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A Mixed-Methods, Randomized, Controlled Feasibility Trial to Inform the Design of a Phase III Trial to Test the Effect of the Handheld Fan on Physical Activity and Carer Anxiety in Patients With Refractory Breathlessness

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Abstract

Context. The handheld fan is an inexpensive and safe way to provide facial airflow, which may reduce the sensation of chronic refractory breathlessness, a frequently encountered symptom.

Objectives. To test the feasibility of developing an adequately powered, multicenter, multinational randomized controlled trial (RCT) comparing the efficacy of a handheld fan and exercise advice with advice alone in increasing activity in people with chronic refractory breathlessness from a variety of medical conditions, measuring: recruitment rates; data quality; and potential primary outcome measures.

Methods. This was a phase II, multisite, international, parallel, non-blinded, mixed-methods RCT. Participants were centrally randomized to fan or control. All received breathlessness self-management/exercise advice, and were followed-up weekly for four weeks. Participants/carers were invited to participate in a semi-structured interview at the study's conclusion.

Results. Ninety-seven people were screened, 49 randomized (mean age 68 years; 49% men) and 43 completed the study. Site recruitment varied from 0.25 to 3.3/month and screening:randomization from 1.1:1 to 8.5:1. There were few missing data except for the Chronic Obstructive Pulmonary Disease Self-Efficacy Scale (two-thirds of data missing). No harms were observed. Three interview themes included 1) a fan is a helpful self-management strategy; 2) a fan aids recovery; and 3) a symptom control trial was welcome.

Conclusion. A definitive, multisite trial to study the use of the handheld fan as part of self-management of chronic refractory breathlessness is feasible. Participants found the fan useful. However, the value of information for changing practice or policy is unlikely to justify

the expense of such a trial, given perceived benefits, the minimal costs and an absence of harms demonstrated in this study.

Trial Registration: **A**ustralian and New Zealand Clinical Trials Registry (ACTRN12614000525684).

Key Words: breathlessness, fan, non-pharmacological, RCT, palliative care, semi-structured interviews

Running Title: Fan, Activity & Breathlessness: The FAB Study

Accepted for publication: December 1, 2015.

AU: PLS MENTION THE NAME OF THE STUDY SOMEWHERE IN THE MAIN TEXT

Introduction

Breathlessness is a devastating symptom prevalent in many progressive chronic illnesses. It affects most people with lung cancer (1), chronic obstructive pulmonary disease (COPD) (2) and heart failure (3). It is a frightening and disabling symptom for both patient and carer, and is associated with poorer survival (4), unscheduled hospital attendance (5) and admission (6,7). Despite advances in managing breathlessness (8, 9), many patients experience chronic refractory breathlessness, often worsening as death approaches (10). The multi-faceted nature of breathlessness means any incremental improvements in its management are likely to benefit patients' well-being and their physical function, while helping to minimize carers' distress (11).

Such patients often experience breathlessness precipitated or exacerbated by exertion or anxiety. A smaller subgroup may experience episodic, unheralded breathlessness for which no precipitating cause can be identified (12,13). Non-pharmacological and pharmacological interventions are the mainstay of breathlessness management (14). Self-efficacy assists patients manage difficult symptoms more effectively, improving quality of life (15). Pharmacological treatments for breathlessness, such as regular, low dose, sustained-release morphine, provide some relief (16-18) but may have adverse effects and may not be suitable or acceptable for some people. Exercise may reduce the impact of breathlessness in some people through increasing self-efficacy and fitness (19, 20). Despite benefits associated with exercise, exercise-induced breathlessness often limits physical activity because it is unpleasant or because patients believe it may be harmful (19), further reducing their capacity to cope with being breathless. Supporting continued physical activity is a key strategy for minimizing chronic refractory breathlessness.

