Effectiveness of a specialised breathlessness service for patients with advanced disease in Germany: a pragmatic fast-track randomised controlled trial (BreathEase)

Michaela Schunk[1,2], Lien Le[3], Zulfiya Syunyaeva[4,5], Birgit Haberland[1], Susanne Tänzler[1], Ulrich Mansmann[2,3], Larissa Schwarzkopf[5,6,7], Hildegard Seidl[2,6,8], Sabine Streitwieser[1], Miriam Hofmann[3], Thomas Müller[3], Tobias Weiß[9], Philipp Morawietz[9], Eva Annette Rehfuess[2,3], Rudolf Maria Huber[4,5], Ursula Berger[2,3] and Claudia Bausewein[1]

[1]Dept of Palliative Medicine, University Hospital, LMU Munich, Munich, Germany. [2]Pettenkofer School of Public Health, Munich, Germany. [3]Institute for Medical Information Processing, Biometry and Epidemiology, Faculty of Medicine, LMU Munich, Munich, Germany. [4]Dept of Medicine V, University Hospital, LMU Munich, Munich, Germany. [5]Member of the German Center for Lung Research (DZL), Comprehensive Pneumology Center Munich, Munich, Germany. [6]Health Economics and Health Care Management (IGM), Helmholtz Zentrum München (GmbH), German Research Center for Environmental Health, Munich, Germany. [7]IFT (Institut für Therapieforschung), Munich, Germany. [8]Quality Management and Gender Medicine, München Klinik gGmbH, Munich, Germany. [9]Atem-und Physiotherapie Solln, Munich, Germany.

Corresponding author: Michaela Schunk (michaela.schunk@med.uni-muenchen.de)

Shareable abstract (@ERSpublications)
The effectiveness of the Munich Breathlessness Service (MBS) was tested in a single-blinded randomised controlled fast-track trial. Significant improvements were shown in mastery of breathlessness and quality of life in patients with advanced illness. https://bit.ly/3nT8jfT

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Abstract

Background The effectiveness of the Munich Breathlessness Service (MBS), integrating palliative care, respiratory medicine and physiotherapy, was tested in the BreathEase trial in patients with chronic breathlessness in advanced disease and their carers.

Methods BreathEase was a single-blinded randomised controlled fast-track trial. The MBS was attended for 5–6 weeks; the control group started the MBS after 8 weeks of standard care. Randomisation was stratified by cancer and the presence of a carer. Primary outcomes were patients' mastery of breathlessness (Chronic Respiratory Disease Questionnaire (CRQ) Mastery), quality of life (CRQ QoL), symptom burden (Integrated Palliative care Outcome Scale (IPOS)) and carer burden (Zarit Burden Interview (ZBI)). Intention-to-treat (ITT) analyses were conducted with hierarchical testing. Effectiveness was investigated by linear regression on change scores, adjusting for baseline scores and stratification variables. Missing values were handled with multiple imputation.

Results 92 patients were randomised to the intervention group and 91 patients were randomised to the control group. Before the follow-up assessment after 8 weeks (T1), 17 and five patients dropped out from the intervention and control groups, respectively. Significant improvements in CRQ Mastery of 0.367 (95% CI 0.065–0.669) and CRQ QoL of 0.226 (95% CI 0.012–0.440) score units at T1 in favour of the intervention group were seen in the ITT analyses (n=183), but not in IPOS. Exploratory testing showed nonsignificant improvements in ZBI.

Conclusions These findings demonstrate positive effects of the MBS in reducing burden caused by chronic breathlessness in advanced illness across a wide range of patients. Further evaluation in subgroups of patients and with a longitudinal perspective is needed.

Introduction

Breathlessness is a common and distressing symptom in advanced stages of malignant and nonmalignant disease [1–4]. Breathlessness is highly prevalent, occurring in up to 80% of patients with advanced cancer,

in ~56–98% of patients with chronic obstructive pulmonary disease (COPD) and in up to 90% of patients with chronic heart failure [5, 6]. Patients with chronic breathlessness resulting from advanced disease report high symptom burden, palliative care needs [7–9], and suffer from anxiety and depression [10]. Negative consequences on health and quality of life (QoL) have been shown, *e.g.* for COPD patients [11]. Breathlessness is one of the most common reasons for emergency department visits and hospital admissions in cancer patients [12–14]. With ageing populations and the current COVID-19 pandemic with potential post-infectious fibrotic lung damage [15], the prevalence of breathlessness is likely to increase further, demanding innovative healthcare approaches. Multidisciplinary research to improve the management of chronic breathlessness has been called for by the American Thoracic Society [4]. In developing and assessing interventions, it is necessary to capture the multidimensional impact of chronic breathlessness on physical, emotional and social health and wellbeing using a range of patient-reported outcomes [2].

