Early View

Original article

BreathEase: rationale, design and recruitment of a randomised trial and embedded mixed methods study of a multi-professional breathlessness service in early palliative care

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BreathEase: rationale, design and recruitment of a randomized trial and embedded mixed methods study of a multi-professional breathlessness service in early palliative care

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Data sharing statement

All individual patient data underlying the results reported in this article (text, tables, figures and appendices) can be made available after anonymization to researchers who provide a methodologically sound proposal; they will need to sign a data access agreement. Information regarding submitting proposals and accessing data is available from the corresponding author. To gain access, proposals should be directed to the corresponding author.

Take home message

The BreathEase Study, a mixed method pragmatic randomized controlled trial (RCT) evaluating the Munich Breathlessness Service (MBS), included a heterogeneous sample, which approximates real-world conditions of early palliative care, and ran qualitative and quantitative trial siblings.

Plain language statement

Our aim is helping people with COPD or other advanced diseases to cope better with chronic breathlessness through a specialized treatment programme. It is led by palliative medicine together with respiratory medicine, specialist physiotherapy and other health professionals. Patients have 4- to 6-weekly appointments. The BreathEase trial has been designed to see if this programme is effective in supporting patients with their breathlessness. Here, we describe the programme and practical issues conducting the trial. We show how we identified participants for this trial and what their characteristics were. This is important because we want our study to be comparable to other studies and to support the evidence of these specialised breathlessness programmes.

Abstract

Background

The Munich Breathlessness Service (MBS) has adapted novel support services to the German context, to reduce burden in patients and carers from breathlessness in advanced disease. It has been evaluated in a pragmatic fast track randomized controlled trial (RCT) (BreathEase, NCT02622412) with embedded qualitative interviews and postal survey. The aim of this paper is to describe the intervention model and study design, analyse recruitment to the trial and compare sample characteristics with other studies in the field.

Methods

Analysis of recruitment pathways and enrolment, sociodemographic and clinical characteristics of participants and carers.

Results

Of 439 people screened, 253 (58%) were offered enrolment and 183 (42%) participated. n=97 (70%) carers participated. 186 people (42%) did not qualify for inclusion, mostly because breathlessness could not be attributed to an underlying disease. All participants were self-referring, 60% through media sources. Eligibility and willingness to participate were associated to social networks and illness-related activities as recruitment routes. Mean age of participants was 71 years (51% women), with COPD (63%), chronic heart failure (8%), interstitial lung disease (9%), pulmonary hypertension (6%) and cancer (7%) as underlying conditions. Postal survey response rate was 89%. Qualitative interviews were conducted with 16 patients and 9 carers.

Conclusion

The BreathEase study has a larger and more heterogeneous sample compared to other trials. The self-referral-based and prolonged recruitment drawing on media sources approximates real-world conditions of early palliative care. Integrating qualitative and quantitative components will allow a better understanding and interpretation of the results of the main effectiveness study.

Introduction

Breathlessness is a common, distressing symptom in advanced cardiorespiratory and malignant diseases, which reduces patients' and carers' quality of Life (QoL), psychological well-being and functional status (1, 2). The complexity of the symptom is exemplified by the inconsistent relationship between the underlying disease and breathlessness perception, and by the wide range of multiple interacting factors influencing symptom perception, including reactions to breathlessness, such as avoidance behaviour that may worsen symptom perception (3, 4). Even while receiving best practice medical treatment of the underlying condition, chronic breathlessness inflicts increased costs on the health system, such as for emergency care during episodes of acute breathlessness (5, 6).

Optimizing management of chronic breathlessness draws on a variety of mostly non-pharmacological approaches to support patients and their families in developing strategies for adaptive self-management (7-9). Breathlessness support services, led by palliative medicine, have been developed in the UK building upon theoretical work, modelling and feasibility studies (10). The Cambridge Breathlessness Intervention Service (CBIS) and the London Breathlessness Support Service (BSS) provide face-to-face support either at home or in outpatient clinics or through a combination of both, with varied treatment schedules and multi-professional input but very similar intervention components (7, 8). Their effectiveness in terms of alleviating symptom distress, strengthening symptom mastery and increasing QoL was demonstrated in three pragmatic RCTs (11-13).

The Munich Breathlessness Service (MBS) has adapted the interventions of CBIS and BSS to the German context. Compared with the UK, specialists in private practices outside hospitals provide broader access to respiratory services in Germany. However, a qualitative study has pointed to healthcare providers' lack of awareness regarding the symptom burden and therapeutic concepts (14). Drawing on experiences from the UK, a more intense and longer intervention was considered appropriate and tested in the MBS, notably emphasizing physiotherapy.

The MBS has been evaluated in the BreathEase study, testing the (cost-) effectiveness of the MBS on mastery of breathlessness and QoL in patients with advanced disease within a RCT design. The main results of this RCT have been published elsewhere (15). This paper focusses on recruitment and enrolment strategies of the BreathEase study, their impact on the sample characteristics and appraises the study design and outcome measurements with its embedded quantitative and qualitative components.

