An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial

Irene J Higginson, Claudia Bausewein, Charles C Reilly, Wei Gao, Marjolein Gysels, Mendwas Dzingina, Paul McCrone, Sara Booth, Caroline J Jolley, John Moxham

Summary

Background Breathlessness is a common and distressing symptom, which increases in many diseases as they progress and is difficult to manage. We assessed the effectiveness of early palliative care integrated with respiratory services for patients with advanced disease and refractory breathlessness.

Methods In this single-blind randomised trial, we enrolled consecutive adults with refractory breathlessness and advanced disease from three large teaching hospitals and via general practitioners in South London. We randomly allocated (1:1) patients to receive either a breathlessness support service or usual care. Randomisation was computer generated centrally by the independent Clinical Trials Unit in a 1:1 ratio, by minimisation to balance four potential confounders: cancer versus non-cancer, breathlessness severity, presence of an informal caregiver, and ethnicity. The breathlessness support service was a short-term, single point of access service integrating palliative care, respiratory medicine, physiotherapy, and occupational therapy. Research interviewers were masked as to which patients were in the treatment group. Our primary outcome was patient-reported breathlessness mastery, a quality of life domain in the Chronic Respiratory Disease Questionnaire, at 6 weeks. All analyses were by intention to treat. Survival was a safety endpoint. This trial is registered with ClinicalTrials.gov, number NCT01165034.

Findings Between Oct 22, 2010 and Sept 28, 2012, 105 consenting patients were randomly assigned (53 to breathlessness support service and 52 to usual care). 83 of 105 (78%) patients completed the assessment at week 6. Mastery in the breathlessness support service group improved compared with the control (mean difference 0·58, 95% CI 0·01–1·15, p=0·048; effect size 0·44). Sensitivity analysis found similar results. Survival rate from randomisation to 6 months was better in the breathlessness support service group than in the control group (50 of 53 [94%] *vs* 39 of 52 [75%]) and in overall survival (generalised Wilcoxon 3·90, p=0·048). Survival differences were significant for patients with chronic obstructive pulmonary disease and interstitial lung disease but not cancer.

Interpretation The breathlessness support service improved breathlessness mastery. Our findings provide robust evidence to support the early integration of palliative care for patients with diseases other than cancer and breathlessness as well as those with cancer. The improvement in survival requires further investigation.

Funding UK National Institute for Health Research (NIHR) and Cicely Saunders International.

Lancet Respir Med 2014; 2: 979–87

Published Online October 29, 2014 http://dx.doi.org/10.1016/S2213-2600(14)70226-7

See Comment page 944

See Online for for podcast interview with Irene Higginson

Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation (Prof I J Higginson PhD, Prof C Bausewein PhD, C C Reilly PhD, W Gao PhD, M Gysels PhD, M Dzingina MSc), **Institute of Psychiatry** (Prof P McCrone PhD), **and Department of Respiratory Medicine** (C J Jolley PhD, Prof J Moxham MD), **King's College London, Denmark Hill, London, UK; Palliative Care Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK** (S Booth MD); **University of Amsterdam, Centre for Social Science and Global Health, Amsterdam, Netherlands** (M Gysels); **and Department of Palliative Medicine, Munich University Hospital, Munich, Germany** (Prof C Bausewein)

Correspondence to: Prof Irene J Higginson, Cicely Saunders Institute, Department of Palliative Care, Policy and Rehabilitation, King's College London, Denmark Hill, London SE5 9PJ, UK
irene.higginson@kcl.ac.uk

Introduction

Breathlessness is a common and distressing symptom in many advanced chronic diseases, causing considerable disability, anxiety, and social isolation.[1–3] Worldwide, more than 75 million people have breathlessness every year, including more than 90% of the 65 million people with severe lung disease,[4] more than 50% of the 10 million with incurable cancer, and 50% of the 23 million with heart failure.[5,6] Breathlessness increases as the disease progresses,[7] is frightening for patients and families, and often results in emergency hospital admission because it is accompanied by feelings of loss of mastery over breathing and panic.[7,8]

Once treatment of the underlying disease is optimised, breathlessness that continues is deemed refractory.[1] Patients with refractory breathlessness in advanced disease have many symptoms and concerns that are complex and interact; consequently palliative care has been recommended.[4,9] In this study, we developed and assessed a new short-term breathlessness support service. This provided one point of access for patients, brought together palliative care and respiratory medicine, and responded to the call for shared care at an earlier stage in disease than usual.[10,11] We hypothesised that patients attending the breathlessness support service, compared with those receiving standard care, would have better mastery of breathlessness at 6 weeks.

Methods

Study design and participants

This trial was a randomised controlled, parallel group, pragmatic, single-blind fast-track trial in South London,

UK, recruiting patients between Oct 22, 2010 and Sept 28, 2012. We screened for potential patients across three large teaching hospitals and via general practitioners.

Patients were included according to a standard proforma completed by the identifying clinician. Patients had to meet all criteria: refractory breathlessness on exertion or rest (MRC dyspnoea scale score ≥2), despite optimum treatment of the underlying disease, as deemed by the identifying clinician; advanced disease such as cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure, interstitial lung disease, and motor neuron disease; willing to engage with short-term home physiotherapy and occupational therapy; and able to provide informed consent. Patients were excluded for any of the following: breathlessness of unknown cause; a primary diagnosis of chronic hyperventilation syndrome; completely house (or hospital or nursing home) bound, despite offer of free transport to clinic; or within 2 weeks of treatment for an acute exacerbation. Such patients were reapproached after 2 weeks.

Protocol, procedures, information sheets, consent forms, and questionnaires were approved through the independent UK Integrated Research Approval System via the ethics committee at King's College Hospital (Ref. 10/H0808/17). We then applied for and were granted NHS Research and Development approval in all recruiting sites. Patients gave written informed consent before enrolment. Our protocol[12] followed CONSORT recommendations. There were no protocol deviations.