Specialist breathlessness services have been developed within palliative medicine offering a complex multidisciplinary intervention that integrates evidence-based nonpharmacological and pharmacological interventions to help in coping with chronic breathlessness [16]. In the UK, the Breathlessness Intervention Service in Cambridge mainly sees patients at home, offering both medical and physiotherapy input [17], and a joint palliative care and respiratory medicine outpatient service (Breathlessness Support Service (BSS)) has been established in London for patients with advanced disease offering two clinic appointments and a physiotherapy home visit [18]. These services showed improvements in patients' distress from breathlessness and mastery of breathlessness, respectively [16, 18]. However, similar services have not yet been established and evaluated outside the UK. As healthcare systems differ in ways that may affect the effectiveness of specialised breathlessness services, *e.g.* a greater provision of specialist respiratory services in Germany compared with the UK, we developed and evaluated the Munich Breathlessness Service (MBS).

The main aim of this trial (BreathEase) was to determine the effect of the MBS on mastery of breathlessness, QoL and symptom burden in patients suffering from breathlessness resulting from advanced disease compared with usual care. Further objectives were to examine the effect of MBS attendance 1) on the burden for the patients' informal carers, 2) on breathlessness severity, psychological outcomes and physical performance, and 3) on healthcare resource use and costs, and 4) to investigate the influence of factors such as cancer status, existence of an informal carer, demographic characteristics and other underlying conditions.

This article addresses the effectiveness of the MBS regarding the main objective, *i.e.* mastery of breathlessness, QoL and symptom burden, as well as regarding objectives relating to the burden for informal carers, breathlessness severity, psychological outcomes and physical performance. Further publications will cover analyses of the other objectives.

Methods

Trial design

We conducted a single-blinded randomised controlled fast-track trial between March 2014 and April 2019, which we report following the CONSORT 2010 statement [19], the CONSORT PRO Extension [20] and the CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments [21]. BreathEase is registered at ClinicalTrials.gov with identifier number NCT02622412. The intervention group received immediate access to the MBS, whereas the control group gained access after a waiting time of 8 weeks. All patients, irrespective of their allocation, continued with standard care throughout the trial with access to respiratory specialists, general practitioners, any disease-orientated treatment (*e.g.* anti-obstructive treatment, oxygen supply if indicated and maintenance chemotherapy) as well as palliative care services as needed.

Participants

Inclusion in the trial was based on the following criteria: patients 1) affected by breathlessness on exertion or at rest resulting from any advanced life-limiting and progressive disease such as cancer, COPD, chronic heart failure, interstitial lung disease or pulmonary hypertension despite best practice medical treatment of the underlying condition, and 2) able to engage (in a cognitive and functional manner) in a multifaceted intervention programme including physiotherapy and self-management. If patients were suffering from acute exacerbations of the underlying conditions at the time of recruitment, they were put on a waiting list for several weeks and then entered the trial after recovery. Exclusion criteria were patients 1) suffering from breathlessness as a result of chronic hyperventilation syndrome, asthma or any other unknown cause, 2) unable to provide informed consent or to physically attend at least one outpatient appointment at the

hospital, and 3) currently treated for malignant disease (concurrent radiotherapy or systemic treatment other than maintenance therapy) or participating in any drug trial focusing on the underlying condition.

Patients' carers were asked to participate in the trial if they were the main informal carer (henceforth referred to as carers) and in almost daily contact. Professional carers were excluded from participation.

Intervention

The MBS operates from Munich University Hospital (Munich, Germany) as a multiprofessional outpatient clinic. It is staffed by doctors from palliative medicine, and provides access to specialist physiotherapists and, if needed, respiratory specialists, psychologists and social workers. Conceived as a short-term intervention, patients have up to two personal contacts with palliative care specialists and three or four specialist respiratory physiotherapy treatments within 6 weeks. The MBS is provided within the German healthcare system. Under statutory health insurance, clinic visits for outpatients are free of charge, but co-payments are required towards physiotherapy and for privately insured patients.

Intervention procedures followed a step-by-step intervention manual, which was fully described in the study protocol before the beginning of the trial. Intervention fidelity was documented for each patient enrolled in the study and for care providers. In view of a dense network of local respiratory specialists in private practice serving the study population, the MBS adapted intervention procedures during the second half of the trial, offering consultation with in-house respiratory specialists only as needed. For an overview of the intervention, see table 1.

Outcome measurement

Effects of interventions are often multidimensional [22, 23]. A single primary end-point may not provide a comprehensive picture of the important effects of an intervention. This study investigates the impact of the MBS on four primary outcome variables, ordered hierarchically by their clinical importance: 1) change in patients' mastery of breathlessness measured using the Chronic Respiratory Disease Questionnaire (CRQ) (Mastery domain), 2) change in patients' QoL measured by the CRQ (all items), 3) change in symptom burden and concerns related to advanced illness assessed with the Integrated Palliative care Outcome Scale (IPOS) (all items), and 4) change in carer burden assessed with the Zarit Burden Interview (ZBI) (all items). In the following, these outcome variables are referred to as "change scores".