In this paper, we describe 1) the full study design and rationale behind the intervention, analyse 2) recruitment and enrolment into the study and compare 3) the sample characteristics at baseline with the CBIS and BSS studies.

Methods

Drawing on a system-based logic model of the MBS intervention, the BreathEase study design and data collection is described, encompassing the RCT and embedded studies.

Design

We conducted a fast track pragmatic observer-blinded RCT. Participants randomized in the control group received the intervention after a waiting period of 8 weeks. Enrolment started in March 2014, ending in October 2018. The study was registered with ClinicalTrials.gov (NCT02622412). Within the RCT, we embedded qualitative interviews and a postal survey to explore study participants' views regarding the intervention (Figure 1). Approval was obtained from the research ethics committee at the Medical Faculty of LMU Munich (no. 523-14).

>insert Figure 1<

Intervention

The MBS is run as a multi-professional outpatient clinic at the Department of Palliative Medicine in cooperation with the Respiratory Department, both at Munich University Hospital. Patients have up to two outpatient appointments at the hospital with palliative medicine clinicians and three or four physiotherapy treatments at a community-based practice within 5–6 weeks. Further input by the multi-professional team (e.g. respiratory specialist, psychologist, social worker) is available as needed. During the trial period, all those requesting to use the service were asked to participate in the trial.

Following the template of Rohwer et al 2017 (16), a system-based logic model of the intervention was developed to illustrate the complex relationships between individual characteristics, the intervention and its delivery, and contextual factors, based on reviews of existing breathlessness services, focused literature searches and within-team brainstorming (Figure 2). Central to the model depicted in Figure 2 is a set of concepts that describe the impact of breathlessness, define the composition and delivery of the intervention and the influence of a range of other factors (3, 6, 8, 9, 17-19). Most influential with respect to the theory underlying the intervention is the Breathing–Thinking–Functioning model of Spathis et al (3), which is the basis for classifying the diverse service components. We postulate two mechanisms of change: First, the intervention is predicted to affect cognitive and behavioural reactions to breathlessness, which enhance self-management through meaning-based coping, improved problem management and emotional regulation (6, 20-22). Second, the intervention supports patients' 'adaptive work' in chronic illness (17). This is achieved by offering recognition through a holistic assessment and encouragement to utilize community-based health

services following the short-term MBS intervention, e.g. lung exercise groups, advanced care planning.

>insert Figure 2<

Recruitment

The study received media coverage in the radio and a local TV station. Short articles in local newspapers were released throughout the study, to increase public awareness and self-referral. Information was provided to local practice-based respiratory specialists and hospitals specialized in respiratory patients, as well as several cardiologists. The service was presented to two local self-help groups, one for patients with COPD and one for patients with Pulmonary Arterial Hypertension (PAH), one hospital-based sports group (PAH) and a respiratory medicine network. Leaflets were distributed regularly within the hospital and at various contact points throughout the city.

The trial operated on the basis of self-referring by patients themselves, although in some cases information were received by clinicians (which is referred to as "clinical referral"). Eligibility was based on up-to-date information (referring to the last 6 months) from doctors' letters provided by those interested in participation and assessed by the clinical investigator. Doctors' letters were not requested when exclusion criteria could be established by the study coordinator beforehand.

Participants

RCT: Broad inclusion and minimal exclusion criteria were employed to approximate real-world conditions of early palliative care (see box in Figure 1).

If people were suffering from acute exacerbations of the underlying condition at the time of recruitment, they were put on a waiting list after eligibility was established and subsequently entered the trial. Eligible individuals were asked whether they had a close family member or friend, defined as someone with almost daily contact. If this was the case, the so-called 'carer' was also asked to participate in the study.

Recruitment pathways were classified according to i) media, ii) clinical referral and iii) social network/illness-related activities. Recruitment outcomes were defined as i) enrolment, ii) declined consent or iii) not eligible. Reasons for exclusion were categorized according to inclusion and exclusion criteria.

Postal survey: All RCT study participants were invited to participate after completing the intervention.

Qualitative interviews: A purposeful sample of 25 study participants (patients and carers) was drawn from the RCT sample after completion of the intervention with age, gender, type of underlying disease and existence of a carer as sampling criteria.

Data collection

RCT: Age, gender and the extent to which breathlessness impacts daily activities, measured with the modified Medical Research Council Dyspnoea scale (mMRC) (23), were recorded for all those screened for study participation, as well as recruitment routes. Study participant characteristics were assessed at baseline. Patients' diagnoses were recorded as documented in doctors' letters, including grading the severity of the illness according to the GOLD Spirometric Classification (24) and the NYHA classification of heart failure (25).