For **Protocol** see http://www.biomedcentral.com/content/pdf/1471-2466-12-58.pdf

See Online for appendix

Panel 1: **Outcome, quality of life and health-care use assessments**

- Chronic Respiratory Disease Questionnaire, a 20-item validated health-related quality of life questionnaire in which experiences are rated on seven-point scales ranging 1 (maximum impairment) to 7 (no impairment)[19,20]
- Severity of breathlessness in the previous 24 h on a 0–10 numerical rating scale (NRS), average, at rest, and on exertion[12]
- London Chest Activity of Daily Living, a questionnaire of the level of disability induced by breathlessness for 15 activities (in four areas: personal care, domestic, physical, and social); each activity is scored 0–5 (0=I wouldn't do it anyway, 5=someone else needs to carry out the activity)[12]
- EQ-5D and EQ-VAS which assess mobility, self-care, usual activities, pain or discomfort, anxiety or depression according to three levels of severity (1=no problems, 2=some or moderate problems, and 3=extreme problems), plus a Visual Analogue Scale (VAS) of present health-related quality of life, scored 0–100[12]
- Palliative care Outcome Scale, a ten-item measure for advanced disease widely validated in cancer and non-cancer; each item is rated 0 (no problem) to 4 (overwhelming problem)[21]
- Hospital Anxiety and Depression Scale (HADS), a 14-item measure of psychological distress with separate anxiety and depression subscales[12]
- Client Services Receipt Inventory (CSRI)[12] in which patients reported the health, voluntary, and social care services received over the past 3 months, or if follow-up since the last research interview[12]

Randomisation and masking

Using data from the baseline interview, the King's Clinical Trials Unit's Online randomisation system, independent of research and clinical teams, randomly assigned (1:1) patients to the intervention (immediate access to breathlessness support service in addition to standard care) or control group (standard best practice; offered breathlessness support service after 6 weeks). Allocation was done by minimisation[13] to balance four potential confounders: cancer versus non-cancer, breathlessness severity (numerical rating scale >3 or not), presence (or not) of an informal caregiver, and ethnic origin (white or other). After randomisation, the clinical trials unit team informed the breathlessness support service clinic administrator of the patient's study group via secure email, who then arranged clinic appointments accordingly. Research nurses and interviewers were masked to treatment allocation. Patients were aware of treatment allocation, and were asked not to disclose this information to interviewers or research nurses. The trial coordinator and the trial administrator were aware of treatment allocation; the coordinator informed the research nurses when, and with whom, they had to do interviews.

Procedures

The breathlessness support service is an additional service to usual UK National Health Service (NHS) care. It is a multi-professional integrated service that combines respiratory, physiotherapy, occupational therapy, and palliative care assessment and management. It brings together assessment and treatment of physical, emotional, psychological, and spiritual concerns, through one point of access. The service comprises (appendix pp 1–2) a first outpatient clinic appointment with respiratory medicine and palliative care clinicians assessing present treatment and concerns. The patient (and family if present) is given a breathlessness pack including information, management, and pacing guidance, a hand-held fan or water spray, and a poem (a short mantra to help breathing and relaxation during crises) and helped to agree a crisis plan. A home assessment is done 2–3 weeks after the clinic visit by a physiotherapist and/or occupational therapist to assess the need for walking and home aids and adaptations, reinforcement of self-management, and further guidance on pacing and exercises, including a DVD when appropriate. 4 weeks after the first clinic visit, a second and final clinic appointment with a palliative care specialist is arranged to agree further actions and a discharge plan.

Service modelling for the breathlessness support service is built on the nurse-led clinic, developed by Bredin and colleagues[14] and the palliative care and physiotherapy approach developed by Booth and colleagues,[15] and systematic reviews,[16] qualitative interviews,[2] cross-sectional[9,17] and longitudinal studies,[18] and consultation with local stakeholders.[12] These data suggested that breathlessness support services should provide one point of access, integrate palliative care with existing services,

offer outpatient and home contact, and focus on improving patient self-management.

Patients randomly assigned to the control group continued with optimum management as provided by their usual services in accordance with relevant UK guidance to ensure best practice (appendix pp 3–5). After the 6 week (primary endpoint) research interview, these patients were offered the breathlessness support service.

Study measurements included the Chronic Respiratory Disease Questionnaire, severity of breathlessness in the previous 24 h, the London Chest Activity of Daily Living questionnaire, EQ-5D and EQ-VAS, the Palliative care Outcome Scale, the Hospital Anxiety and Depression Scale (HADS), and the Client Services Receipt Inventory (panel 1). These measurements were collected in a standard questionnaire booklet consisting of demographic, clinical, outcome assessments, and use of health-care services. Research data were collected in face to face interviews with patients, usually in their own homes, at baseline and 6 weeks follow-up (the primary endpoint). In addition face to face qualitative interviews were conducted after the trial was completed.

At baseline and 6 weeks follow-up, interviewers measured pulmonary function and oxygen saturation with a portable spirometer and finger pulse oximeter.