TABLE 1 Step-by-step Munich Breathlessness Service (MBS) intervention

Time	Type of contact	Professional	Action
Week 1	Clinic visit	Physicians from palliative and respiratory medicine	Palliative medicine: assessment of intensity and quality of breathlessness, including emotional stress of patient and carer; review of symptom burden and concerns in advanced illness (IPOS); nonpharmacological measures for symptom control (*e.g.* information brochure, hand-held fan, mantras, relaxation CD); development of breathlessness plan for emergency situations; if needed: referral to social worker or psychologist; if needed: medication (*e.g.* morphine) Respiratory medicine (either from hospital or in practices): assessment of cause of breathlessness; review of treatment plan (including medication and long-term oxygen use); review of results from functional tests and physical examinations
	Letter to patients	Physician (palliative medicine)	Summary of assessment and recommendations, development of MBS treatment plan; copy to referring physician(s)
Weeks 2–5	Physiotherapy visits	Physiotherapist	Exercise and positions to facilitate breathing; breathing techniques; exercise plan; assessment of need for medical aids
Week 3	Telephone (optional)	Physician (palliative medicine)	Follow-up on response to recommendations
Week 6	Clinic visit	Physician (palliative medicine)	Assessment of intensity and quality of breathlessness (including emotional stress of patient and carer); review of symptom burden and concerns in advanced illness (IPOS); review of MBS treatment plan (including individualised recommendations for nonmedical treatments and medication use); if needed: referral to specialists
	Letter to patients	Physician (palliative medicine)	Summary of progress in breathlessness management, further recommendations; copy to referring physician(s)

IPOS: Integrated Palliative care Outcome Scale.

The CRQ is a validated and reliable QoL measure for patients with chronic lung disease [24, 25]. The CRQ contains 20 items across four domains: dyspnoea (five items), fatigue (four items), emotional function (seven items) and mastery (four items). QoL is calculated by adding the responses to all 20 items. Scale range in the CRQ is 1–7, with higher values indicating lower burden. We used the self-administered individualised format, which requires eliciting the activities that made respondents feel most short of breath. Symptom burden and concerns related to advanced illness were assessed with the German version of the IPOS (Patient version, 1-week recall period) [26]. Carer burden was assessed with the 22-item version of the ZBI, measuring personal and role strain [27, 28].

Secondary outcome variables were the numerical rating scales (NRSs) for average breathlessness over the last 24 h, anxiety and depression assessed with the Hospital Anxiety and Depression Scale (HADS) [29], and lower extremity function measured with the Short Physical Performance Battery (SPPB) [30]. Further measurements included NRSs for breathlessness at rest and on exertion, the EuroQol generic health status instrument with five dimensions and five levels (EQ-5D-5L) as a generic QoL measure [31], as well as lung function tests (forced expiratory volume in 1 s and forced vital capacity) measured with spirometry using a hand-held device (CareFusion Micro I; BD, San Diego, CA, USA) and arterial oxygen saturation measured by pulse oximetry.

Outcomes were measured at four time-points: T0=baseline (prior to randomisation), T1=end of intervention (intervention group)/end of waiting period (control group) (from T0+week 8) T2=after intervention (intervention group)/end of intervention (control group) (from T0+week 16) and FU=follow-up by telephone (from T0+week 28). T2 and FU data are not included in the present analysis.

The study nurse facilitated the completion of the self-administered questionnaires through home visits to the patients (T0–T2) and with one telephone interview (FU). Carers completed paper-based questionnaires. Study procedures were specified in advance and described in a manual to ensure consistency over the course of the study. Any unfavourable medical occurrence, severe or nonsevere, was recorded during the study and examined by the lead clinician. Sample description included the Charlson Comorbidity Index and Australia-modified Karnofsky Performance Status (AKPS) [32, 33]

Sample size

Sample size estimation performed prior to recruitment required 80 patients per group to detect a mean difference of 0.45 in the change score of CRQ QoL and CRQ Mastery with a standard deviation of 1 [25] at a significance level of α=0.05 with a power of 80%. This sample size also allows for the detection of medium effects in IPOS scores and the ZBI, expecting 60 carers per group. Mid-term blinded sample size re-estimation based on outcome data suggested no adjustment. Drawing on experience from the London BSS trial [18], we expected an uptake of 50% with 25% attrition and planned screening of 430 patients to have 160 patients with complete data for analysis at T1.

Randomisation

Baseline assessment of patients was undertaken before allocation to the intervention group (fast-track) or the control group (waiting group). Patients were randomised by the Institute for Medical Information Processing, Biometry and Epidemiology, LMU Munich (Munich, Germany) immediately following the baseline interview using a 1:1 allocation ratio, with a web-based application (electronic case report form (eCRF)) that accessed the randomisation list stored in a central database. Randomisation was stratified by disease (cancer/noncancer) and the existence of a carer (yes/no). Results led to predetermined handling within the eCRF system, notifying medical and administrative staff in the MBS team to arrange appointments for the intervention.

Blinding

The study nurse collecting the outcome assessment was blinded to group allocation. Patients were asked in a telephone call from the study coordinator before the interview not to disclose their allocation group to the study nurse. Blinding failures related to outcome assessment were documented. The statistician responsible for data analysis was blinded to the allocation of patients. Care providers implementing the intervention or standard care were not informed about the group allocation of patients; however, there was no enforcement or assessment of blinding.