Outcomes were measured with standardized self-administered questionnaires at T0 = baseline (prior to randomization); T1 = week 8 from T0, T2 = week 16 from T0) and follow-up (FU) (week 28 from T0) (see Figure 1). To reduce burden for study participants, home visits by a qualified study nurse were offered to collect the data at T0–T2; FU was organized by telephone interview. Recruitment, enrolment and baseline data collection were pre-tested in a pilot study with n=8 participants. Data were entered in an electronic record system (eCRF).

Postal survey and qualitative interviews: The 23-items-questionnaire was sent out 4–6 weeks after completion of the intervention. Semi-structured Interviews were conducted 4–6 weeks after completion of the intervention and, if possible, after completion of the postal survey.

Data were checked with double entry on randomly selected data subsets.

Variables and Outcomes

Study participant characteristics included age, sex, underlying disease and comorbidities, education, presence and tasks of the carer, marital status and household composition. Comorbidity was assessed with the Charlson Comorbidity Index (26) and functional performance with the Australian modified Karnofsky Performance Scale (27).

The RCT had four primary outcomes: Mastery of breathlessness and QoL were both measured on the validated Chronic Respiratory Disease Questionnaire (CRQ) (28). Palliative care needs and specific symptoms were assessed with the validated German version of the Integrated Palliative care Outcome Scale (IPOS) (29, 30). Carers' burden was assessed with the Zarit Burden Interview (ZBI) (31).

Secondary outcomes included the numerical rating scale (NRS) on the strength of breathlessness (on average, at rest and on exertion during the last 24 h), lung function, the Hospital Anxiety and Depression Scale, the Short Physical Performance Battery (SPPB), QoL assessed with the German tariff of EQ-5D-5L (32) and the FIMA questionnaire on health service utilization and medication (33).

Carers' QoL was assessed with the EQ-5D-5L and supplemented by three items concerning insomnia and sleep quality. All adverse events defined as any unfavourable medical occurrence (e.g. infections, hospital admissions) were recorded throughout the trial. Survival was followed up for all participants until the end of the study. All outcomes are depicted in Table 1.

Table 1: Overview of quantitative outcomes and associated measures

	Baseline	T1 (8 weeks)	T2 (16 weeks)	FU (28 weeks)	End of study
CRQ*	x	x	x	x	
IPOS*	x	x	x	x	
NRS breathlessness*	x	x	x	x	
HADS*	x	x	x	x	
EQ-5D-5L, VAS	x	x	x	x	
SPPB*	x	x	x		
Lung function	x	x	x		
Oxygen saturation	x	x	x		
Health Service Utilisation and Medication (FIM-P)	x	x	x	x	
Patient survival					x
Adverse events	x	x	x	x	
Carer Zarit Burden Inventory (ZBI)	x	x	x		
Carer EQ-5D-5L, VAS	x	x	x		
Carer sleep quality	x	x	x		

*CRQ total score and subscores (Mastery; Dyspnoea; Fatigue; Emotional Function), self-administered individualized version; IPOS total score and subscores (Somatic symptoms; Emotional problems; Quality and communication) NRS (On average in the last 24 h; At rest in the last 24 h; On exertion in the last 24 h); HADS (Depression; Anxiety); SPPB total score and subscores (Balance, Gait speed, Chair stand).

The postal survey addressed the perceived benefit of recommendations, materials and exercises provided as well as overall satisfaction with the MBS, its accessibility and scope and the participation in the study. Topics of the qualitative interviews were the perception of symptom burden, coping mechanisms, and whether or not attendance of the MBS was successful in supporting longer-term self-management capacities.

Sample size calculation

The study's hypotheses involve changes in the four primary outcomes outlined above. To detect a mean difference of 0.45 in the change score of CRQ QoL and CRQ Mastery of breathlessness with a standard deviation of 1 (28) at a significance level of $\alpha=0.05$ and a power of 80%, 80 participants were required per group. Based on the London BSS trial, a conservative calculation estimated the

uptake into the trial to be about 50% of referred participants and attrition to be 25%, resulting in a planned screening of 430 people in order to recruit a total of 160 participants into the study.

Data analysis of recruitment, enrolment and sample characteristics

Recruitment pathways, recruitment outcome and time for screening are descriptively analysed. Reasons for exclusion are mapped by type and frequency. Logistic regression models are used to assess the effects of gender, age, breathlessness (mMRC) and recruitment route on a) eligibility (y/n) and b) consent to participation (y/n). Study participant and carer characteristics are described in total and for women and men seperately (mean, SD). Missing data are reported.

Results

Recruitment and enrolment

From February 2015 to October 2018, we screened 439 people; of those, 253 were offered enrolment (58%) and 183 (42%) were successfully recruited. Trial length was 3.5 years, 2 years longer than planned. Media recruitment was the most common route in the total screened (58%) and in those enrolled (44%). However, enrolment was most successful in people recruited via social network/illness-related activities and least successful in those recruited via the media. Recruitment routes in comparison to recruitment outcome are shown in Table 2. In our sample, the overall attrition during the screening process was n=256 (58%) of the total n=439, which is higher than the estimated 50% before the trial.