There is emerging evidence that facial airflow can reduce the sensation of breathlessness (21). In studies evaluating a U.K. Breathlessness Intervention Service (BIS) (22-24), patients and

carers consistently cited the fan as an important intervention. A randomized controlled crossover study of “fan to face” versus “fan to leg” in patients with breathlessness at rest due to any etiology demonstrated relief (25). Another phase II, parallel group trial of “fan to face” versus acupressure wristband in people with advanced cancer/COPD demonstrated that 50% were still using the fan at two months compared with only 20% using the wristband (26). A recent randomized controlled trial (RCT) of medical air versus oxygen showed equal benefit from both (27), with the authors concluding that the effective agent may have been the simple passage of air.

This phase II study explored the feasibility of conducting an adequately powered, multicenter, multinational RCT comparing the efficacy of a handheld fan and exercise advice with exercise advice alone in increasing activity levels in people with optimally treated etiologies of breathlessness from any cause to evaluate: 1) Is *recruitment* possible in terms of number and rate? 2) What are the *data quality* and *utility* of the proposed outcome measures? 3) What is the best *primary outcome measure* for any subsequent phase III study? and 4) Is there any signal of a *dose response*?

Methods

Study Design

This was a phase II, multisite, international, parallel arm, non-blinded, feasibility RCT with a qualitative substudy. Participants were allocated to an intervention or control arm according to a block randomization schedule generated by a central registry using a 1:1:2 ratio: low flow rate (Fan A); high flow rate (Fan B); No Fan. Each site had access to sequentially numbered, opaque, sealed envelopes with the allocation concealed from the investigating team.

All groups received standardized advice regarding breathlessness self-management exercises. Participants were followed-up weekly for four weeks.

Participants and their carers' were invited to participate in a semi-structured interview as they finished the study, purposively sampled to include all groups, and by etiology of breathlessness. A topic guide, developed from the literature and expertise of the research team, was used to: a) explore the experience of using the fan (or not) and its impact on activities, well-being and self-efficacy; and b) understand the experience of study participation. Interviews were conducted at the participants' homes, or clinical setting of choice.

Participants and Setting

Eligible participants provided written informed consent and were community-dwelling adults with refractory breathlessness caused by a variety of medical conditions and scoring 3 or higher on the modified Medical Research Council (mMRC) dyspnea scale (28). Those who had used a handheld fan within the previous week, had a documented cognitive impairment or were too unwell were excluded. All participants were informed that the trial intervention was the fan, and if allocated to the control arm, a fan would be provided at study completion. Participants were identified from cardio-respiratory, oncology and palliative care outpatient clinics and day hospices at two U.K. services and two Australian sites.

Interventions

In addition to verbal advice, participants received an information leaflet, which contained some breathing control exercises, positions for recovery from breathlessness, advice about the importance of exercise, some simple exercises to try and, for those randomized to the fan, instructions on its use. With permission, the leaflets were adapted from the Cambridge Breathlessness Intervention Service (BIS) (29).

Study Outcomes

Outcomes included:

1. Recruitment rate, screening/randomization ratio, attrition rate;
2. Proportion/pattern of missing data in the proposed phase III outcome measures:
    a. *Activity*: 1) ActivPAL™ monitor of average step count (30), 2) six-minute walk test (6MWT) (31), 3) Lifespace Mobility Assessment (32), 4) Australia-modified Karnofsky Performance Status (AKPS) (33);
    b. *Self-efficacy*: 1) General Self-Efficacy Scale (GSES) (34) (patient and carer), and 2) COPD Self-Efficacy Scale (35);
    c. *Breathlessness assessment*: 1) intensity and unpleasantness using 0-10 numerical rating scale (NRS) (36, 37); and 2) fan use questionnaire;
    d. *Health service use*
3. Carer burden (Zarit-6) (38). Variance of candidate primary outcome measures; qualitative interview responses;
4. Any evidence of a dose / response relationship.

All study measures were assessed at baseline (Day -8 to 0) and at four weeks (Day 28).

Sample Size

It was considered that at least 30 participants should be sufficient to address the stated feasibility questions, and inform the sample size for a phase III trial given that fully powered studies on clinical interventions in breathlessness only have a total recruitment of between 100 and 300 to have clinically meaningful results (39).