Statistical methods

Patients' characteristics and baseline measurements were reported using descriptive statistics (mean, mode, median, interquartile range (IQR) and/or standard deviation). The evaluation of the impact of the MBS on outcomes was based on an intention-to-treat (ITT) approach. We tested the four different outcomes CRQ

Mastery, CRQ QoL, IPOS and ZBI step-by-step in this order. In case of a nonsignificant result in the hierarchical testing procedure in the primary efficacy analysis, the following test procedure is stopped and further analyses of the primary outcomes are performed as secondary analyses [34]. This procedure requires no adjustment for multiple testing. We also report the exploratory analyses of secondary outcomes (NRS average 24 h, HADS and SPPB).

Missing data were treated with multiple imputation, assuming missing values at random [35]. Model-based multiple imputation included study group, stratification variables and baseline variables (end-points, diagnosis, gender, age, household composition, Charlson Comorbidity Index and AKPS). Carers were excluded from analyses if baseline values of the main end-point (ZBI) were missing.

To assess the mean effect of the intervention on each outcome, separate multiple linear regression analyses compared the change score achieved (*i.e.* difference in the outcome's value at T1 and T0) between the intervention and control groups. The regression coefficient represents the mean effect that the intervention has on the changes in outcomes (*i.e.* change scores). The analyses were adjusted for the baseline score and the stratification variables (diagnosed with cancer (yes/no) and having an informal carer (yes/no)). For the outcome ZBI, covariates considered were baseline values of the end-point and cancer diagnosis.

Sensitivity analyses applied a worst-case imputation (CRQ Mastery=1, CRQ QoL=1, IPOS=50). For the primary end-point ZBI, sensitivity analyses were conducted using complete cases. Supplementary ITT analyses were conducted to assess the influence of potential confounders on the effect of the MBS regarding the four primary outcomes. Primary efficacy analyses were also conducted with the per-protocol study population who had not dropped out before T1 and showed no time- or therapy-based protocol deviations.

Main efficacy analyses as well as the secondary analyses, including the hierarchical testing and the order of the tested outcomes, were planned in advance and fully described in the study protocol and the statistical analysis plan, following the International Conference on Harmonisation Guidelines [36]. Analyses were carried out using R version 3.5.2 (cran.r-project.org).

Results

Participant flow

439 patients were screened, of whom 183 were included in the study (uptake 41.7%). The first patient was randomised in March 2015. After reaching the required sample size, the last follow-up was in April 2019. Figure 1 shows the enrolment, allocation and follow-up of all patients until T1 assessment. Randomisation allocated 92 and 91 patients to the intervention and control groups, respectively.

Median (range) time between baseline assessment (T0) and T1 was 8.0 (6.3–11.0) weeks. The full CONSORT 2010 flow diagram is presented in supplementary figure A1. The attrition rate of the study at T1 was 22 out of 183 (12.0%). Loss to follow-up clustered around the intervention in both groups (figure 1). At T1, dropout was 17 out of 92 (18.5%) in the intervention group compared with five out of 91 (5.5%) in the control group. At FU, dropout in both groups was equal. Reasons for dropout are provided in supplementary table A2.

Baseline data

Baseline characteristics of the study sample are shown in tables 2 and 3. Randomisation achieved a well-balanced sample.

Numbers analysed

The complete study population (n=183) entered efficacy analysis for the primary outcomes. We observed no single missing items in the primary outcomes CRQ Mastery, CRQ QoL and IPOS in participants continuing the study. All missing values in these outcomes resulted from dropout of the respective study participants. For details of time- and therapy-based protocol deviations, see supplementary figure A1. Blinding failed in some instances because of patients' unmasking their allocation or logistical defects (11 out of 161 (6.8%) at T1). Per-protocol analyses were conducted with 153 patients; other sensitivity and supplementary analyses were conducted with the complete study population.

Outcomes

The main analysis (ITT with multiple imputation) showed a statistically significant improvement in CRQ Mastery of 0.367 (95% CI 0.065–0.669) score units at T1 for the early intervention group (table 4). For the end-point CRQ QoL, there was a statistically significant improvement of 0.226 (95% CI 0.012–0.440). We