Table 2: Recruitment routes by recruitment outcome

	Enrolment (n=183) 42%	Declined consent (n=70) 16%	Not eligible (n=186) 42%	Total screened (n=439)
Newspaper, n	73	35	112	220
TV/radio, n	6	4	13	23
Internet, n	2	2	10	14
Media (total) n (row %, column %)*	**81 (32, 44)**	**41 (16, 60)**	**135 (53, 73)**	**257 (100, 58)**
Hospital	29	11	14	54
Primary care physician	10	5	6	21
Practice-based specialist	8	4	4	16
Clinical referral (total) n (row %, column %)*	**47 (52, 26)**	**20 (22, 29)**	**24 (26, 13)**	**91 (100, 21)**
Self-help/lung sport groups	19	2	0	21
Friends/social network	12	1	6	19
Leaflet (hospital)	8	0	8	16
Leaflet (unspecified)	7	0	3	10
Open day (e.g. cancer help)	4	3	1	8
Social Network/Illness-related activitie (total) n (row %, column %)*	**50 (68, 27)**	**6 (8, 8)**	**18 (24, 10)**	**74 (100, 17)**
Missing	5	3	9	17 (4)

*Numbers in brackets are 1) row%: the percentage relative to the number of total screened (last column) in the same row and 2) column%: the percentage relative to the total in the same column

We did not limit the length of time for screening for each individual. The time for screening for those who declined participation was longest on average (113 days (SD 165; median 51 days, min 0, max 997)), compared to 50 days (SD 70; median 28 days, min 0; max 626) from those enrolled and 66 days (SD 106; medium 26 days, min 0 max 843) for those not eligible. When looking at the time for screening by recruitment routes, the largest share of decision processes for those getting in touch via the media route was 2-6 months (41%), compared to the clinical and social network referral routes, where most have completed the decision processes by 1 month (43% and 47%, resp.)(cf. figure 3). Almost a fifth of those approaching the study via the media route (n=48, 19%) were decided within 5 days. With one exception, these were all people who met an exclusion criterion.

>insert Figure 3<

Table 3 shows reasons for exclusion, including overlaps between categories. An underlying medical condition that could not be ascertained was the most frequent cause of exclusion (39%). The defining disease had to be causally linked to symptom breathlessness, and it had to be a life-limiting progressive disease, such as COPD or interstitial lung disease (ILD), which would qualify palliative care services for attending to these patient. 35% of patients interested in the MBS did not meet these criteria or were not receiving best practice medical treatment. Owing to slow recruitment, all potentially eligible participants were followed up by prolonged efforts, often associated with logistical issues, such as transportation problems, or with difficulties in getting hold of up-to-date information on their medical conditions. Organisational reasons applied to about one third of patients, in n=30 they were the only reason for exclusion.

Table 3: Reasons for exclusion

	Total exclusions (n=186) n (%)*	
Underlying medical condition could not be ascertained	72 (39)
Non-medical organizational reasons, e.g. lives outside study catchment area, contact broken off	67 (36)
No progressive and advanced life-limiting disease causing breathlessness, or not receiving best practice medical treatment	66 (35)
Acute illness or currently in hospital/rehabilitation	31 (17)
Low symptom burden	17 (9)
Cognitive impairment	10 (5)
Insufficient German to participate in study	4 (2)
Cancer patients with treatment other than maintenance therapy	3 (2)
Participation in other clinical trial focusing on underlying condition	0

*Multiple answers possible. Minor overlaps in Venn diagram are not reported. Venn diagram: https://www.biovenn.nl/

Patient characteristics were analysed with regard to fulfilling the inclusion criteria (resp. not meeting exclusion criteria) and with regard to choosing to decline enrolment, following the offer (Table 4). Younger (<60 years) and older age (> 80 years) as well as moderate symptom burden (MRC=1) was significantly associated with a lower chance to be considered eligible to participate. Recruitment via social networks and via clinical referral were associated with higher chances of eligibility. Furthermore, people recruited via social networks were less likely to decline compared to people recruited via media information. Compared to men, women declined enrolment more often.