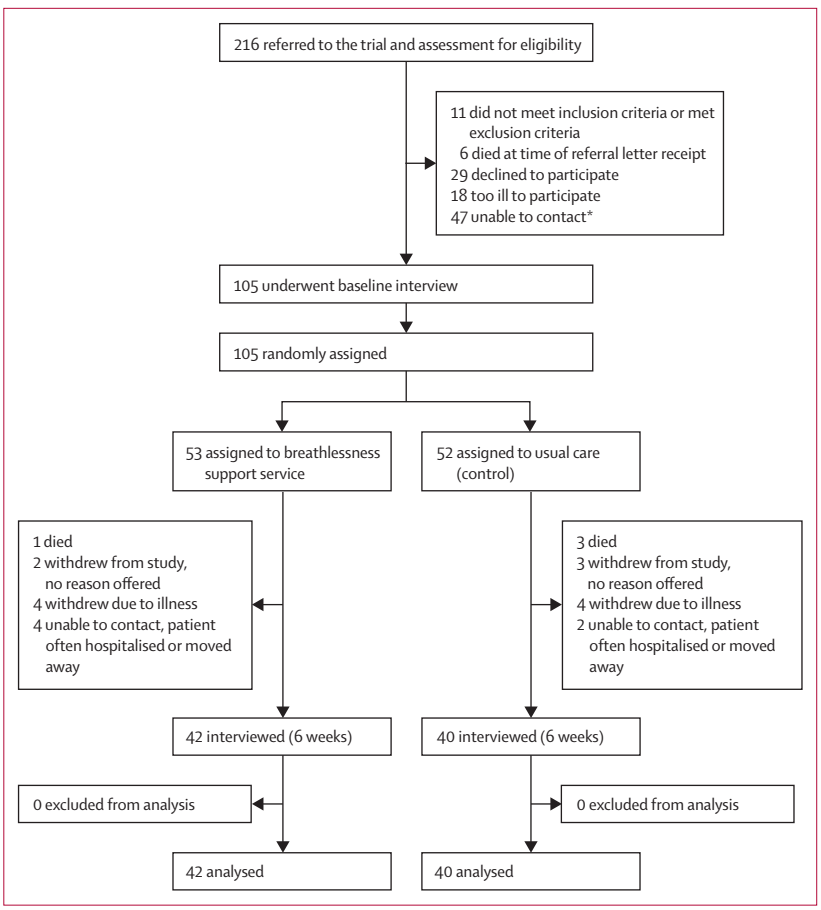

Figure 1: **Trial profile**
*Our biggest loss before consent was the 47 individuals (21·8% of 216 referred to the trial, and 42·3% of those not consented and randomly assigned) whom we were unable to contact. Appendix p 9 shows the efforts made to contact people.

Outcomes

The primary outcome was breathlessness mastery at 6 weeks as recorded in the 6 week face to face interview, determined according to one domain of the quality of life measure, the Chronic Respiratory Disease Questionnaire[12,19] (panel 1). Mastery is the average of four questions about the feeling of control over the disease and its effects on quality of life and function (range=1 [maximum impairment] to 7 [no impairment]). Secondary outcomes included: severity of breathlessness on exertion in the previous 24 h, activity (assessed by London Chest Activity of Daily Living questionnaire), other domains of the Chronic Respiratory Disease Questionnaire (breathlessness, fatigue, and emotional function), quality of life (EQ-5D), palliative needs (assessed by Palliative care Outcome Scale), depression and anxiety (measured by the Hospital Anxiety and Depression Scale [HADS]), and spirometry. Patient survival (since randomisation) was planned to be calculated from dropout and missing data, with exact dates extracted from clinical records, as a safety secondary endpoint, as recommended in clinical trials.[22] We also planned to collect and analyse caregiver burden data. But it proved difficult to contact lay caregivers for consent because many used the research nurse visit as an opportunity to go out while someone was with the patient. Only 11 caregivers were interviewed at baseline and only four at 6 week follow-up. Therefore these data were not analysed further.

20 patients were purposefully selected for qualitative interviews, after completing the trial, to include a mix of ages, sex, diagnoses, and presence of caregiver. The interviews were semi-structured and followed a topic guide on patients' expectations, experiences, and views about the content, format, and effect of the breathlessness support service. Questions were open-ended and not based on pre-existing theory. Interviews were tape-recorded and transcribed verbatim.

Statistical analysis

On the basis of our primary outcome, the Chronic Respiratory Disease Questionnaire mastery domain, we estimated that more than 34 patients per group would detect a mean difference of 0·70 (SD 1), a p value of less than 0·05 at power 80%.[19,20] To allow for a conservative estimated attrition of 40% we planned to recruit at least 110 patients into the study.

All randomly assigned participants were included in the intention-to-treat analysis. Missing data were explored according to cause.[23] Continuous variables, expressed as means and standard deviations, were compared with the Student's *t* test. Categorical variables were compared with χ^2 test or Fisher's exact test, as appropriate. As

	Overall (n=105)	Breathlessness support service group (n=53)	Control group (n=52)
Age (years)	67 (10)	66 (11)	68 (11)
Sex			
Men	61 (58%)	28 (53%)	33 (63%)
Women	44 (42%)	25 (47%)	19 (37%)
Diagnosis			
Chronic obstructive pulmonary disease	57 (54%)	29 (55%)	28 (54%)
Cancer*	21 (20%)	11 (21%)	10 (19%)
Interstitial lung disease	19 (18%)	7 (13%)	12 (23%)
Heart failure	5 (5%)	4 (8%)	1 (2%)
Other†	3 (3%)	2 (4%)	1 (2%)
Has carer or family member			
Yes	75 (71%)	38 (72%)	37 (71%)
No	30 (29%)	15 (28%)	15 (29%)
Clinical characteristics			
FEV_1 (L)‡	1·25 (0·70)	1·3 (0·78)	1·2 (0·65)
Predicted FEV_1 (%)‡	46·2 (23·3)	48·0 (24·3)	44·5 (22·4)
VC (L)‡	1·9 (0·96)	2·0 (1·0)	1·8 (0·9)
Predicted VC (%)‡	57·9 (25·7)	59·3 (25·5)	56·6 (26·0)
FEV_1/VC (%)	65·0 (19·0)	64·5 (19·4)	65·5 (18·8)
PEF (L/min)	227·3 (124·5)	232·5 (118)	222·3 (130)
SaO_2 %‡§	93·6 (3·9)	93·8 (4·0)	93·3 (3·7)
Quality of life measures			
NRS breathlessness average 24 h (0–10)¶	5·9 (2·0)	6·2 (2·0)	5·7 (1·9)
NRS breathlessness worst at rest (0–10)¶	4·9 (2·6)	5·1 (2·7)	4·8 (2·6)
NRS breathlessness on exertion 24 hours (0–10)¶	8·3 (1·4)	8·4 (1·5)	8·3 (1·4)
CRQ HRQL (score range 20–140)‡	60·9 (19·1)	59·3 (18·7)	62·7 (19·6)
CRQ dyspnoea (score range 1–7)‡‖	2·2 (0·80)	2·1 (0·7)	2·3 (0·9)
CRQ emotion (score range 1–7)‡‖	3·6 (1·3)	3·6 (1·3)	3·7 (1·3)
CRQ fatigue (score range 1–7)‡‖	2·9 (1·3)	2·7 (1·2)	3·0 (1·3)
CRQ mastery (score range 1–7)‡‖	3·4 (1·5)	3·5 (1·4)	3·3 (1·5)
EQ-5D index‡**	0·35 (0·33)	0·37 (0·32)	0·34 (0·34)
EQ-5D-HRQL VAS (score range 0–100)‡	51 (20)	52 (18)	50 (22)
LCADL total score (score range 0–75)¶	44·6 (12·9)	45·1 (13·9)	44·2 (12·2)
POS total score (score range 0–40)¶	15·1 (6·5)	15·4 (6·0)	14·8 (6·9)
HADS anxiety (score range 0–21)¶	9·2 (2·7)	9·5 (3·0)	9·0 (2·3)
HADS depression (score range 0–21)¶	9·9 (3·2)	10·0 (3·0)	9·9 (3·3)
Costs and health-care use			
Hospital inpatient days in previous 3 months	4·5 (7·2)	4·5 (6·8)	4·6 (7·6)
Cost of formal care in the previous 3 months	£3390 (3749)	£2911 (2729)	£3709 (4484)