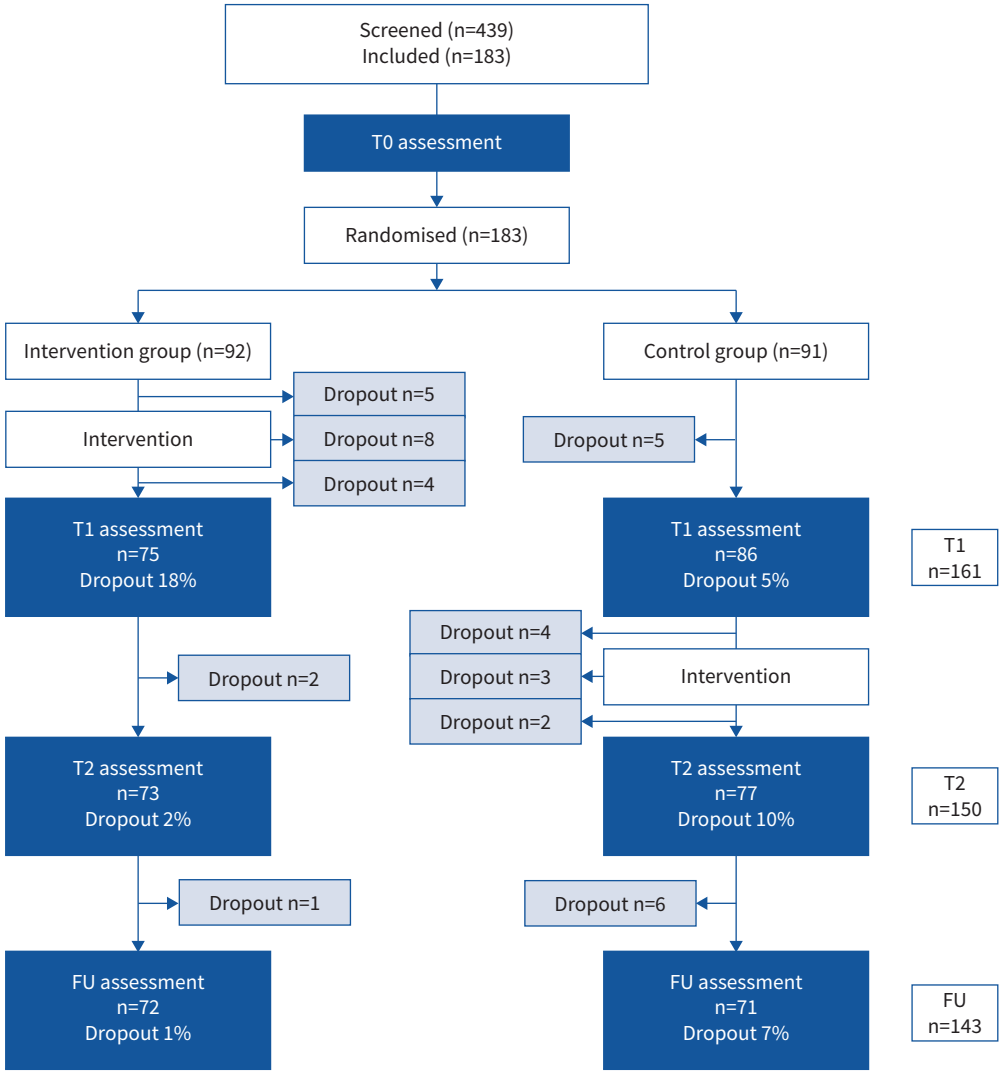

FIGURE 1 Study flow diagram. T0: baseline (prior to randomisation); T1: end of intervention (intervention group)/end of waiting period (control group) (from T0+week 8); T2: after intervention (intervention group)/end of intervention (control group) (from T0+week 16); FU: follow-up by telephone (from T0+week 28).

could not detect significant changes in IPOS. Exploratory analyses with the outcomes ZBI, NRS, HADS Anxiety, HADS Depression and SPPB Sum score could only identify small effects of the intervention that were not statistically significant.

For CRQ Mastery, CRQ QoL and IPOS, baseline values had a significant impact on the change scores. The higher the score at T0 (indicating less breathlessness and better QoL), the smaller the differences at T1 (results not shown). Stratification variables controlled for in the analysis had no significant effect except for HADS Depression, where having an informal carer was associated with less symptom burden (−1.255, 95% CI −2.231–−0.279).

Regarding the primary outcomes, the results of the supplementary and per-protocol analyses supported the results of the main analyses. The sensitivity analyses using worst-score imputation showed nonsignificant effect estimates for all primary outcomes (supplementary tables A3–A5).

Adverse events

Of 156 adverse events recorded up to T1, 72 (46%) were reported by the intervention group and two of them (3%) were related to the intervention. Both were minor and of short duration, *i.e.* side-effects of

