UK HU6 7RX.

Email: [miriam.johnson@hyms.ac.uk](mailto:miriam.johnson@hyms.ac.uk). Tel: +44(0)1482 463309

This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for  
publication in the European Respiratory Journal, prior to copy-editing, formatting and typesetting.

This version of the manuscript may not be duplicated or reproduced without prior permission from  
the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for

any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication.

**Word count:** 3664**Summary take home message:** *Chronic breathlessness syndrome:* breathlessness and disability despite optimally treated underlying pathophysiology

## **ABSTRACT**

**Question:** Breathlessness that persists despite treatment for underlying conditions is debilitating. Identification of this discrete entity as a clinical syndrome should raise awareness amongst patients, clinicians, service providers, researchers and research funders.

**Methods:** Using the Delphi method, expert group consultations and one-to-one interviews (N=17) generated questions and statements subsequently circulated in 3 survey rounds (N= 34; N=25; N=31) to an extended international group from various settings (clinical and laboratory; hospital, hospice and community), basic sciences and clinical specialties. The *a priori* target agreement was 70%. Findings were discussed at a multi-national workshop.

**Results:** The agreed term, *chronic breathlessness syndrome*, was defined as breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability. A stated duration was not needed for “chronic”. Key terms for French and German translation were also discussed and the need for further consensus recognised, especially with regard to cultural and linguistic interpretation.

**Answer:** We propose criteria for *Chronic Breathlessness Syndrome*. Recognition is an important first step to address the therapeutic nihilism that has pervaded this neglected symptom and could empower patients and caregivers, improve clinical care, focus research, and encourage wider uptake of available and emerging evidence-based interventions.

## INTRODUCTION

Breathlessness, experienced as part of everyday living, is one of the most common forms of distress, experienced by approximately 10% of the general population, [1] rivaling pain in prevalence worldwide.[2]. Like pain, breathlessness can resist treatment of identified underlying condition(s), but nonetheless may itself be a primary target of medical management, irrespective of causative disease. In the case of pain, this situation is encompassed by the term "chronic pain syndrome".[3] No comparable syndrome is identified for breathlessness. The question arises whether the experience of breathlessness persisting despite adequate treatment of causative conditions should be delineated as a syndrome.

A clinical syndrome (**literally "a running together," from *syn-* "with" (see *syn-*) + *dromos* "a running, course"**[4]) is a constellation of clinical findings caused by an underlying disease(s) that may or may not be accompanied by laboratory or imaging abnormalities. The clinical findings may constitute a range of symptoms and physical findings, or describe one symptom in a particular context(s) and may include response to interventions targeted at the syndrome itself. The syndrome should be recognisable in clinical and research settings. Examples of clinical syndromes include delirium and chronic pain syndrome, acute respiratory distress syndrome, obstructive sleep apnoea syndrome and Tourette's.

Although difficult to prove "cause and effect", the description of a clinical syndrome has appeared to be associated with an increased awareness of its importance for clinicians, patients, service managers, commissioners, researchers and research funders. For example, since the delineation of the chronic pain syndrome, many health services now have chronic pain clinics and there is an International Society for the Study of Pain with its journal "Pain". This Society has led the way in research into chronic pain leading to a greater understanding of the mechanisms and management of chronic pain. [3] This opened the way to develop effective interventions targeted at specific

pathological process(es) or symptomatic treatment, and to guide development and validation of its assessment/measurement.

A variety of chronic medical conditions cause breathlessness as a key symptom: cardiorespiratory diseases, neuromuscular disorders, obesity, physical deconditioning, frailty, and cancer (respiratory or not). It is also a feature of several conditions where no somatic disorder can be identified such as chronic hyperventilation syndrome and related entities. Algorithms to guide the investigation of breathlessness, aid diagnosis and treatment of the underlying condition(s) are available, often leading to improvement of breathlessness.[5] However, despite optimal treatment of the underlying cause(s), breathlessness often persists at rest or on minimal exertion, worsening over time as the underlying cause(s) progress.[6, 7]

Breathlessness leads to serious limitations and distress for patients and their families with a negative impact on emotional function, with resulting low mood and poor quality of life often accompanied by episodes of more intense breathlessness and panic.[8, 9] Activities that healthy people take for granted can become challenging for people who are chronically breathless. Clinicians may not recognise the impact of chronic breathlessness given that people experiencing this will most often adjust their lifestyle to minimise the frequency and duration of more intense breathlessness.

Under-reported by patients and under-recognised by clinicians who focus on the underlying disease(s) or only see patients when acutely unwell, chronic breathlessness remains hidden from view[10] despite being an independent predictor of: survival;[11-14] restricted activities of daily living; [12] and emergency health service use.[15, 16] The importance of ongoing breathlessness as a symptom is still poorly recognised despite recent calls by researchers for this to be a research priority for people with chronic obstructive respiratory disease (COPD)[17] and for access to tailored management as a human right.[18] .