Data are absolute numbers or mean (SD) unless otherwise stated. FEV_1=forced expiratory volume in 1 s. PEF=peak expiratory flow. VC=vital capacity. POS=Palliative care Outcome Scale. POS-S=Palliative care Outcome Scale-Symptom Score. CRQ=Chronic Respiratory Questionnaire. HRQL= health-related quality of life. HRQL VAS= health-related quality of life visual analogue scale. LCADL=London Chest Activity of Daily Living scale. HADS=Hospital Anxiety and Depression Scale. SaO_2 %=oxygen saturation. NRS=numerical rating scale. *Appendix p 6 shows breakdown of primary cancer type. †Other diagnoses were: left lower lobe collapse of unknown aetiology associated with severe symptoms; lupus, shrinking lung syndrome, and rheumatoid arthritis; severe asthma and gastro-oesophageal reflux disease. ‡Scale interpretation: high score better. §Measured for 13 patients (three in breathlessness support service group and ten in control group) while on supplemental oxygen (mean [SD] SaO_2 91·8 [5·1]) and the remainder on room air (mean [SD] 93·8 [3·6]). ¶Scale interpretation: high score worse. ||CRQ subdomains averaged on the 1–7 scale to give comparability across subscales. **EQ-5D index scores based on the standard UK population-based preference weights with the standard scoring algorithm; 0·0=death and 1·0=perfect health.

Table 1: **Baseline characteristics**

prespecified, we used independent samples Student's *t* test to compare patient mastery (primary outcome) and secondary outcomes at 6 weeks, by trial group. Sensitivity analysis explored the robustness of results: first, accounting for differences in patient diagnoses and baseline scores using analysis of covariance (ANCOVA); second, with multiple imputations of missing data;[23] and third with pre-post analysis of breathlessness support service and control groups.

Survival was calculated from date of randomisation to date of death and plotted using the Kaplan-Meier method. Patients who were still alive on Sept 1, 2013, after the last patient was recruited were censored at this date. We calculated the survival rates to 180 days (6 months) from consent in both groups. With all data to 1 year from last recruitment, we assessed overall survival difference between two groups with the generalised Wilcoxon (Breslow) test, which is more sensitive in the detection of early differences in survival,[24] which is important in the fast-track or wait-list design.

We calculated costs by combining Client Service Receipt Inventory data with UK 2011–12 unit costs.[25] Cost data are usually skewed; therefore, we used a bootstrapped regression model to produce confidence intervals. Statistical significance was accepted for p values less than 0·05.

Qualitative interviews were imported into NVivo version 7 and content analysis explored patients' own views and experiences of the breathlessness support service, and in particular how issues related to the primary and secondary outcomes. We created categories inductively, with attention to terms and content, from the interview data. Through a process of constant integration of categories and their properties, or constant comparison, the findings became relevant at a more abstract level. We used simple counting when possible to discover more definite patterns in views. Member checks and teamwork were used to establish credibility.

This trial is registered with ClinicalTrials.gov, number NCT01165034.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 22, 2010, and Sept 28, 2012, we screened 216 eligible patients. 105 consented and were randomly assigned (figure 1). Participants were identified from respiratory medicine (50 [48%]), palliative care services (23 [22%]), general practices (15 [14%]), physiotherapy services (13 [12%]), and heart failure services (four [4%]). The median time to first clinic appointment was 19 days, some patients were delayed beyond this because of health

problems or hospital admissions. Table 1 shows the baseline characteristics. Patients had severe disease: forced expiratory volume in 1 s (FEV_1) was 46% predicted, vital capacity 58% predicted, oxygen saturation (SaO_2%) at rest 93%, average breathlessness 5·9/10, on exertion 8·3/10. Their average Chronic Respiratory Questionnaire breathlessness mastery was 3·4. Their average total Palliative care Outcome Score was 15/40, indicating important unmet palliative care concerns; for the HADS, the mean scores were 9 for anxiety and 10 for depression, both above the cutoff for clinical significance.

At week 6, 82 of 105 (78%) patients completed assessments. The main reasons for attrition were illness or death (figure 1). Attrition to the primary outcome was slightly lower than estimated (22% not 40%); therefore, we agreed to stop recruitment after 105 patients had consented. Missing data, death, and dropout were not associated with baseline mastery score, FEV_1 or other key variables except oxygen saturation (appendix p 7). Four patients died by week 6, two had cancer (one in breathlessness support service group), and two had interstitial lung disease (both in control group).

We recorded a significant improvement in the primary outcome, the mastery domain of the Chronic Respiratory Disease Questionnaire, in the breathlessness support service group compared with the control group at 6 weeks (table 2). Patients receiving the breathlessness support service had on average a 16% improvement for breathlessness mastery over the control group (mean difference 0·58, effect size 0·44, control group mean score 3·57). Results were similar to those from our sensitivity analysis of the primary outcome: ANCOVA adjusted for diagnosis, p=0·037; ANCOVA adjusted for diagnosis and baseline score, p=0·05; multiple imputation (number of imputations 45) based on baseline score of the measure of interest, p=0·07; adjusted for baseline score, diagnosis, FEV_1, SaO_2 %, p=0·072; control and intervention groups were imputed separately. In further post-hoc sensitivity analyses, first excluding patients referred or identified via palliative care services, and second excluding those with cancer (because of potential bias of palliative care effect), we noted 6 week mean mastery scores of, respectively, 4·18 (SD 1·2) in the intervention group and 3·54 (1·4) in the control group (p=0·043) and 4·19 (1·2) in the intervention group and 3·52 (1·3) in the control group (p=0·033).