TABLE 2 Demographics and baseline (T0) characteristics

	Total	Intervention group	Control group
Sex			
Female	93/183 (50.82)	48/92 (52.17)	45/91 (49.45)
Male	90/183 (49.18)	44/92 (47.83)	46/91 (50.55)
Age years	71.30±8.59 71.78 (10.24) (39.48–94.24)	71.87±8.90 72.67 (8.43) (41.06–94.24)	70.72±8.28 71.24 (10.42) (39.48–86.06)
Charlson Comorbidity Index	1.62±1.68 1 (2) (0–8)	1.71±1.54 1.5 (1) (0–7)	1.53±1.82 1 (2) (0–8)
Household composition			
Living alone	71/183 (38.80)	36/92 (39.13)	35/91 (38.46)
Living with partner/others	112/183 (61.20)	56/92 (60.87)	56/91 (61.54)
Is there a carer?			
Yes	138/183 (75.41)	70/92 (76.09)	68/91 (74.73)
No	45/183 (24.59)	22/92 (23.91)	23/91 (25.27)
Main diagnosis			
COPD	115/183 (62.84)	54/92 (58.70)	61/91 (67.03)
Chronic heart failure	14/183 (7.65)	7/92 (7.61)	7/91 (7.69)
Interstitial lung disease	17/183 (9.29)	10/92 (10.87)	7/91 (7.69)
Pulmonary hypertension	10/183 (5.46)	6/92 (6.52)	4/91 (4.40)
Cancer	13/183 (7.10)	7/92 (7.61)	6/91 (6.59)
Other	14/183 (7.65)	8/92 (8.70)	6/91 (6.59)
LTOT			
Yes	41/183 (22.40)	22/92 (23.91)	19/91 (20.88)
No	142/183 (77.60)	70/92 (76.09)	72/91 (79.12)
Functional status (AKPS)			
100 (no symptoms)	0/183 (0)	0/92 (0)	0/91 (0)
90 (minor symptoms)	18/183 (9.84)	10/92 (10.87)	8/91 (8.79)
80 (some symptoms)	75/183 (40.98)	34/92 (36.96)	41/91 (45.05)
70 (unable to do normal activity)	59/183 (32.24)	30/92 (32.61)	29/91 (31.87)
60 (occasional assistance)	24/183 (13.11)	13/92 (14.13)	11/91 (12.09)
50 (considerable assistance)	6/183 (3.28)	5/92 (5.43)	1/91 (1.10)
40 (bed 50% of time)	1/183 (0.55)	0/92 (0)	1/91 (1.10)
<40	0/183 (0)	0/92 (0)	0/91 (0)
Functional status (AKPS scale[#]) (N=183/91/91)	3.61±0.98 3 (1) (2–7)	3.66±1.03 4 (1) (2–6)	3.55±0.93 3 (1) (2–7)
FVC L (N=175/88/87)	60.57±21.81 57 (33) (12–119)	61.64±21.68 58 (35.5) (16–109)	59.49±22.01 56 (32) (12–119)
FEV_1 L (N=182/92/90)	1.24±0.65 1.15 (0.95) (0.22–3.42)	1.27±0.66 1.16 (0.97) (0.29–3.01)	1.21±0.65 1.11 (0.94) (0.22–3.42)
FEV_1/FVC % (N=175/88/87)	65.93±19.98 68 (34) (24–99)	68.15±20.2 71 (29.5) (24–99)	63.69±19.6 64 (32) (26–99)
S_{pO_2} in patients without LTOT % (N=141/70/71)	95.05±2.25 96 (3) (87–98)	95.16±2.31 96 (3) (88–98)	94.94±2.20 96 (4) (87–98)
S_{pO_2} in patients with LTOT % (N=40/22/18)	94.35±4.66 96 (4) (80–99)	94.86±3.36 95.5 (5) (85–99)	93.72±5.93 96 (3) (80–99)

Data are presented as n/N (%) or mean±SD, median (interquartile range) and (minimum–maximum); where indicated, data for the number of subjects is presented as N for total/intervention/control groups. COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; AKPS: Australia-modified Karnofsky Performance Status; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry. #: AKPS scale values divided by 10.

TABLE 3 Outcome measurements at baseline (T0)

	Total	Intervention group	Control group	Subjects
CRQ Mastery	4.09±1.20 4.25 (1.75) (1–7)	4.17±1.25 4.25 (2.06) (1–7)	4.00±1.15 4.25 (1.50) (1–6.25)	183/92/91
CRQ QoL	3.72±0.82 3.83 (1.10) (1.65–5.8)	3.77±0.80 3.73 (1.01) (1.8–5.8)	3.67±0.84 3.85 (1.22) (1.65–5.45)	183/92/91
CRQ Dyspnoea	2.81±0.71 2.8 (0.8) (1–4.6)	2.88±0.65 2.8 (0.85) (1.4–4.6)	2.74±0.77 2.8 (1) (1–4.6)	183/92/91
CRQ Fatigue	3.65±1.06 3.5 (1.5) (1.25–6.5)	3.69±1.07 3.5 (1.25) (1.25–6.5)	3.6±1.06 3.75 (1.5) (1.5–6.5)	183/92/91
CRQ Emotional function	4.19±1.14 4.14 (1.57) (1.86–6.57)	4.22±1.11 4.29 (1.43) (1.86–6.57)	4.16±1.17 4.14 (1.71) (1.86–6.57)	183/92/91
IPOS Sum	22.79±8.27 22 (12) (4–43)	22.97±7.83 22 (10) (4–42)	22.6±8.74 21 (12.5) (5–43)	183/92/91
IPOS Symptoms	12.59±5.17 12 (7) (2–26)	12.8±5.15 13 (7) (2–26)	12.37±5.20 11 (8) (2–24)	183/92/91
IPOS Communication	3.84±2.59 4 (3) (0–12)	3.91±2.5 4 (3) (0–11)	3.77±2.68 4 (3) (0–12)	183/92/91
IPOS Emotional	6.36±3.35 6 (5) (0–15)	6.25±3.24 6 (4.25) (0–15)	6.46±3.48 6 (5) (0–15)	183/92/91
ZBI Sum	21.35±12.86 22 (19) (0–56)	20.77±13.58 21.5 (21.5) (0–56)	21.85±12.32 22 (16) (0–54)	95/44/51
NRS (average 24 h)	5.36±1.79 5 (3) (1–10)	5.04±1.75 5 (2) (1–8)	5.67±1.78 6 (2) (1–10)	183/92/91
NRS at rest	2.81±1.74 2 (2.5) (1–10)	2.63±1.59 2 (2.25) (1–8)	2.99±1.86 2 (2) (1–10)	183/92/91
NRS on exertion	7.42±1.87 8 (2) (1–10)	7.08±1.86 7.5 (2) (2–10)	7.76±1.83 8 (2) (1–10)	183/92/91
HADS Anxiety	6.93±3.85 7 (6) (0–17)	6.87±3.8 7 (6) (0–15)	6.99±3.92 7 (5.5) (0–17)	183/92/91
HADS Depression	7.92±4.24 8 (6) (1–21)	7.78±3.89 8 (6) (1–16)	8.07±4.59 8 (6) (1–21)	183/92/91
EQ-5D-5L	0.86±0.19 0.94 (0.18) (0.15–1)	0.86±0.19 0.92 (0.20) (0.26–1)	0.87±0.19 0.94 (0.16) (0.15–1)	183/92/91
EQ VAS	59.27±17.91 60 (20) (10–100)	59.57±16.08 60 (20) (19–90)	58.98±19.67 60 (30) (10–100)	183/92/91
SPPB Total	7.75±2.8 8 (2) (0–12)	7.75±2.93) 8 (2.25) (0–12)	7.74±2.68 8 (2.75) (0–12)	182/92/90
SPPB Balance	3.4±1.16 4 (1) (0–4)	3.45±1.19 4 (0.25) (0–4)	3.36±1.13 4 (1) (0–4)	182/92/90
SPPB Gait speed	3.04±1.12 3 (1) (0–4)	3.01±1.21 3 (1) (0–4)	3.07±1.03 3 (1) (0–4)	182/92/90