Currently, breathlessness that persists despite optimal treatment of the underlying conditions is sometimes referred to as "refractory breathlessness" or "refractory dyspnea".[19, 20] However, this terminology has not been the object of a formal definition and has never been formally proposed as a syndrome. Furthermore, the term refractory suggests complete resistance to treatment and therefore fails to convey a message of recognition in order to manage at least symptomatically; several interventions to reduce the symptom safely irrespective of its cause are available or under investigation.[21-23] Recognition of breathlessness that persists in spite of optimal treatment as a clinical syndrome could be useful in the ways outlined above.[24]

The aim of this study was to assess whether international expert consensus could be reached about:

- i) whether such breathlessness could and should constitute a clinical syndrome; and
- ii) if so, how this syndrome should be named and defined?

### **Methods:**

A 3-stage process was employed. The first two stages were conducted in accordance with the Delphi method.[25] For stage 3, the results were presented and discussed during an international workshop.

#### *1. Expert group consultations and single interviews.*

International published experts in the field of breathlessness were invited to contribute to a group or individual consultation by Skype or telephone identified and conducted by DC and MJ (N=17).

Delegates were invited from UK and continental Europe, USA and Australia to include a wide range of professional disciplines. Using snowball sampling, a non-probability sampling technique whereby existing participants recruit to the study from among their contacts, invitees were asked to identify and invite other key opinion leaders.

A topic guide was used to ensure each consultation included key areas but allowed other topics to arise. This followed a process of posing questions to generate ideas and debate, clarification and focus on areas of agreement and then identification of the remaining areas of debate to be further explored during the survey rounds. The key areas included: whether chronic breathlessness could and should constitute a clinical syndrome; if so, its name and definition; and the purpose that defining a syndrome would serve.

Detailed notes of agreements and disagreements were taken contemporaneously by MJ and DC, and used to identify those issues where delegates had agreed and those where disagreement identified questions to use in the survey rounds.

## *2. Survey rounds*

A target 70% agreement for each question was pre-specified. Three sequential survey rounds (responses n= 34; n=25; n=31) were individually completed using an online platform (Qualtrics Insight Platform, Utah, 2002). The first survey (Invitation and Survey available as online only text) was developed to explore views on a preliminary name and definition, as well as specific questions relating to each concept within the definition. The survey was sent to an extended group of experts (the consultation group and others) by email (n= 52) and was introduced with a summary of the prior iteration of agreement already reached from the expert groups after round one. In addition to choosing their preferred option provided for each question, each participant was invited to generate additional views and clarifications as supplementary free text.

At the end of the first survey, respondents were asked if they were willing to participate in subsequent rounds. Those who agreed were sent surveys 2 and 3. Collated agreements circulated in successive rounds meant that responses were anonymous to other members of the group reducing

the risk that some may feel pressure to conform to the views of others. Survey completion was taken as implied consent. As a result of each survey round, the name and definition were modified and options narrowed as consensus developed. As part of the last survey, a summary of the free text comments contributed by respondents was also provided.

### *3. Workshop*

The findings of the first two steps were presented and discussed at an international meeting for those interested in breathlessness research (Dyspnea 2016, Paris: <http://www.dyspnea2016inparis.fr/>). Specific discussions explored how such a name and definition would be translated usefully into different language and cultural settings.

#### *Role of the Funding source*

This unfunded study was conducted within resources.

#### *Ethics*

Ethical approval was not required for the Delphi process as researchers sought expert professional opinions only.

#### **FINDINGS:**

##### **Group Consultations and Interviews**

Four group consultations comprising a total number of 13 participants (N = 5; N = 4; N = 2; N = 2) were held between 17<sup>th</sup> July and 10<sup>th</sup> August 2015 each lasting approximately one hour. In addition, MJ interviewed four individuals. Invitees included experts from the following disciplines: respiratory medicine, cardiovascular medicine, primary care, medical, nursing, respiratory physiology, neuroimaging, intensive care, oncology and palliative care.



There was agreement that the symptom of breathlessness in these clinical settings should be raised to a clinical syndrome in the context of:

- i. persistence of breathlessness due to a causative medical condition(s) despite optimal treatment for the condition(s); and
- ii. negative consequences of the breathlessness.

It was agreed that recognition of a clinical syndrome would help to address the invisibility of such breathlessness. Further, for people experiencing this breathlessness, participants concurred that a recognised syndrome would help to validate their own experiences and give permission for patients to discuss their ongoing breathlessness with their clinicians. It was also felt that gaining research funding was rendered more difficult by a lack of recognition of chronic breathlessness by reviewers and research funders.