We noted no significant differences in patient-reported secondary outcomes between study groups at 6 weeks (table 2). For all items, except anxiety, the breathlessness support service group had better scores than the control group; this was largest, but not significant, for the London Chest Activity of Daily Living questionnaire and breathlessness on exertion. Findings of pre-post analysis within groups (appendix p 8) showed significant improvements in the breathlessness support service group between baseline and 6 weeks for seven outcomes: mastery, total quality of life score, dyspnoea, and emotion, assessed by Chronic Respiratory Disease Questionnaire, average breathlessness per 24 h, on exertion breathlessness per 24 h, and Palliative care Outcome Scale total score. No outcome showed deterioration. The control group had a significant improvement between baseline and 6 weeks for only Palliative care Outcome Scale total score, and significant deteriorations for London Chest Activity of Daily Living questionnaire and HADS.

We noted a significant difference in survival for the whole sample that appeared early after randomisation (generalised Wilcoxon 3·90, p=0·048). Survival was similar between the study arms for patients with cancer, but significantly different for patients without cancer: all 42 patients without cancer in the breathlessness support service group were alive through to 6 months (180 days), of the 42 control patients without cancer at baseline, 38 were alive at 90 days, and 32 at 180 days (table 3 and figure 2). The standard care group received the breathlessness support service by 120 days.

	Breathlessness support service group (n=42)	Control group (n=40)	Difference between breathlessness support service and control (95% CI)	p value
Primary outcome (CRQ mastery)*†	4·15 (1·7)	3·57 (1·4)	0·58 (0·01 to 1·15)	0·048
Secondary outcomes				
NRS breathlessness average 24 h‡	5·38 (2·2)	5·71 (2·1)	−0·33 (−1·28 to 0·62)	0·49
NRS breathlessness worst at rest 24 h‡	4·12 (2·8)	4·47 (3·3)	−0·35 (−1·71 to 1·01)	0·61
NRS breathlessness on exertion 24 h‡	7·45 (2·4)	8·18 (1·8)	−0·73 (−1·69 to 0·22)	0·13
CRQ HRQL*	71 (19)	67 (20)	4·21 (−4·52 to 12·94)	0·34
CRQ dyspnoea*†	2·54 (1·1)	2·46 (0·9)	0·08 (−0·38 to 0·52)	0·75
CRQ emotion*†	4·07 (1·3)	3·93 (1·3)	0·14 (−0·42 to 0·71)	0·16
CRQ fatigue*†	3·09 (1·1)	3·07 (1·5)	0·02 (−0·56 to 0·62)	0·93
EQ-5D index*	0·44 (0·31)	0·35 (0·29)	0·092 (−0·23 to 0·04)	0·18
EQ-5D HRQL VAS*	56 (20)	55 (18)	1 (−6·67 to 10·34)	0·67
LCADL total score‡	45 (13)	50 (15)	−5 (−12·22 to 1·02)	0·10
POS total score‡	12·15 (6·8)	12·42 (6·5)	−0·27 (−3·29 to 2·75)	0·86
HADS anxiety‡	9·2 (2·8)	9·1 (2·7)	0·1 (−0·93 to 1·24)	0·78
HADS depression‡	10 (2·8)	11 (2·5)	−1 (−1·82 to 0·30)	0·16
Days in hospital, since randomisation	0·8 (3·6)	1·3 (4·3)	−0·52 (−0·14 to 1·91)	0·58
Spirometry				
FEV_1 (L)*	1·30 (0·78)	1·29 (0·62)	0·11 (−0·26 to 0·48)	0·56
Vital capacity (L)*	2·01 (1·10)	1·80 (0·96)	0·21 (−0·34 to 0·75)	0·44
PEF (L/min)	254·5 (141·9)	244·3(108·0)	10·3 (−59·9 to 80·5)	0·38
SaO_2%*	93·0 (4·4)	94·2 (3·1)	−1·19 (−3·01 to 0·64)	0·17

Data are mean (SD) unless otherwise stated. p values were calculated with two-sided Student's *t* test for independent samples. CRQ=Chronic Respiratory Disease Questionnaire. NRS=numerical rating scale. HRQL=Health-related Quality of Life. EQ-5D=quality of life. LCADL=London Chest Activity of Daily Living survey. POS=Palliative care Outcome Scale. HADS= Hospital Anxiety and Depression Scale. FEV_1=forced expiratory volume in 1 s. PEF=peak expiratory flow. SaO_2%=oxygen saturation. *Scale interpretation; high score better. †CRQ sub-domains averaged on the 1–7 scale to give comparability across subscales. ‡Scale interpretation: high score worse.

Table 2: **Comparison of patient mastery (primary outcome) and secondary outcomes measured at week 6 of study, by trial group**

	Enrolment (n)	Alive at 45 days (n, %)	Alive at 90 days (n, %)	Alive at 120 days (n, %)	Alive at 180 days (n, %)
Breathlessness support service					
Cancer	11	10 (91%)	9 (82%)	9 (82%)	8 (73%)
COPD	29	29 (100%)	29 (100%)	29 (100%)	29 (100%)
Interstitial lung disease	7	7 (100%)	7 (100%)	7 (100%)	7 (100%)
Heart failure	4	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Other	2	2 (100%)	2 (100%)	2 (100%)	2 (100%)
Total	53	52 (98%)	51 (96%)	51 (96%)	50 (94%)
All non-cancer	42	42 (100%)	42 (100%)	42 (100%)	42 (100%)
Control					
Cancer	10	9 (90%)	8 (80%)	7 (70%)	7 (70%)
COPD	28	28 (100%)	26 (93%)	26 (93%)	22 (79%)
Interstitial lung disease	12	10 (83%)	10 (83%)	8 (67%)	8 (67%)
Heart failure	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Other	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Total	52	49 (94%)	46 (88%)	43 (83%)	39 (75%)
All non-cancer	42	40 (95%)	38 (90%)	36 (86%)	32 (76%)

COPD=chronic obstructive pulmonary disease.