Statistical Analysis

The quantitative data were analyzed using STATA v. 13.0 statistical software (StataCorp LP, College Station, TX). The primary focus of the analyses was on data collected on Day 28 after randomization. As a feasibility study, data were analyzed descriptively. For the potential phase III outcomes, the intervention group was classified as "fan" and "no fan" irrespective of flow rate, and independent sample *t*-tests or Chi-squared tests were applied. Comparisons between groups on the changes between baseline and Day28 of main study outcomes also were conducted using a non-parametric approach (Mann-Whitney *U* test) given that results were not normally distributed and not independent. A type I error rate of 5% was adopted for all hypothesis testing. As a pilot study, no data were imputed. The quantitative data are reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

The qualitative data were analyzed using a thematic framework (40) and reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) guidelines (41) ensuring attention to: clarification and justification; procedural rigor; representativeness; interpretive rigor; reflexivity and evaluation rigor; and transferability. Codes generated from the data allowed emerging themes to be identified. Typical quotes were selected and their context preserved.

Ethics

Human Research Ethics approvals and institutional permissions were obtained. The trial was registered before the first person was enrolled. (Australian and New Zealand Clinical Trials Registry (ACTRN12614000525684).

Results

This study recruited between February 2013 and April 2014.

Recruitment Feasibility

Of 97 screened participants, 49 were randomized and 43 completed the trial (Fig. 1) Recruitment per site varied from 0.25/month to 3.3/month and the screening to randomization from 1.1:1 to 8.5:1. Only six participants withdrew, all because of deterioration in health and all of whom were in the control arm.

Only 10 caregivers were recruited, and only seven completed the study. In view of this small number, the data from the GSES and Zarit-6 are not presented here, although they are available on request.

Participant Characteristics

Baseline demographic and clinical characteristics were well-balanced between the treatment and control groups (Table 1). The average age of participants was 68 years, with equal numbers of men (49%) and women (51%) recruited. Approximately two-thirds had an AKPS score of 70 or above indicating an ability for self-care but not work. The mean AKPS for participants who withdrew was 64.3 (SD $\pm$ 9.8). On average, participants had a moderate intensity of breathlessness that restricted walking on level ground to 100 yards.

Volume and Patterns of Missing Data

Missing data for each potential phase III outcome variable are summarized. Data were missing as follows: two data points (5%) on the average steps per day (one in each arm); two data points (5%) on the GSES (all in the control arm); and five data points (12%) on the 6MWT (four in the treatment and one in the control arms). However, there was a significant amount of missing data in the COPD Self-Efficacy Scale, with 16 (67%) and 13 (68%) data points missing for the treatment and control arms, respectively. Study nurses reported that participants found completing the COPD Self-Efficacy Scale to be repetitive and less relevant than the GSES.

Outcomes

Table 2 shows the potential Phase III outcome variable measures for both groups at week four, and the comparisons of the differences (week 4 minus baseline) for the outcomes between the treatment and control groups. The sample size did not allow exploration of a fan / dose response. None of the outcome variables yielded a significant difference between groups. No harms or unintended effects were observed in either the intervention or control groups.

Outcomes also were informed by the semi-structured interviews, summarized in the following section.

Semi-Structured Interviews

A purposive sample of 12 trial participants took part in the semi-structured interview. While all trial participants were invited to have a consenting family carer join the interview, only one patient-dyad interview was undertaken. . Interview recruitment occurred until no new qualitative information was generated. Seven interview participants were from the fan arm and five from the control.

Three main themes were expressed: two regarding the fan: the fan as a helpful self-management strategy, and the fan helps reduce recovery time; and one regarding the trial as a positive experience (Table 3).

1. The Fan as a Helpful Self-Management Strategy. There was a strong perception that integrating the fan into daily activities had helped self-management and control of breathlessness, with improved confidence about exertion. The fan could be tailored to particular situations. Some participants found the fan helpful to use before, during and as part of their recovery from exertion. Others used the fan in place of “as needed” beta-agonist metered dose inhalers (MDIs).