### Surveys

The extended group also included occupational therapy and physiotherapy clinicians. The development of agreement can be seen in Table 1. All reached the pre-set target of  $\geq 70\%$  agreement, except the part of the definition relating to how the treatment of the underlying disease should be phrased (68%). All 35 respondents to survey 1 agreed to participate in surveys 2 and 3. A summary of the free text comments provided to the respondents between surveys 2 and 3 can be seen in eTable 1. Survey response rate was 34/52 (51%) for survey 1; 25/34 (74%) for survey 2 and 31/34 (91%) for survey 3.

<< insert Table 1 about here >>

By survey 3, participants agreed that the name of the syndrome should be “chronic breathlessness syndrome” (77%) and should be defined as: breathlessness even though “...evidence-based

treatments of underlying pathophysiology of the causative disease(s) are optimised” (68%), “which contributes to physical limitations and/or a variety of adverse psychosocial, spiritual or other consequences” (77%). The term “chronic” did not need a stated duration (80%). Rather than continue to another round, 68% agreement for the treatment question was considered to be sufficient.

## Workshop

Participants in the workshop agreed that chronic breathlessness should be defined as a clinical syndrome. It was suggested that the definition regarding the adverse consequences of chronic breathlessness should reflect the language of the World Health Organisation (WHO) definition of disability to ensure global consistency.[26] The WHO International Classification of Functioning, Disability and Health (ICF)[26] defines disability as an overarching term for the interaction between individuals with a health condition (e.g. COPD) and personal and environmental factors (e.g. negative attitudes, inaccessible transportation and public buildings, or limited social supports).

There was extended and useful discussion about the trans-national translation of the name and definition of the syndrome particularly from the participants from the United Kingdom, Australia, France and America. For example the term “dyspnea” was more familiar to American delegates, but it was recognized that the lay term, “breathlessness”, should be used. The other contender was “short of breath”, but, on balance, it was felt that the addition of “chronic” made it clear that the syndrome referred to troublesome breathlessness. German attendees felt that no additional words to define breathlessness were needed; “refractory” would be unhelpful in German, giving the sense of “no hope”, and “short of breath” had a particular meaning which was inappropriate. For Swedish participants, it was felt that “chronic breathlessness “was acceptable”. In French, an adjective was thought to be needed and the term "*persistante*" in addition to, or in place of, "chronic". Although the English speakers felt that "chronic" implicitly contained the notion of “pathological”, this was not

the case for French speakers. There was concern about the term "*dyspnée*" because the lay term "*essoufflement*" (exact French translation of "breathlessness") encompasses both "worrying" and "non-worrying" situations (as in being "out of breath" -*essoufflé*- after acute exertion). However, "*essoufflement persistant*" or "*essoufflement chronique persistant*" could be discussed.

It was decided that a specific project aiming at providing the best French translation of "Chronic breathlessness syndrome" could be conducted secondarily by the Dyspnea working group of the French learned society for respiratory medicine (Société de Pneumologie de Langue Française).

It is hoped that this start toward some international consensus will stimulate further debate and discussion including translation into other languages and cultures.

#### **DISCUSSION.**

Using the Delphi method enhanced by an extended discussion among participants at an international meeting of experts on breathlessness, we attained broad consensus on the utility of recognizing a distinct clinical entity that can be named "Chronic Breathlessness Syndrome". We define this syndrome as the experience of breathlessness that persists despite optimal treatment of the underlying pathophysiology and results in disability for the patient. Participants decided that a descriptor such as "refractory" was not needed (and indeed, was considered unhelpful by some) in the title or in the definition.

A pathophysiological basis is not required in order to delineate a clinical syndrome. However, there is emerging evidence suggesting that the perception of chronic breathlessness in patients and acute breathlessness induced in healthy volunteers differ in some respects although they share common pathways. Neuroimaging studies indicate that people living with chronic breathlessness may have a higher level of breathlessness "vigilance" even when comfortable at rest compared with healthy

volunteers [27] and central perception of chronic breathlessness due to COPD involves activation of the frontal associative cortex (fear and memory) not seen in healthy volunteers. [28] Further, people with COPD have a higher neural respiratory drive at rest than healthy volunteers. [29][30] Neural respiratory drive closely correlates with breathlessness intensity and has been suggested as a biomarker for chronic breathlessness.[30]

The personal, behavioural and social adjustments in patients with chronic breathlessness are clearly of a different kind and order than those experiencing acute, episodic breathlessness. In addition, the clinically important difference for breathlessness intensity is smaller for chronic breathlessness (1 point change in 0-10 numerical rating scale, compared with 2 point change for acute breathlessness). [20, 31]. The experiences are different, and thus benefit is likely to be perceived differently. A change of 2 points may be needed to reassure the distressed, terrified person with acute, episodic breathlessness that they are not going to die. Conversely an improvement of 1 point for the person living with chronic breathlessness as a daily limitation may mean that they are able to make their own cup of tea, or manage to the toilet on their own.