Table 3: **Survival: number of patients alive by study group and diagnosis during the first 6 months of the study**

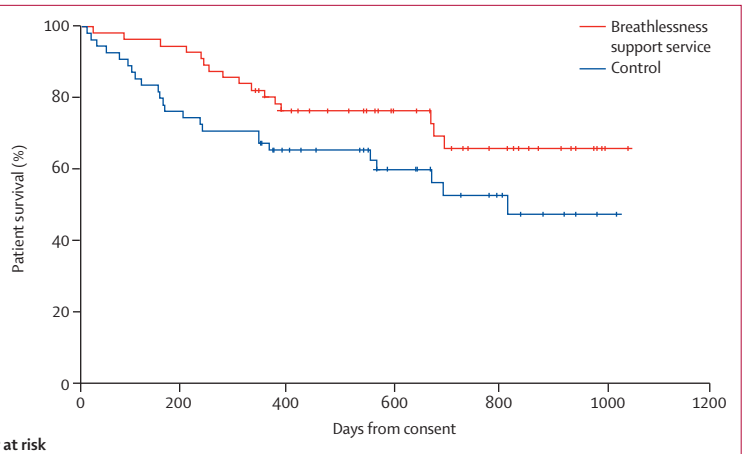

Figure 2: **Kaplan-Meier estimates of survival according to study group**
Survival was calculated from the time of randomisation to the time of death, if death occurred during the study period, or to the time of censoring (Sept 1, 2013). Median days between randomisation to Sept 1, 2013, was 745 (range 338–1075) for the breathlessness support service group and 711 (345–1045) for the control group. Tick marks show censoring of data. Overall generalised Wilcoxon (Breslow) was 3·90, p=0·048. In subgroup analysis, this pattern was not recorded for patients with cancer (0·01, p=0·97; n=21); but it became more marked for patients with diseases other than cancer (6·04, p=0·01; n=84). The pattern was recorded for patients with chronic obstructive pulmonary disease and separately in those with interstitial lung disease, although numbers are small for those with interstitial lung disease.

At 6 weeks, we noted no significant differences between total formal care costs in the two groups. 6 week mean costs were £1422 in the breathlessness support service group (bootstrapped 95% CI 897–2101) and £1408 in the control group (899–2023). Costs varied greatly between individuals.

Improved knowledge, confidence, and insight into how to function despite breathlessness were identified as potential mechanisms in the qualitative analysis through which the breathlessness support service improved patient mastery (appendix pp 10–11).

Discussion

This is the first randomised trial of a breathlessness support service integrating palliative care and respiratory medicine, and the first powered trial to test early integrated palliative care including patients without cancer (panel 2). The breathlessness support service integrated respiratory medicine, palliative care, physiotherapy, and occupational therapy for patients with advanced conditions and refractory breathlessness. The service responds to calls for earlier integration of palliative care including for patients without cancer.[10] At 6 weeks, the primary outcome, breathlessness mastery, improved more in the breathlessness support service group than in the standard care group. Qualitative data provided evidence of the breathlessness support service improving confidence, function, and control over breathlessness. No secondary patient-reported outcomes were significantly different between groups, although there was evidence in the pre-post analysis that the breathlessness support service group had improved activities of daily living and reduced breathlessness on exertion and depression. We recorded no harms of the breathlessness support service. The number of inpatient bed days and total formal care costs, on the basis of patient-reported total service use, were similar between groups.

Refractory breathlessness is a difficult clinical problem, usually the second most common symptom after pain in patients with advanced chronic disease, with high costs for society.[3] Oxygen has a role for individuals with severe hypoxaemia at rest or exercise desaturation, but is of little symptomatic value when patients are not hypoxic.[39] Low-dose, sustained-release opioids safely reduce breathlessness without respiratory depression,[40] but no other effective drugs exist.[1,3,41] Non-pharmacological treatments (eg, rollator devices, fan therapy, breathing control, and muscle strengthening) can provide benefits[16] as can multidisciplinary rehabilitation programmes, but in advanced disease, many patients are unable to attend or benefit.[16,34] In this context, palliative care can have a role (panel 2), but robust trials are scarce.

Although the finding of improved mastery in patients in the breathlessness support service group might not be surprising, this service (integrated palliative and respiratory care) is not standard, and usual care did not achieve the same result. All patients had advanced and deteriorating disease, in the palliative phase of a progressive illness, in which breathlessness progressively increases up to death. Therefore, the finding of little change in our secondary outcomes is not surprising, especially ones such as spirometry. These data suggest that we included an appropriate group of patients.

The American Thoracic Society defines breathlessness as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".[3] Like pain, breathlessness is a subjective experience resulting from complex interactions between pathological, physiological, and emotional elements. Therefore, it is difficult to choose the correct outcome to measure in breathlessness trials. We chose a well established quality of life measure's mastery domain, rather than levels of breathlessness, for several reasons. First, ratings of breathlessness levels are very variable and patients can have breathlessness attacks several times a day without constant breathlessness. Therefore, helping these patients to master their attacks might be more important than reducing the severity of one attack. Second, breathlessness is a limited endpoint because people perform activity to the highest level of breathlessness they can bear, but hope to do more before they reach that point. Breathlessness support services aimed to support and provide patients with coping strategies and interventions to help them master their breathlessness, while accepting that the disease cannot be cured and its natural history changed. Thus, the amount of perceived breathlessness mastery is probably a more important component of quality of life than is amount of breathlessness. As the qualitative results suggest, patients found this point important.

We found a difference in survival between study groups; patients in the control group had poorer survival in the early period of the study compared with patients in the breathlessness support service group. This difference was not found for patients with cancer, but was significant for patients with diseases other than cancer, mostly in those with COPD and interstitial lung disease. We do not have reliable data for the longevity of the disease or prognosis before randomisation, which limits interpretation of this finding. However, our results support another trial of early palliative care,[31] although we are the first to find a survival difference for patients with diseases other than cancer. Therefore, these results need further exploration and testing in future trials, as does the optimum timing of the breathlessness support service.

The breathlessness support service had some similar components to the breathlessness intervention service developed in Cambridge, UK in the late 2000s,[15] including one point of entry, integration of palliative care with physiotherapy, some specific interventions, and education. However, there are differences between the services; we included assessment by respiratory medicine (a component valued by patients in the qualitative interviews), asked patients to attend outpatient clinics (the breathlessness intervention service is home based), and used the poem for crisis management.