Table 4: Patient characteristics by recruitment outcome

	Total (n=439)	Eligible (n=253)	Not eligible (n=186)	Odds Ratio (95% CI) §# modelling eligibility	Enrolled (n=183)	Declined (n=70)	Odds Ratio (95% CI) #¶ modelling enrollment
Age groups n (%)*							
< 60 years	45 (10)	19 (8)	26 (15)	0.32 (0.15; 0.71)**	17 (9)	2 (3)	4.71 (0.58; 38.19)
60 - 69 years	97 (22)	68 (27)	29 (17)	1.20 (0.68; 2.12)	52 (28)	16 (24)	0.91 (0.43;1.90)
70 - 79 years (ref.)	197 (45)	124 (50)	73 (42)	Ref.	90 (49)	34 (52)	Ref.
> 80 years	82 (19)	38 (15)	44 (26)	0.39 (0.22; 0.70)**	24 (13)	14 (21)	0.49 (0.21; 1.15)
Female n (%)	237 (54)	138 (55)	99 (53)	1.10 (0.71; 1.71)	93 (51)	45 (64)	0.47 (0.25; 0.88)*
(ref. Male)		115 (45)	87 (47)	Ref.	90 (49)	25 (36)	Ref.
mMRCn† n (%)							
1 "moderate"	85 (19)	25 (10)	60 (33)	0.27 (0.15; 0.52)***	16 (9)	9 (13)	0.50 (0.18; 1.41)
2 "strong" (ref.)	134 (31)	85 (34)	49 (27)	Ref.	68 (37)	17 (25)	Ref.
3 "very strong"	214 (49)	142 (56)	72 (40)	0.90 (0.54; 1.49)	99 (54)	43 (62)	0.83 (0.41; 1.67)
Recruitment route‡							
Media (ref.)	257 (58)	122 (50)	135 (76)	Ref.	81 (46)	41 (61)	Ref.
Clinical	91 (21)	67 (27)	24 (14)	2.82 (1.55; 5.14)***	47 (26)	20 (30)	1.07 (0.52; 2.18)
Social	74 (17)	56 (23)	18 (10)	3.15 (1.67; 5.94)***	50 (28)	6 (9)	4.76 (1.70; 13.38)**

*Age at first contact (missing n=18 (n=4 declined; n=14 not eligible)); † modified Medical Research Council Dyspnoea scale (mMRC) (0=breathless with strenuous exercise; 1= breathless when hurrying on the level/walking up; 2=stop for breath when walking at my own pace; 3=stop for breath after about 100 m; 4=breathless when getting dressed; (missing: n=1 declined; n=5 not eligible); for the regression model mMRC categories 0 and 1 and mMRC categories 3 and 4 were merged due to low cell counts (category "0": n=0 enrolled, n=0 declined, n=13 excluded; category "4": n=6 enrolment, n=8 declined n=8 not eligible). ‡ missing n=17 (n=5 enrolled; n=3 declined, n=9 excluded) § Missings in regression model: n=35 ¶Missings in regression model: n=12 # p-Values: ***<0.001; **<0.1 *<0.5

The postal survey was sent out to 149 study participants and yielded n=132 responses (89% response rate). Qualitative interviews were conducted with 25 study participants, i.e. 16 patients and 9 carers. Two study participants and one carer declined participation in the qualitative study without giving reasons, one study participants died before the interview was scheduled.

Sample characteristics

Table 5 characterizes the study participants and carers. Most patients (49%) were in the age group 70–79 years. Sex distribution was almost equal. Half the sample (53%) was married, 61% were living with a partner/others and 75% had a carer. Men in the sample, compared to women were more often

married (73 % vs. 33%), living with others (77% vs. 46%) and had a carer (87% vs. 65%). About two-thirds of study participants suffered from COPD (63%) as the underlying condition. Other diseases were chronic heart failure (CHF, 8%), ILD, 9%), pulmonary hypertension (6%), cancer (7%) and diseases such as bronchiectasis or emphysema. Most study participants were rated on the Australian Karnofsky scale as having some symptoms that limited their normal activity (80%) or as not being able to carry out normal activity (70%). 97 carers (67% female), mostly participants' partners (87%), were included in the study with a mean age of 66.3 years. Caring tasks extended from less than 10 h per week (61%) to more than 50 h per week (9%), with female carers spending more time/week with caring activities, compared to male carers.