#### Implications for clinical practice and policy

Widespread opinion from a variety of specialties and professions was sought so that the proposed definition, with its common language, would be broadly relevant across research methods and clinical practices as well as to patients living with chronic medical conditions leading to chronic breathlessness. Whereas it is good clinical practice to seek out and assess a symptom systematically, this is not routine in many settings where the focus is optimising the underlying disease treatments. Systematic documentation of chronic breathlessness in healthcare settings alone is unlikely to be sufficient to alter practice in the context described here, and from work in pain, assessment alone is unlikely to improve symptom control.[32] The delineation of *chronic breathlessness syndrome* provides focus for directed systematic clinical enquiry including targeted intervention. Usual practice

often stops at the point of optimised treatment of the underlying disease(s) (“nothing more we can do”). However, there are non- pharmacological *and* pharmacological evidence-based interventions for chronic breathlessness as a therapeutic target,[21, 23, 33-37] but these remain underused in clinical practice. Routine assessment will increasingly help to standardise the timely use of these treatments and foster a robust multi-disciplinary team approach whereby patients are referred routinely for active management of breathlessness by respiratory physiotherapists and psychologists and considered systematically for regular, low dose oral extended release morphine. We cannot guarantee that the recognition of this syndrome will change clinical practice and clinical outcomes, however, *without* its recognition we *will* not see progress and patients will not derive the benefit they deserve.

Education about these interventions is crucial as clinicians may be reluctant to look for something they believe they cannot treat. With regards to service provision, the identification of *chronic breathlessness syndrome* may result in evidence-based breathlessness services becoming the standard of care. Multi-disciplinary and multi-speciality breathlessness services are already developing, (e.g., pulmonary and cardiology) albeit with a focus on diagnosis. A next step could be for such specialised clinics to expand their scope to research and practice of breathlessness palliation.

Although much of the literature relating to the management of the symptom of breathlessness has come from palliative care to date, this clinical presentation is seen by family medicine/general practice, respiratory medicine, cardiology, geriatrics and palliative care. Therefore, the responsibility to address the chronic breathlessness syndrome is one that *must* be shared by the medical community as a whole.

The overt recognition of chronic breathlessness syndrome will empower patients and their caregivers to more easily raise their symptom burden in clinical consultations, rather than suffering in silence. Likewise, ensuring that the community more broadly is aware of the syndrome will facilitate conversations to drive better care.

The syndrome of chronic pain provides a useful parallel in some aspects. Recognition that chronic pain is a different entity to acute pain and thus should be managed differently [3] was pivotal in improving understanding, management and service provision of this common and difficult condition.

The devastating impact on psycho-social function with resultant disability, often caught up in a deteriorating cycle of unhelpful adaptation to the symptom by reducing activity is common to both. An understanding of this has informed the multi-disciplinary nature of chronic pain clinics with an emphasis on physiotherapy and psychological approaches to management and appears pertinent to chronic breathlessness. Likewise, the more recently proposed clinical entity, “dyspnea crisis” [38] is highly pertinent to this discussion in that crisis often occurs on a background of chronic breathlessness. There are notable differences, however, in that “chronic pain syndrome” includes a plethora of subtypes described in a complex taxonomy,[39] and unlike severe breathlessness, the experience of chronic pain is rarely associated with a fear of imminent death.

There may be concerns that recognition of chronic breathlessness as a syndrome may lead to inappropriate and excessive prescribing of opioids, particularly for patients who may be vulnerable to overdose such as patients with advanced COPD.[34, 40] We suggest that a *chronic breathlessness syndrome* would stimulate a posology of opioid prescription based on evidence-based effectiveness and safety data rather than the current variations in practices, including inadequately evaluated regimens. This which would allow greater net benefit and place pharmacological treatment within a step-wise approach to management founded on non-pharmacological management.[41]

#### Implications for research

*Chronic breathlessness syndrome* will create a common language between and within groups of researchers. More consistent descriptions of study populations will help application of findings. A distinct entity which stimulates a structured and mechanistic approach should also help target research priorities towards further understanding of the pathophysiology of chronic breathlessness, identification of further potential therapeutic targets and optimal service delivery models.

Recognition of *chronic breathlessness syndrome* could also create a profile for potential funders.

Importantly, the involvement of patients and family caregivers in the development of consensus can now be addressed given the frame which this initial work provides.

## Strengths and limitations

This paper deliberately sought the views of opinion leaders, that is, members of the community of clinicians and researchers who are influential not because they have opinions, but because their opinions are sought after and published. The opinions of this wide range of respondents from around the world were successfully synthesised into a definition that could be used in a number of other languages. This definition spans people working in the basic sciences as well as a variety of clinical specialities.

The limitations are those that are inherent to Delphi processes. Not all respondents completed all surveys, but the response rate for surveys 2 and 3 was good. There was no clear pattern in the non-respondents in the first survey. Given the broad nature of the professional background of participants, a slightly lower *a priori* agreement threshold of 70% was set. However, one question failed to reach this, and most gained more than a more usual agreement of 75%. There may be concerns that a Delphi method is open to a bias towards inclusion of only like-minded experts. However, there was vigorous debate throughout the survey rounds, nearly requiring a 4th survey. Further, the Paris Dyspnea 2016 workshop was *not* part of the Delphi process. It was attended by people who were independent from it and who were unaware that this would be on the agenda in this manner; they were not hand-picked.