Our study has limitations. We were only able to single mask the groups. Our primary outcome measure was subjective; patients who knew their study group could

***Panel 2:* Research in context**

Systematic review

In the past 4 years there have been calls for early integration of palliative care to support patients with advanced disease.[10,11] We searched the scientific literature for evidence by extending three systematic reviews and one narrative review that assessed early palliative care in hospitals and at home.[26–30] We updated their search terms and also searched for any studies with the keywords: palliative, integration, and early. Additionally, we searched for trials of service interventions for patients with breathlessness (or dyspnoea or dyspnea) in advanced diseases (chronic obstructive pulmonary disease [COPD] or interstitial lung disease or heart failure or cancer) and on refractory breathlessness. Although many qualitative and descriptive studies have been done, we identified only four trials of early palliative care; three of these for patients with cancer. Temel and colleagues[31] and Bakitas and colleagues[32] found early palliative care significantly improved quality of life; the recent Zimmermann and coworkers trial[28] found similar benefits. In non-cancer, there is one published phase 2 trial of early palliative care in patients with multiple sclerosis, which suggested early integrated palliative care improved symptom control.[33] Although many interventions and services have been proposed to help patients with chronic breathlessness, such as pulmonary rehabilitation,[34] and national initiatives such as IMPRESS aimed at the development of integrated population-based approaches to prevent, detect, and care for people affected by COPD,[35] there are few for patients with the more advanced stages of illness or refractory breathlessness. We identified two randomised trials, one in progress. Bredin and colleagues[14] tested a nurse-led clinic for patients with lung cancer, not palliative care. A coauthor of this study, Booth, did observational work[15] and is currently trialling a community-based palliative care and physiotherapy service, the breathlessness intervention service, but this does not have out-patient clinics or include respiratory medicine.[36] In Canada, Rocker and Cook[37] developed the INSPIRED model of care for patients with advanced COPD to offer a more integrated approach to care, with personalised action plans, advance care planning, and palliative treatments. We could find no randomised trials of INSPIRED but observational data suggest the model reduces repeat admissions and is welcomed by patients. Horton and colleagues[38] did an observational study to test the feasibility of home-based palliative care for patients and caregivers living with advanced COPD (30 patients enrolled and 13 provided outcome assessments).

Interpretation

In this randomised controlled trial of 105 patients with refractory breathlessness, we noted that patients who received an integrated palliative care and respiratory breathlessness support service had significantly improved breathlessness mastery at 6 weeks. Mastery assessed patients' feeling of control over their breathlessness and its effects on quality of life and function, and was on average 16% higher for those patients receiving the breathlessness support service. The breathlessness support service did not show a significant advantage for other secondary outcomes, although there was a tendency for improvement in the ability to undertake activities of daily living, lesser depression, and lower breathlessness on exertion. Our findings were supported by qualitative data. We did not find a difference in formal care costs. Like Temel and colleagues' trial,[31] survival was better for the group receiving early breathlessness support service than the control group, although in this instance for patients with diseases other than cancer. In both these studies, survival was a secondary outcome, which suggests further research is needed. Our study supports the early integration of palliative care with respiratory medicine in non-cancer (eg, COPD, interstitial lung disease, and heart failure), focused on a group with refractory breathlessness. By being based mainly in outpatient settings and for a short term, the breathlessness support service meets the Block and Billings criteria of being scalable.[11] As our trial was of one service, we suggest that the breathlessness support service warrants testing in multicentre randomised trials, and further studies comparing different models and the timing of integration are needed.

have been subject to the placebo effect. However, participants were unaware that mastery was an endpoint because it was not emphasised in interviews and relevant questions were dispersed within the questionnaire. Additionally, the research nurse could have seen breathlessness support service equipment (eg, hand-held fan and information sheets) in the home, which could have biased their interviews. Our inclusion and exclusion criteria prevented extrapolation of study results to patients in the last month of life. Further, our outcome follow-up was short because of the fast-track nature of the trial. Although this short follow-up gave us acceptability from referrers and patients, it restricted our assessments, especially of care costs and long-term survival; the trial was not designed specifically to test for survival. We recruited from a small number of sites in urban areas where usual care at specialist centres was probably of an unusually good standard, with expert staff who were motivated to take part in this research. We were unable to contact more than a fifth of patients screened and eligible for the study, and could not pursue this further because of data protection and ethics approval requirements. Therefore, we do not know how our recorded effects translate to other routine scenarios and settings. Some patients were identified via palliative care services, which might have affected our results; however, the difference in our primary outcome remained when these effects were excluded.

Our primary outcome had an effect size of 0·44, smaller than that proposed in our sample size calculation. Puhan and colleagues[20] recommended an effect size of 0·7 for patient self-administered and 0·38 for interviewer-administered questionnaires. We find it surprising that a difference in interviewer should make such a difference in effect size, although this might be related to less variation in interviewer-administered formats. However, perhaps we should have used the more conservative 0·38 in our sample size estimation.

This trial provides support for a more integrated approach to management of breathlessness within a breathlessness support service, which improves patient mastery without affecting overall care costs. The recorded improvement in survival needs further investigation. The breathlessness support service needs testing in multicentre, longer term trials including a wider range of urban and rural settings.

Contributors

IJH, CB, CJJ, WG, PMC, and JM conceived the idea of the study and secured funding. IJH, CB, CJJ, CCR, and JM set up the study. JM, CCR, CJJ, and IJH provided the intervention. CB and CCR oversaw the study. CCR checked and cleaned the data. CCR, WG, and IJH analysed the quantitative data, MG the qualitative data, and MD and PMC the economic data. SB provided critical comment and advice on the protocol, set up, intervention modelling, and analysis stages. IJH, CB, and CCR produced the first draft of the paper. All authors commented on and contributed to the final draft. IJH is the guarantor. All authors had full access to all of the data of the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded mainly by a National Institute for Health Research (NIHR) grant from Research for Patient Benefit (PBPG-0808-17311). This report presents independent research funded by the NIHR under its Research for Patient Benefit (RfPB) programme (PB-PG-0808-17311). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Additional support for the work and interviews was from an NIHR senior investigator award and the Cicely Saunders International breathlessness programme. The UKCRC-registered King's Clinical Trials Unit at King's Health Partners is part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC). The funders of the study had no role in protocol design, collection or analysis of the data, or interpretation or writing of the results. We thank all the patients who participated in this research; everybody who identified and screened patients for this study, especially the Palliative Care, Respiratory Medicine and Physiotherapy Departments at King's College Hospital (London, UK), and the Community Palliative Care teams across Guy's and St Thomas' Hospitals (London, UK); H Bellas (physiotherapist), E Brink (social worker), J Kelly (clinical nurse specialist), and the occupational therapists for their input in the delivery of breathlessness support service, and C Pannell and S de Wolf-Linder (research nurses) for their interviews with patients; members of our project advisory group for their advice during the course of the study and in particular J Taylor of St Christopher's Hospice (London, UK) for allowing us to use the Breathlessness poem; C Murphy and colleagues at the Clinical Trials Unit at King's Health Partners for their support in the randomisation, D Yi for support of the economic analysis, and M Costantini for comments on an earlier draft of this paper; and J Fuller and J Davies for providing administrative support during this project.