Table 5: Baseline characteristics of patients and carers

Variables				Women	Men
Patients			**n=183**	**n=93**	**n=90**
Age	years mean (SD)		71.3 (8.6)	70.6 (8.8)	71.1 (8.5)
	years min; max		39.5; 94.2	39; 94	41; 90
Age groups, n (%)	< 60 years		17 (9)	8 (9)	9 (10)
	60 - 69 years		51 (28)	26 (28)	25 (28)
	70 - 79 years		90 (49)	47 (51)	42 (48)
	> 80 years		25 (13)	12 (13)	13 (14)
Sex, n (%)	female		93 (50.8)	-	-
Marital status, n (%)	married		97 (53)	31 (33)	66 (73)
	single		25 (14)	16 (17)	9 (10)
	widowed		30 (16)	25 (27)	5 (6)
	divorced/separated		31 (17)	21 (23)	10 (11)
Household composition, n (%)	living alone		71 (39)	50 (54)	21 (23)
	living with partner/others		112 (61)	43 (46)	69 (77)
Carer, n (%)	yes		138 (75)	60 (65)	78 (87)
Education, n (%)	9 years		69 (38)	35 (38)	34 (38)
	10 years		66 (36)	40 (43)	26 (29)
	12-13 years		48 (26)	18 (19)	30 (33)
Diagnosis, n (%)	COPD		115 (63)	63 (68)	52 (58)
	Stage* I		5 (4)	3 (5)	2 (4)
	II		33 (29)	18 (29)	15 (29)
	III		34 (30)	18 (29)	16 (31)
	IV		43 (37)	24 (38)	19 (37)
	Chronic Heart Failure+		14 (8)	5 (5)	9 (10)
	NYHA I		1 (7)	0	1 (11)
	NYHA II		5 (36)	2 (40)	3 (33)
	NYHA III		7 (50)	2 (40)	5 (56)
	NYHA IV		1 (7)	1 (20)	0
	Interstitial Lung Disease		17 (9)	5 (5)	12 (13)
	Pulmonary Hypertension		10 (6)	6 (6)	4 (4)
	Cancer[a]		13 (7)	6 (6)	7 (8)
	Other		14 (8)	8 (9)	6 (7)
Australian modified Karnofsky Performance Scale, n (%)	90% (minor symptoms)		18 (10)	11 (8)	7 (8)
	80% (some symptoms)		75 (41)	37 (40)	38 (42)
	70% (unable to perform normal activity)		59 (32)	30 (32)	29 (32)
	60% (occasional assistance)		24 (13)	12 (13)	12 (13)
	50% (considerable assistance)		6 (3)	3 (3)	3 (3)
	40% (bed 50% time)		1 (1)	0	1 (1)
Charlson Comorbidity Index *Scale range: 0-37 worst*	mean (SD) min-max[b]		1.6 (1.7) 0-8	1.5 (1.5)	1.7 (1.8)
Carers			**n=97**	**n=66**	**n=31**
Carer age[a]	mean (SD)		66.3 (12.0)	64.1 (12.6)	70.2 (10.2)
	years min; max		29; 86	36; 85	29; 86
Carer age groups, n (%)	< 60 years		23 (28)	18 (34)	5 (17)

	60 - 69 years	21 (25)	12 (23)	9 (30)
	70 - 79 years	33 (40)	21 (40)	12 (40)
	> 80 years	6 (7)	2 (4)	4 (13)
Carer gender, n (%)	female	66 (68)	-	-
Carer education, n (%)	9 years	37 (38)	23 (37)	14 (45)
	10 years	24 (25)	18 (29)	6 (19)
	12-13 years	33 (34)	22 (35)	11 (35)
Carer marital status, n (%)	married	80 (85)	54 (86)	26 (84)
	single	7 (7)	5 (8)	2 (6)
	divorced/separated	7 (7)	4 (6)	3 (10)
Carer relationship to patient, n (%)	partner	72 (75)	48 (75)	24 (77)
	children/other	23 (25)	16 (25)	7 (23)
Care activities, n (%)	<10 h per week	53 (61)	30 (53)	23 (77)
	>=10 and <20 h per week	7 (8)	7 (12)	0
	>=20 and <50 h per week	19 (22)	14 (25)	5 (17)
	>=50 h per week	8 (9)	6 (11)	2 (7)

Missings: carer age n=14 carer education n=3; carer marital status n=3; carer residence n=2; carer relationship n=2; care activities n=10; *GOLD Spirometric Classification for Airflow Limitation based on Post-Bronchodilator FEV1 † New York Heart Association (NYHA) functional classification

Discussion

BreathEase is a pragmatic fast track observer-blinded RCT and embedded mixed methods study, assessing the effectiveness of the MBS for patients with advanced disease.

Two pioneer breathlessness services in the UK have been tested in three effectiveness trials indicating benefits, albeit by a small margin (11-13). This may result from methodological difficulties of pragmatic trials. Studies in such settings are very valuable for their high external validity and applicability to routine practice; however, they need increased sample sizes to deliver robust estimates (34). Despite realistic sample size calculations, challenges of recruitment are often underestimated, and trials do not achieve the target sample size (31). BreathEase has managed to attain the predetermined sample size, with prolonged recruitment. To date, it represents the largest study evaluating a breathlessness service.

Sample characteristics compared with other studies

The BreathEase sample is broadly representative of the target population of patients with a high symptom burden despite optimal treatment of the underlying (progressive, life-limiting) disease. Our sample is more heterogeneous than other trials in terms of underlying diseases. Our sample has more patients with COPD (68%) than the study of Higginson et al (52%), but less than that of Farquhar et al (85%) (12, 13). No other studies included patients with CHF or pulmonary hypertension, but there was a greater proportion of cancer and ILD patients in the study by Higginson et al (cancer 21 %, compared with 7% in our sample; ILD 18% compared with 9% in our sample) (13). One of the trials exclusively enrolled patients with cancer (Farquhar et al 2014) (11). Men and women are represented in almost equal numbers in the BreathEase sample, which is noteworthy, as the prevalence and incidence of illnesses such as COPD is higher in men (35). Women's perception of symptom burden

may be higher (36) and there may be gender-related differences in that women find it easier to seek help (37).