Participants used the fan in a variety of ways (a routine prophylactic intervention, for acute exacerbations of breathlessness), and incorporated it with the exercise advice and other management strategies as part of a complex intervention. The common theme was one of reclaiming control, with accompanying improvement in quality of life.

2. The Fan Helps Reduce Recovery Time. Several participants noted that one of the best aspects of using the fan was that it helped reduce their breathlessness recovery time after exertion.

3. The Trial: A Positive Experience. Overall, participants had a very positive experience in the trial, both enjoying the experience for themselves, but also the hope that it may help others. Participants also welcomed a study investigating breathlessness as a "symptom" rather than as a "disease" as most participants experienced focusing on managing the underlying disease, and viewing persistent breathlessness as being the inevitable result of smoking.

Managing Participant Expectations and Apprehensions. The participants appreciated the detailed study explanation and clear study information sheets. While some participants were apprehensive about the physical activity component of the study, they felt reassured by the research nurse.

Getting the Equipment Right. The participants' reports of managing the fan and activity monitor were mixed. While some appreciated wearing the activity monitor (ActivPAL™), and had no problems using it, others experienced some challenges, and some had trouble with malfunctioning fans.

Study Assessments. In general, participants found the study assessments acceptable, although many felt the COPD Self-Efficacy Scale was repetitive or irrelevant.

Discussion

It is feasible to conduct a multisite trial to test the effectiveness of the handheld fan in this patient population in terms of recruitment, completion and acceptability of study measures. Despite the challenges of conducting a multisite feasibility study, this is an important step. The team has gained invaluable insights into the elements that need to be refined if such a study were to go forward.

There was a good screen to randomization ratio in all sites except one where a combination of diverse factors impacted on recruitment rates; these factors included a proportion of eligible participants having unstable social circumstances, the structure of the ambulatory care respiratory clinics, and a large heart-lung transplant unit that was recruiting similar patients to competing studies. The best recruitment rate was seen in a tertiary academic respiratory unit where a register of patients willing to be directly contacted about potential studies was used as an initial eligibility screen. These patients had chronic nonmalignant lung disease and, despite having significant breathlessness, were relatively clinically stable. Two sites recruiting primarily through palliative care services also achieved good screen-randomization ratios, demonstrating recruitment feasibility in this population. However, attrition because of disease deterioration was higher from these sites.

Participants found that most study measures were acceptable with the exception of the COPD Self-Efficacy Scale (35). Much has been written about the difficulties of recruiting to palliative care trials, and we confirmed the effects of good research-clinical team relationships, effective ways of accessing eligible patients, and outcome measure burden/relevance (42-44). In particular, this study showed that although an outcome measure might appear ideal and well-validated in relevant patient populations, it may not perform well in a different context. It was

particularly important to test the acceptability of an activity monitor before setting out on a definitive trial, and the study also has allowed simplification of measures of activity. We note that all withdrawals occurred in the control arm, and it is possible that this attrition may have been partly a result of participants' desire to try the intervention or, alternatively, as this study could not be blinded, there may have been too little potential perceived gain for participants in the comparator arm to continue with the study.

Implications for the Design of a Definitive Trial

Value of Information from a Definitive Trial. The reason we conduct pilot studies is to evaluate whether or not a subsequent phase III trial should be conducted (45). The need to generate a quality evidence base for new interventions is unquestionable. The value proposition, however, of turning this pilot study of the fan as a single intervention into an adequately powered phase III study needs to be seriously questioned for the following key reasons:

1. The intervention has no documented harms, is inexpensive even in resource-challenged settings, is simple to use, is widely available, does not require a prescription by a health professional, could never be registered as a medical device, and the qualitative data were clear that participants found the fan helpful.

2. Further, the qualitative data showed that participants incorporated the fan into their daily lives in a complex manner. This is consistent with the recently published clinical trials (which were not published when this trial was planned) (11, 24), whereby the fan forms a component of a complex intervention for breathlessness management.