Inherent with the methodology, the number of participants is limited. Therefore, the respondents' views cannot be fully representative of all concerned. We expect that this proposition of "chronic breathlessness syndrome" will generate reactions and debate and we acknowledge that this term may evolve as a result. Linguistic and cultural specificities may lead to variations around the world and there may be further discussion on how the chosen terminology applies to certain clinical situations. For example, a participant in the Dyspnea 2016 workshop, noted that "breathlessness that persists in spite of optimal treatment of the underlying conditions" is frequently experienced by

critically ill patients receiving prolonged mechanical ventilation.[42] However, in this setting, the word "chronic" may not be relevant to intensivists to characterize the corresponding category of patients, and could be replaced by "persistent". The very fact that questions and debates will arise in reaction to the present proposition should be considered as a first marker of its relevance.

## **CONCLUSIONS**

We propose *chronic breathlessness syndrome* as a framework for further discussion. Whatever the name (or names) agreed finally and recognised globally, such recognition of a distinct clinical syndrome is likely to improve clinical care, focus research and, ultimately, reduce suffering through empowering patients and their caregivers. Additional development is warranted, including engagement of patients and family caregivers to refine understanding and application. Using the syndrome as the basis for wider use of evidence-based interventions is an important first step to address the therapeutic nihilism that has pervaded this area of practice.

**ACKNOWLEDGEMENTS:** We thank the participants for giving their time and expertise to this project. MJ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

**DECLARATION STATEMENT:** With regard to this work, Dr Currow is a paid consultant and receives payment for intellectual property with Mayne Pharma and is a consultant with Specialist Therapeutics Australia Pty. Ltd. Dr Johnson is a clinical consultant for Mayne Pharma (institutional payment). All other authors report no conflicts of interest.

**FUNDING:** This project was unfunded



## Reference List

1. Currow DC, Plummer JL, Crockett A, Abernethy AP: A community population survey of prevalence and severity of dyspnea in adults. *J Pain Symptom Manage* 2009;38(4):533-545.
2. Harstall, C. and Ospina, M. How prevalent is chronic pain? *Pain clinical updates*. Vol. XI, No. 2, 1-4. 2003. International Association for the Study of Pain. 15-7-2016.  
Ref Type: Report
3. Addison RG: Chronic pain syndrome. *Am J Med* 1984;77(3A):54-58.
4. Harper, D. Online etymology dictionary. <http://www.etymonline.com> . 2016. 13-11-2016.  
Ref Type: Electronic Citation
5. Pratter MR, Abouzgheib W, Akers S, Kass J, Bartter T: An algorithmic approach to chronic dyspnea. *Respir Med* 2011;105(7):1014-1021.
6. Currow DC, Smith J, Davidson PM, Newton PJ, Agar MR, Abernethy AP: Do the trajectories of dyspnea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. *J Pain Symptom Manage* 2010;39(4):680-690.
7. Ahmadi Z, Lundstrom S, Janson C, Strang P, Emtner M, Currow DC, Ekstrom M: End-of-life care in oxygen-dependent COPD and cancer: a national population-based study. *Eur Respir J* 2015;46(4):1190-1193.
8. Booth S, Silvester S, Todd C: Breathlessness in cancer and chronic obstructive pulmonary disease: using a qualitative approach to describe the experience of patients and carers. *Palliat Support Care* 2003;1(4):337-344.
9. Disler RT, Green A, Lockett T, Newton PJ, Inglis S, Currow DC, Davidson PM: Experience of advanced chronic obstructive pulmonary disease: metasynthesis of qualitative research. *J Pain Symptom Manage* 2014;48(6):1182-1199.
10. Gysels M, Higginson IJ: Access to services for patients with chronic obstructive pulmonary disease: the invisibility of breathlessness. *J Pain Symptom Manage* 2008;36(5):451-460.
11. Nishimura K, Izumi T, Tsukino M, Oga T: Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;121(5):1434-1440.
12. Smith A, Currow DC, Abernethy AP, Johnson MJ, Maoi Y, Boscardin WJ, Ritchie C: Prevalence and Outcomes of Breathlessness in Older Adults: a National Population Study. *Journal of the American Geriatric Society* 2016;*in press*.
13. Hammond EC: Some preliminary findings on physical complaints from a prospective study of 1.064.004 men and women. *Am J Public Health Nations Health* 1964;54:11-23.
14. Waller K, Kaprio J, Kujala UM: Dyspnea and all-cause mortality: 28-yr follow-up study among adult twins. *Med Sci Sports Exerc* 2014;46(8):1538-1545.