Continued

TABLE 3 Continued

	Total	Intervention group	Control group	Subjects
SPPB Chair stand	1.31±1.14 1 (1) (0–4)	1.29±1.16 1 (1.25) (0–4)	1.32±1.12 1 (1) (0–4)	182/92/90

Data for outcome measurements are presented as mean±SD, median (interquartile range) and (minimum–maximum); data for the number of subjects is presented as N for total/intervention/control groups. CRQ: Chronic Respiratory Disease Questionnaire; QoL: quality of life; IPOS: Integrated Palliative care Outcome Scale; ZBI: Zarit Burden Interview; NRS: numerical rating scale; HADS: Hospital Anxiety and Depression Scale; EQ-5D-5L: EuroQol generic health status instrument with five dimensions and five levels; EQ VAS: EuroQol Visual Analogue Scale; SPPB: Short Physical Performance Battery.

medication prescribed by the MBS (subsequently stopped) and a temporary skin reaction following an allergy test recommended by the MBS.

Discussion

The MBS constitutes a novel service in Germany, providing a multiprofessional, symptom-based short-term intervention for people experiencing poor health-related QoL caused by breathlessness in advanced stages of disease. Led by palliative care specialists, in cooperation with respiratory specialists and specialised respiratory physiotherapy lasting 5–6 weeks, the MBS is characterised by its holistic treatment approach and self-management support.

This study presents the results of a randomised controlled fast-track trial testing the effectiveness of the intervention. We found statistically significant improvements in the primary end-points CRQ Mastery and CRQ QoL over standard care, providing evidence that the intervention succeeded in reducing the burden caused by chronic breathlessness. The findings demonstrate that patients with diverse advanced diseases at different stages benefit from this add-on to usual care in the German healthcare system, which emphasises a coordinated, multiprofessional and interdisciplinary approach to care [37]. The new MBS, which is anchored in a variety of medical specialities, contributes to high-quality healthcare provision beyond treatment of the underlying disease. This underlines the call for chronic breathlessness being defined as a "syndrome", delineating systematic clinical enquiry and targeted intervention [2].

Locating findings in the literature

The observed difference of 0.367 (95% CI 0.065–0.669) in the change score for CRQ Mastery is in line with the findings of three previous studies examining breathlessness support services. Higginson *et al.* [18]

TABLE 4 Results of the primary and secondary analyses

	Adjusted regression coefficient[#]	SE	95% CI	p-value[¶]
CRQ Mastery[+]	0.367	0.154	(0.065–0.669)	0.017
CRQ QoL[+]	0.226	0.109	(0.012–0.440)	0.037
IPOS	−1.864	1.116	(−4.051–0.323)	0.095[§]
ZBI	−2.533	2.13	(−6.708–1.642)	
NRS (average 24 h)	−0.550	0.283	(−1.105–0.005)	
HADS Anxiety	−0.407	0.462	(−1.313–0.499)	
HADS Depression	−0.583	0.427	(−1.420–0.254)	
SPPB Sum score	−0.095	0.346	(−0.773–0.583)	

CRQ: Chronic Respiratory Disease Questionnaire; QoL: quality of life; ZBI: Zarit Burden Interview; IPOS: Integrated Palliative care Outcome Scale; NRS: numerical rating scale; HADS: Hospital Anxiety and Depression Scale; SPPB: Short Physical Performance Battery. [#]: adjusted regression coefficients (adjusted for the CRQ Mastery Score at T0, cancer status and the presence of an informal carer) of the multiple linear regression analyses on the change scores show the intervention effects for the main outcomes; [¶]: Wald tests of multiple linear regression models on change scores adjusted for the CRQ Mastery Score at T0, cancer status and the presence of a carer; [+]: higher value of the CRQ indicates better outcome of the patients; [§]: nonsignificant result in the hierarchy of testing, consequently no further tests of significance.

found a difference between intervention and control groups of 0.58 (95% CI 0.01–1.15) comparing absolute measurements at 6 weeks, using a two-sided t-test for independent samples. FARQUHAR *et al.* [38] reported a difference of 0.43 (95% CI −0.02–0.89) at 4 weeks in their study of patients with advanced nonmalignant disease, adjusting for baseline values. In a study of patients with advanced cancer, CRQ Mastery scores adjusted for baseline values improved by 0.20 (95% CI −0.35–0.76) at 2 weeks [16]. The last two studies had smaller sample sizes and results were not statistically significant but support a consistently positive impact of the intervention. In comparison, our results refer to an observation period of 8 weeks.