Underlying diseases and baseline values of symptom- and illness-related burden are important sample characteristics, just like age and gender, which may affect the outcome of the intervention. They should be controlled for when effectiveness is compared across studies, ideally using pooled individual data for meta-analysis (38).

Impact of recruitment and enrolment strategies

Differences in sample characteristics are related to recruitment and enrolment strategies. In the BreathEase study, media appearance was employed throughout the study to reach the target sample size and to compensate for low referral rates from clinicians. There might have been disinterest or fears that patients using this novel service might choose to switch to other specialists or come back with new expectations, for example regarding referrals to physiotherapy. Benefits of adapting the recruitment strategy to local circumstances and the importance to have support from clinicians have been described (39, 40). Our results underline the importance of local self-help groups and illness-specific networks as facilitator to recruitment.

All study participants, including those referred from clinicians, contacted the study centre on their own initiative, and most had learned about the study via the media. In the study by Higginson et al, clinicians identified potentially eligible study participants based on information in clinical records, who were then contacted by mail through the study team (13). Ethical and data protection considerations did not allow for such an approach in our study. The self-referral-based recruitment routes in BreathEase may have allowed for a greater focus on individual concerns related to the symptom of breathlessness and more heterogeneity in disease severity.

As part of the prolonged recruitment, all late responders were followed up using automated prompts in the trial electronic web-based application. Time for screening was longest in those who declined participation. This may have reduced potential bias in view of the effectiveness of the intervention. Holle et al (41) demonstrated an example of recruitment to a population representative survey in which late responders were less healthy and showed less favourable health behaviour.

Exclusion criteria also covered logistical reasons, such as long distances to the hospital or a lack of assistance with transport to attend at least one personal appointment at the hospital. In the study by Higginson et al, transport was offered to the hospital appointment (13). In those who declined participation, accessibility issues may also have played a role. Women were less likely to participate. This may be related to the lower likelihood to have a carer or to be living with partner/others. Although strategies to minimize patient and carer burden have been suggested for effective recruitment in palliative care trials (40, 42), providing transport to the MBS would have reduced the transferability of results, as this would not be offered in routine care. Data collection was organized

as home visits, so that the additional burden through study participation was time, but not related to mobility.

Appraisal of study design and outcome measurement

Pragmatic trials need high-quality outcome measures validated in this patient group (34). Overall, the outcome measures used in our study follow the research recommendation to use a core set of validated patient and carer measures (43). BreathEase is the first trial that uses the IPOS as a primary outcome measure in addition to disease-related instruments. Relating to the logic model of the intervention (Figure 1), validated and standardized outcome instruments to measure behavioural and affective psychological constructs such as self-efficacy, coping mechanisms or emotional regulation would be needed. They were not included in the BreathEase trial because they are unavailable or difficult to use in view of the patient group with advanced illness and breathlessness as a symptom. Integrating qualitative and quantitative components into the BreathEase study will allow for a better understanding and interpretation of the results of the main effectiveness study from the patients' perspective with the interaction between individual attitudes, behaviours and experiences with the multiple component service and its setting (44, 45).

Forthcoming papers will analyse whether and how attendance at the MBS was effective regarding increased mastery of breathlessness in longitudinal perspective (quantitative analysis) and the interaction between individual attitudes and behaviours and experiences with the multiple component service, its setting and context (qualitative and mixed methods analyses). Analyses will further consider intervention fidelity, economic evaluation, patient satisfaction and the impact of adverse events on the effectiveness of the intervention.

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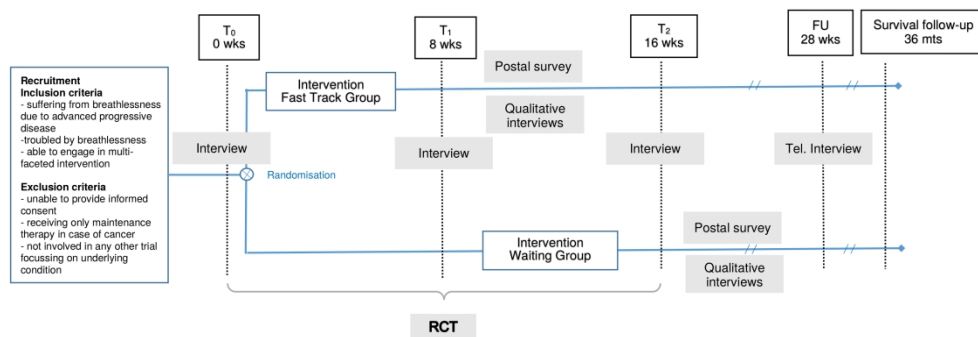
Figure 1: BreathEase study design