15. Niska R, Bhuiya F, Xu J: National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report* 2010;(26):1-31.
16. Langlo NM, Orvik AB, Dale J, Uleberg O, Bjornsen LP: The acute sick and injured patients: an overview of the emergency department patient population at a Norwegian University Hospital Emergency Department. *Eur J Emerg Med* 2013.
17. Currow DC, Abernethy AP, Allcroft P, Banzett RB, Bausewein C, Booth S, Carrieri-Kohlman V, Davidson P, Disler R, Donesky D, Dudgeon D, Ekstrom M, Farquhar M, Higginson I, Janssen D, Jensen D, Jolley C, Krajnik M, Laveneziana P, McDonald C, Maddocks M, Morelot-Panzini C, Moxham J, Mularski RA, Noble S, O'Donnell D, Parshall MB, Pattinson K, Phillips J, Ross J, Schwartzstein RM, Similowski T, Simon ST, Smith T, Wells A, Yates P, Yorke J, Johnson MJ: The need to research refractory breathlessness. *Eur Respir J* 2016;47(1):342-343.
18. Currow DC, Abernethy AP, Ko DN: The active identification and management of chronic refractory breathlessness is a human right. *Thorax* 2014;69(4):393-394.
19. Booth S, Bausewein C, Higginson I, Moosavi SH: Pharmacological treatment of refractory breathlessness. *Expert Rev Respir Med* 2009;3(1):21-36.
20. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC: Clinically Important Differences in the Intensity of Chronic Refractory Breathlessness. *J Pain Symptom Manage* 2013;46(6):957-963.
21. Ekstrom M, Nilsson F, Abernethy AA, Currow DC: Effects of opioids on breathlessness and exercise capacity in chronic obstructive pulmonary disease. A systematic review. *Ann Am Thorac Soc* 2015;12(7):1079-1092.
22. Ekstrom MP, Abernethy AP, Currow DC: The management of chronic breathlessness in patients with advanced and terminal illness. *BMJ* 2015;349:g7617.
23. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, McCrone P, Booth S, Jolley CJ, Moxham J: An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014;2(12):979-987.
24. Johnson MJ, Currow DC: Chronic refractory breathlessness is a distinct clinical syndrome. *Curr Opin Support Palliat Care* 2015;9(3):203-205.
25. Hsu C, Sandford BB: The Delphi technique: making sense of consensus. *Practical Assessment, Research & Evaluation* 2007;12(10):1-8.
26. WHO. International Classification of Functioning, Disability and Health (ICF): Towards a Common Language for Functioning, Disability and Health. 1-23. 2002. 6-7-2016.  
Ref Type: Report
27. Johnson MJ, Simpson MI, Currow DC, Millman RE, Hart SP, Green G: Magnetoencephalography to investigate central perception of exercise-induced breathlessness in people with chronic lung disease: a feasibility pilot. *BMJ Open* 2015;5(6):e007535.
28. Herigstad M, Hayen A, Evans E, Hardinge FM, Davies RJ, Wiech K, Pattinson KT: Dyspnea-related cues engage the prefrontal cortex: evidence from functional brain imaging in COPD. *Chest* 2015;148(4):953-961.

29. Jolley CJ, Luo YM, Steier J, Reilly C, Seymour J, Lunt A, Ward K, Rafferty GF, Polkey MI, Moxham J: Neural respiratory drive in healthy subjects and in COPD. *Eur Respir J* 2009;33(2):289-297.
30. Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J: Neural respiratory drive and breathlessness in COPD. *Eur Respir J* 2015;45(2):355-364.
31. Karras DJ, Sammon ME, Terregino CA, Lopez BL, Griswold SK, Arnold GK: Clinically meaningful changes in quantitative measures of asthma severity. *Acad Emerg Med* 2000;7(4):327-334.
32. Bennett MI, Flemming K, Closs SJ: Education in cancer pain management. *Curr Opin Support Palliat Care* 2011;5(1):20-24.
33. Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P, Briffa M, Johnson MJ, Abernethy AP: Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage* 2011;42(3):388-399.
34. Ekstrom MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC: Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014;348:g445.
35. Farquhar MC, Prevost A, McCrone P, Brafman-Price B, Bentley A, Higginson IJ, Todd C, Booth S: Is a specialist breathlessness service more effective and cost-effective for patients with advanced cancer and their carers than standard care? Findings of a mixed-method randomised controlled trial. *BMC Med* 2014;12(1):194.
36. Johnson MJ, Kanaan M, Richardson G, Nabb S, Torgerson D, English A, Barton R, Booth S: A randomised controlled trial of three or one breathing technique training sessions for breathlessness in people with malignant lung disease. *BMC Med* 2015;13:213.
37. Livermore N, Dimitri A, Sharpe L, McKenzie DK, Gandevia SC, Butler JE: Cognitive behaviour therapy reduces dyspnoea ratings in patients with chronic obstructive pulmonary disease (COPD). *Respir Physiol Neurobiol* 2015;216:35-42.
38. Mularski RA, Reinke LF, Carrieri-Kohlman V, Fischer MD, Campbell ML, Rocker G, Schneidman A, Jacobs SS, Arnold R, Benditt JO, Booth S, Byock I, Chan GK, Curtis JR, Donesky D, Hansen-Flaschen J, Heffner J, Klein R, Limberg TM, Manning HL, Morrison RS, Ries AL, Schmidt GA, Selecky PA, Truog RD, Wang AC, White DB: An official American Thoracic Society workshop report: assessment and palliative management of dyspnea crisis. *Ann Am Thorac Soc* 2013;10(5):S98-106.
39. Task Force on Taxonomy of the International Association for the Study of Pain. Classification of Chronic Pain. Descriptions of chronic pain syndromes and definitions of pain terms. Merskey, H. and Bogduk, N. 2nd Edition, 1-215. 1994. Seattle, IASP Press. 30-12-2016.  
Ref Type: Report
40. Vozoris NT, Wang X, Fischer HD, Gershon AS, Bell CM, Gill SS, O'Donnell DE, Austin PC, Stephenson AL, Rochon PA: Incident opioid drug use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. *Br J Clin Pharmacol* 2016;81(1):161-170.
41. Rocker GM, Sinuff T, Horton R, Hernandez P: Advanced chronic obstructive pulmonary disease: innovative approaches to palliation. *J Palliat Med* 2007;10(3):783-797.