References

1 Currow DC, Abernethy AP, Ko DN. The active identification and management of chronic refractory breathlessness is a human right. *Thorax* 2014; **69:** 393–94.

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

3 Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; **185:** 435–52.

4 Sorenson HM. Palliative care for lung disease: start early, stay late. *Lancet Respir Med* 2013; **1:** 279–80.

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

6 Austin J, Williams R, Ross L, Moseley L, Hutchison S. Randomised controlled trial of cardiac rehabilitation in elderly patients with heart failure. *Eur J Heart Fail* 2005; **7:** 411–17.

7 Seow H, Barbera L, Sutradhar R, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. *J Clin Oncol* 2011; **29:** 1151–58.

8 Barbera L, Taylor C, Dudgeon D. Why do patients with cancer visit the emergency department near the end of life? *CMAJ* 2010; **182:** 563–68.

9 Bausewein C, Booth S, Gysels M, Kuhnbach R, Haberland B, Higginson IJ. Understanding breathlessness: cross-sectional comparison of symptom burden and palliative care needs in chronic obstructive pulmonary disease and cancer. *J Palliat Med* 2010; **13:** 1109–18.

10 The Lancet. Prioritising palliative care. *Lancet* 2014; **383:** 1694.

11 Block SD, Billings JA. A need for scalable outpatient palliative care interventions. *Lancet* 2014; **383:** 1699–700.

12 Bausewein C, Jolley C, Reilly C, et al. Development, effectiveness and cost-effectiveness of a new out-patient Breathlessness Support Service: study protocol of a phase III fast-track randomised controlled trial. *BMC Pulm Med* 2012; **12:** 58.

13 Altman DG. Practical statistics for medical research, 1st edn. London: Chapman & Hall, 1991.

14 Bredin M, Corner J, Krishnasamy M, Plant H, Bailey C, A'Hern R. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ* 1999; **318:** 901–14.

15 Booth S, Moffat C, Farquhar M, Higginson IJ, Burkin J. Developing a breathlessness intervention service for patients with palliative and supportive care needs, irrespective of diagnosis. *J Palliat Care* 2011; **27:** 28–36.

16 Bausewein C, Booth S, Gysels M, Higginson IJ. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev* 2008; **11:** CD005623.

17 Malik FA, Gysels M, Higginson IJ. Living with breathlessness: a survey of caregivers of breathless patients with lung cancer or heart failure. *Palliat Med* 2013; **27:** 647–56.

18 Bausewein C, Booth S, Gysels M, Kuhnbach R, Haberland B, Higginson IJ. Individual breathlessness trajectories do not match summary trajectories in advanced cancer and chronic obstructive pulmonary disease: results from a longitudinal study. *Palliat Med* 2010; **24:** 777–86.

19 Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; **42:** 773–78.

20 Puhan MA, Guyatt GH, Goldstein R, et al. Relative responsiveness of the Chronic Respiratory Questionnaire, St. Georges Respiratory Questionnaire and four other health-related quality of life instruments for patients with chronic lung disease. *Respir Med* 2007; **101:** 308–16.

21 Hearn J, Higginson IJ. Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. *Qual Health Care* 1999; **8**: 219–27.

22 US Department of Health and Human Services, Food and Drug Administration. Guidance for industry. Clinical trial endpoints for the approval of cancer drugs and biologics. Department of Health and Human Services. 2007. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf (accessed Aug 18, 2014).

23 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med* 2012; **367:** 1355–60.

24 Crowley J, Breslow N. Statistical analysis of survival data. *Annu Rev Public Health* 1984; **5**: 385–411.

25 Curtis L. Unit costs of health and social care. Canterbury: PSSRU Canterbury, 2012.

26 Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. *JAMA* 2008; **299:** 1698–709.

27 Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard oncology care for patients with advanced cancer. *CA Cancer J Clin* 2013; **63:** 349–63.

28 Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; **383:** 1721–30.

29 Dalgaard KM, Bergenholtz H, Nielsen ME, Timm H. Early integration of palliative care in hospitals: a systematic review on methods, barriers, and outcome. *Palliat Support Care* 2014; published online March 13 DOI:10.1017/S1478951513001338.

30 Gomes B, Calanzani N, Curiale V, McCrone P, Higginson IJ. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database Syst Rev* 2013; **6**: CD007760.

31 Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 733–42.

32 Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA* 2009; **302**: 741–49.

33 Higginson IJ, McCrone P, Hart SR, Burman R, Silber E, Edmonds PM. Is short-term palliative care cost-effective in multiple sclerosis? A randomized phase II trial. *J Pain Symptom Manage* 2009; **38:** 816–26.

34 D-C Man W, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ* 2004; **329:** 1209.

35 Williams S, Baxter N, Holmes S, Restrick L, Scullian J, Ward M. IMPRESS Guide to the relative value of interventions for people with COPD. A population-based approach to improving outcomes for people with chronic obstructive pulmonary disease based on the cost of delivering those outcomes. London: British Thoracic Society and the Primary Care Respiratory Society UK, 2012. http://www.impressresp.com/index.php?option=com_docman&task=doc_view&gid=51&Itemid=82 (accesssed Sept 18, 2014).

36 Farquhar MC, Prevost AT, McCrone P, et al. Study protocol: phase III single-blinded fast-track pragmatic randomised controlled trial of a complex intervention for breathlessness in advanced disease. *Trials* 2011; **12:** 130.

37 Rocker GM, Cook D. 'INSPIRED' approaches to better care for patients with advanced COPD. *Clin Invest Med* 2013; **36:** 114–20.

38 Horton R, Rocker G, Dale A, Young J, Hernandez P, Sinuff T. Implementing a palliative care trial in advanced COPD: a feasibility assessment (the COPD IMPACT study). *J Palliat Med* 2013; **16:** 67–73.

39 Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010; **376:** 784–93.

40 Currow DC, Ekstrom M, Abernethy AP. Opioids for chronic refractory breathlessness: right patient, right route? *Drugs* 2014; **74**: 1–6.

41 Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2010; **1:** CD007354.