Population/patients: Patients suffering from breathlessness due to any advanced life-limiting and progressive disease while receiving best practice medical treatment of the underlying condition, and their informal carers

Intervention theory:
Breathlessness affects patients' breathing, thinking & functioning
Intervention goals: Supporting self-management and patients' adaptive work through cognitive and behavioural reactions to breathlessness, holistic needs assessment and health care service planning

Intervention design:
Components/measures:
Breathing: breathing techniques, body positioning, handheld fan, airways clearance techniques, rituals, medications
Thinking: relaxation techniques, mindfulness
Functioning: physical activity, walking aids, pacing

Process:
Assess and listen to patients (and informal carers), introduce measures, provide accessible information, establish shared meaning and goals, manage diagnostic and therapeutic options, support self-management

Intervention delivery:
Delivery: Face-to-face, telephone
Provider characteristics: Palliative care physician, specialist physio-therapist, respiratory medicine physician
optional: psychologist, social worker, other professionals
Setting: Outpatient clinic, community-based health care professionals
Execution: 6-8 weeks, timing variable; at any time during disease trajectory

Outcomes:
Breathlessness mastery
Breathlessness burden and distress
Coping with breathlessness crisis

Long-term outcomes:
Depression and anxiety
Quality of life
Functional status
Emotional well-being

Undesired outcomes:
Emergency situations
Over-utilisation of services
High treatment burden

Non-health outcomes:
Cost-effectiveness

Influencing factors
Health service availability, quality, accessibility
Health care provider culture & values
Financial, social resources
Self-help networks/community support
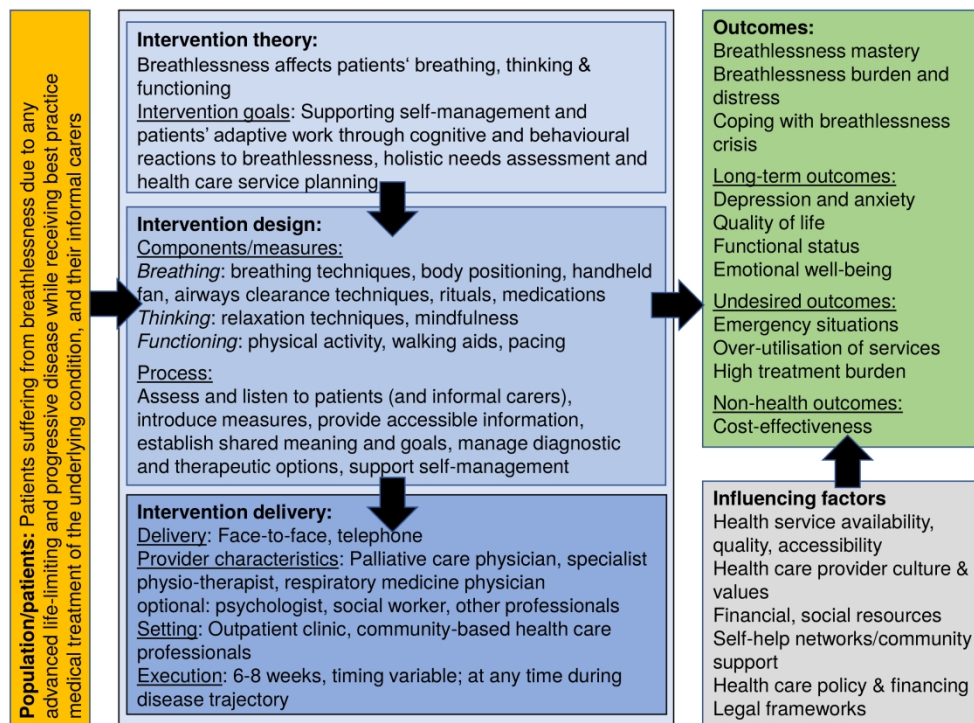Health care policy & financing
Legal frameworks
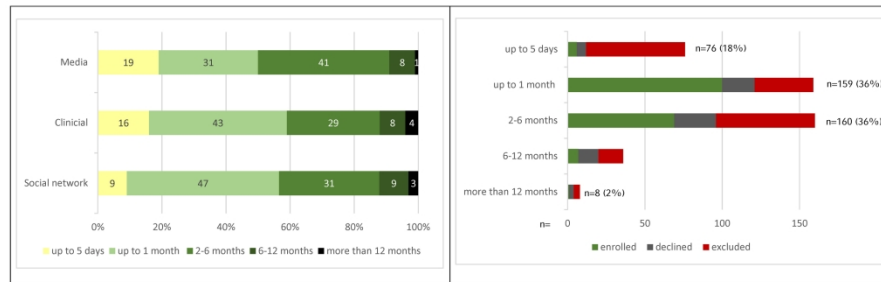
Figure 2: Logic Model of MBS Intervention

Figure 3: Screen times by recruitment route and recruitment outcome

Figure 3: Screen times by recruitment route and recruitment outcome