42. Schmidt M, Banzett RB, Raux M, Morelot-Panzini C, Dangers L, Similowski T, Demoule A: Unrecognized suffering in the ICU: addressing dyspnea in mechanically ventilated patients. *Intensive Care Med* 2014;40(1):1-10.

**Table 1. Development of agreement over successive surveys.**

Survey*	Survey 1* N= 35	Survey 2* N = 27	Survey 3* N = 31
<b>Name of syndrome</b>	"chronic" 67% "chronic" only needed 15% "refractory" 58% "persistent"...48% "intractable"...3% "intolerable"...3%	Chronic breathlessness 26% Chronic refractory breathlessness 60% Chronic persistent breathlessness 14%	<b>Chronic breathlessness 77%</b> Chronic refractory breathlessness 23%
<b>Definition</b>			
Chronic	<b>"if using chronic or persistent, this should be individually assessed and not further defined."</b> 80% 1 month/3 month/from this point 20%		
Treatment of underlying disease	"Treatment of underlying medical disease(s) is optimised" 63% "The underlying medical disease(s) is receiving best possible treatment" 31% no preference 6%	Treatment of underlying pathophysiology is optimised 41% The patient is receiving optimal evidence based treatment for the underlying pathophysiology 59%	Treatment of underlying pathophysiology is optimised 32% <b>Evidence-based treatment of underlying pathophysiology is optimised 68%</b>
Negative consequences of breathlessness	"None of the above* are needed for the definition" 55% "Significant physical limitations" 33% "Anxiety" 6% "deconditioning"3%	None needed 37% ...[breathlessness]contributing to physical limitations and/or a variety of adverse psychosocial, spiritual or other consequences 59.3% ...[breathlessness]contributing to physical Limitations 3.7%	None needed for the definition 23% <b>...[breathlessness]contributing to physical limitations and/or a variety of adverse psychosocial, spiritual or other consequences 77%</b>

\*see survey in Appendix 1 for the detail

## eSURVEY AND INVITATION

Dear <<name>>,

We are pleased to invite you to participate in a Delphi survey to see if we can produce an agreed name and definition of a new clinical syndrome of chronic breathlessness caused by medical conditions.

### The survey should take 5 minutes to complete.

A clinical syndrome is a constellation of clinical findings caused by an underlying disease(s). The clinical findings may constitute a range of symptoms and physical findings, or describe one symptom in a particular context(s) and may include response to interventions targeted at the syndrome itself. The syndrome should be recognisable in the clinical and research settings. Examples of clinical syndromes include heart failure, delirium, sepsis, parkinsonism and chronic pain.

During July and August 2015, experts from the following disciplines: respiratory medicine, cardiovascular medicine, primary care, medical, nursing, respiratory physiology, neuroimaging, intensive care, oncology and palliative care were consulted.

There was agreement that the symptom of breathlessness could be raised to a clinical syndrome of *chronic refractory breathlessness* if the breathlessness:

- due to a causative medical condition(s) *persists* despite treatment for that condition;
- leads to negative consequences for the patient; and
- responds to interventions aimed at the breathlessness.

There was also consensus that recognition of a clinical syndrome would influence clinical practice, service provision and policy, researchers and research funding.

However, although suggestions for the name and definition were generated, it was agreed that wider consultation through Delphi survey rounds would be important.

If you could take a few minutes of your time to complete the following survey questions (by clicking on the link below). Please also indicate if you would be willing to take part in subsequent rounds.