Adding the data of our study to a recently conducted meta-analysis of five trials (n=420), the overall body of evidence assessing the effectiveness of breathlessness support services increases considerably, yielding a greater precision of effect estimates [39, 40]. The outcome measurements chosen in our study are widely used in studies on the effectiveness of interventions for chronic breathlessness in advanced disease and reflect the multidimensional effects of chronic breathlessness [41, 42]. Notably, the CRQ Mastery domain relates to important psychological outcomes, such as appraisal and a feeling of control, whereas other measures capture physical changes (NRS) and psychological distress (HADS) [43, 44].

Strengths and limitations of this study

The strengths of this study are the large sample size and the heterogeneity of patients participating, thus approximating real-world conditions to a greater extent than previous studies. As a potential limitation, an increased awareness of breathlessness management over the long duration of our study could have affected our findings. However, there was no indication of improved services or any change in standard care over the time period. Furthermore, within the scope of the MBS, offering consultation with an in-house respiratory physician was provided as default at first and later switched to optional. This did not change the quality of care and, for this reason, there was no need to change the analysis. Limitations are that blinding of study participants was not possible because of the nature of the intervention, the imbalance in dropout rates at T1 and the small effect size, discussed further in the following.

The CRQ Mastery change score did not reach the threshold of the minimum clinically important difference of 0.5, which is reported most frequently although some lower estimations can be found in the literature [45]. However, this threshold lies within the confidence interval of the estimated effect in our study. The small effect size may partly result from bias introduced by the Hawthorne effect, where enrolment in the trial also affects expectations in the control group, which the CRQ may have picked up. Moreover, trial populations in the studies setting a minimum clinically important difference for the CRQ may not be comparable to our study. FARQUHAR *et al.* [38] refer to "the smaller margins of benefit and the greater spread of benefits in palliative care interventions, with a cumulative effect from the addition of several smaller quantitative outcome benefits". Although the results of our trial cannot establish clinical significance of the intervention effect, they signal the need for further investigation regarding factors that may impact the size of the intervention effect.

Trials with outcome measures that reflect subjective experience are particularly susceptible to overestimating treatment effects unless blinding procedures are used [46]. However, practical difficulties with blinding were substantial, particularly because outcome assessment took place in participants' homes. Blinding of study participants was not possible on account of the nature of the intervention. This may have affected reporting of outcomes by patients and may have led to larger than expected differences in change scores between the intervention and control groups.

The attrition rate in our trial (21.9%) was lower than the 25% assumed in the power calculation. Dropout was highest in the subgroup with cancer, similar to previous palliative care trials [47]. Over the course of the study, dropout rates between the intervention and control groups were balanced (20 participants in both groups). However, at the T1 measurement, the intervention group showed a higher proportion of patients who were lost to follow-up, possibly caused by the burden relating to participating in the multicomponent intervention. Importantly, comparison of the two groups at baseline showed that they were well balanced regarding stratification and baseline variables.

Conclusions

Improvements in mastery of breathlessness and in QoL in patients with advanced disease were previously reported for UK patients. Our study confirmed these improvements for patients in the German healthcare system, where direct access to respiratory specialists is provided. This emphasises the importance of a holistic treatment approach combined with self-management support, as well as the feasibility of implementing a short-term intervention that could be expanded more equitably across the German health

system [48, 49]. With pooled data across trials, improvements should be analysed for different subgroups. Further analysis of our data, drawing on findings from qualitative and mixed methods studies conducted alongside the efficacy trial, will provide a deeper understanding of intervention effectiveness.

This study is registered at ClinicalTrials.gov with identifier number NCT02622412. We first submitted the record to ClinicalTrials.gov on 31 October 2015, 7 months after the first patient had been enrolled. At that time, we had recruited 32 patients (17% of the total). The submission was posted on 4 December 2015. The delay in registration was caused by the heavy workload at the beginning of the trial. We had obtained approval from the ethics committee on 8 January 2015. In July 2015, we dropped an inclusion criterion (requiring modified Medical Research Council dyspnoea scale grade $\geqslant$2 for inclusion of patients) in an amendment to the study protocol. At that time, we had become aware that we had not intended to exclude patients with an intermittent burden of breathlessness. No further changes to inclusion and exclusion criteria were made throughout the study. All individual patient data that underlie the results reported in this article after anonymisation can be made available to researchers who provide a methodologically sound proposal; they will need to sign a data access agreement. To gain access, proposals should be directed to the corresponding author.

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