## SURVEY

### NAME OF SYNDROME

A1. The following relates to the **name**. Show the **name** you feel would best identify the syndrome to both lay and professional audiences.

Do you want to describe it as: (**indicate one response from each of the two columns**)

Chronic	intractable	breathlessness	syndrome
Persistent	refractory		
Refractory	persistent		

intractable                      chronic  
Descriptor not needed    Descriptor not needed  
Other.....                      Other .....

Please add any comments:

A2. With regard to the **timescale of the breathlessness**, please indicate the **one descriptor** that should be used.

- a. If using 'chronic' or 'persistent', this should be individually assessed and not further defined
- b. If 'chronic', should this refer to breathlessness which:
  - a. Will be chronic from this point forward
  - b. Has been present for 1 month
  - c. Has been present for 3 months
  - d. Has been present for 6 months
  - e. Has been present for 12 months
- c. If persistent, should this refer to breathlessness which:
  - a. Will be persistent from this point forward
  - b. Has been present for 1 month
  - c. Has been present for 3 months
  - d. Has been present for 6 months
  - e. Has been present for 12 months

Please add any comments:

### **DEFINITION OF SYNDROME**

The following relate to the **definition**.

During consultation, it was agreed that the symptom of breathlessness could be raised to a clinical syndrome if the breathlessness remained a problem despite treatment for that condition and resulted in negative consequences for the patient.

Please underline the statement which best describes the treatment of the underlying disease.

- a. Treatment of underlying medical disease(s) is optimised
- b. The underlying medical disease(s) is receiving best possible treatment
- c. No preference

Please add any comments:

B3. With regard to negative consequences of the breathlessness, please indicate any which should be explicitly included in the definition:

- a. Significant physical limitations
- b. Deconditioning
- c. Social isolation

- d. Depression
- e. Anxiety
- f. Financial concerns
- g. Spiritual distress
- h. Health service utilisation
- i. *Unscheduled* health service utilisation
- j. None of the above are needed for the definition

Please add any comments:

**Thank you very much for your help.** Please indicate here if you would be happy to receive the next Delphi survey round.



**eTable 1. Summary of freetext comments circulated with survey 3**

1. **Name.** The main area of disagreement related to whether a descriptive word e.g. “refractory” should be part of the NAME, or only used in the DEFINITION.
  - The term “refractory” carries the implication that there's no point in doing anything about it as it won't respond to therapy – which is not what we are trying to convey with the name of this syndrome. It risks being misunderstood by clinicians, patients and the lay public.
  - The word refractory is particularly misleading for German speakers.
  - A change of "chronic breathlessness" to "refractory breathlessness" would need education through under and post graduate training for nurses and doctors.
  - Keep the name simple. Chronic Breathlessness Syndrome *implies* that breathlessness persists despite treatment of the underlying cause. We don't say "Chronic Persistent Bronchitis," or "Chronic Intractable Pain Syndrome"
  - Chronic has the same acceptable meaning as persistent or "always there" and therefore you don't need two words in the definition that commonly mean the same thing.
  - You don't need refractory in the title of the syndrome, but it does need to be defined in the detail.
2. **Treatment.**
  - The definition refers to breathlessness which persists despite treatment directed at the *underlying disease pathophysiology*, rather than its effects or symptoms. That is – “despite disease treatments” – rather than “despite breathlessness treatments” . Other comments are included below:
    - optimal suggests that it is evidence based without the need for this qualification.
    - optimal "evidence-based" is important to state, otherwise the treatment utilized could be suboptimal
    - This 'syndrome' would help identify patients with COPD/CHF/ etc who despite pharmacological therapy are still breathless (where the mechanisms: deconditioning, anxiety and depression, dysfunctional breathing are similar). This would help identify patients that would benefit from a generic 'breathlessness' approach.
    - ... pulmonary rehabilitation can, for example, be included as an option as treatment for Chronic Breathlessness Syndrome caused by a chronic lung disease
3. **Consequences.**
  - There are so many, that listing becomes too complicated, could just have a “catch all” of “negative consequences regarding the physical, psychological, social and spiritual dimension”.
  - Consequences are individual to the person, but given the characteristics defined by your original panel of experts, some acknowledgement of consequences in the definition should be included.
  - These are "correlates" or "covariates" - they vary or change because of the phenomenon (symptom) of chronic breathlessness -...they are conceptually outside the phenomenon- not the phenomenon itself. If included in the definition it will be conceptually incorrect.
  - In order to be a syndrome, I think that it needs to have any negative abnormal consequence. Breathlessness is normal during certain levels of exertion. Some could say that "chronic" would separate normal from abnormal breathlessness but that word can be understood in many ways.
  - Description of negative consequences helps to de-medicalise the definition and identifies the illness experience. Both are important to include.
  - Think these are helpful for people who are not specialist yet
  - Not all limitations are physical, but they can be just as devastating!