Therefore, research funding investment would be better made in understanding the pathophysiological mechanisms involved in perceived relief from the fan. Future clinical work could build on the recently published work demonstrating the effectiveness of such a complex

intervention on mastery over (11) or distress resulting from (24) breathlessness. A "how to use" guide could be created for improved self-efficacy, with freely available, web-based instructions for use as part of a complex intervention and to enable incorporation into routine clinical management plans. In view of this key consideration, we did not perform sample size estimations on the data from this pilot.

Design. In view of the potential for excess attrition in the control arm, a definitive design would allow all participants to receive the complex intervention at some point. Designs such as a stepped-wedge trial or wait-list design, would allow this, and it is interesting to note that both Farquhar and colleagues and Higginson and colleagues used a wait-list design (11, 24).

Primary Outcome. Taking into account data completion and qualitative data, the primary outcome for further work would focus on the symptom of breathlessness, such as "mastery over" or "distress as a result of" or "worst breathlessness unpleasantness." This captures the sense that the most important aspect, valued by participants, was the perception that they were able to manage the breathlessness better, thus restricting its power to restrict and frighten. None of the outcomes measured in this study showed statistically significant change, but it was not designed to discard the null hypothesis.

Secondary Outcomes. We would retain the GSES but omit the COPD Self-Efficacy Scale. We would retain an activity monitor as a measure of *actual* daily step activity but omit the 6MWT, which necessitated a clinic visit. In light of the clearly expressed view from participants that the fan reduced recovery time from exertion-induced breathlessness, a measure of recovery time from breathlessness induced by simple exercises used in the home or clinic setting will be added. Previous feasibility work has shown that people with mMRC dyspnea grade 4 breathlessness can complete seated exercise using a physiotherapy band to pre-defined levels of

intensity (46). In addition, a striking finding from the interviews was that participants perceived that they needed to use their "reliever" inhaler less often in keeping with the fan acting as a strategy to promote self-efficacy and is consistent with other studies (22). If this is confirmed in a definitive trial, this would have significant health service cost implications and possibly reduced beta-agonist related toxicities. Therefore, we would add a measure of compliance for this medication.

Study Settings. Although the recruitment rate and retention was best in the respiratory unit, a mix of respiratory units and palliative care teams would be used, as recruitment also was feasible from palliative care units and provides greater generalizability for study results.

Generalizability. Bearing in mind the feasibility aims of this trial, our findings are applicable for study designs in a variety of settings and conditions causing refractory breathlessness.

Limitations

It was recognized that reporting bias may be introduced by the therapist and outcome measurement researcher being the same person and thus rendering any form of blinding impossible. However, as this was a feasibility study and the outcome was to measure the variability around response, any bias would be consistent for all arms of the study and, therefore, it was considered difficult to justify single blinding. Other non-pharmacological intervention trials for refractory breathlessness have attempted to maintain assessor blinding, but found half of the participants broke the blinding through disclosure (24).

Strengths of the Study

The addition of qualitative interviews with a subgroup is a strength of this study, identifying that the fan gave overall benefit in managing breathlessness as part of a general

strategy. The interviews also highlighted aspects of relief that had not been included in the protocol (recovery from exertion-induced breathlessness). The overall positive reports are consistent with a previous qualitative evaluation of breathlessness management programs where the fan has been described as beneficial (22).

Conclusions

This study confirms the feasibility of a definitive multisite trial to study the use of the handheld fan as part of self-management of chronic refractory breathlessness. It also shows the importance of conducting preliminary work to address protocol uncertainties. However, the value of information for changing practice or policy is likely to justify the expense of such a trial.

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The authors extend their gratitude to the study participants who gave their time and energy to this study.

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Table 1. Comparison of Patient Characteristics at Baseline Between Treatment and Control Groups

Patient Characteristics	Treatment (*n*=24)	Control (*n*=25)
Age	68.5 (11.6)	67.7 (8.7)
Male sex	12 (50%)	14 (56%)
Primary disease		
COPD	12 (50%)	11 (46%)
Cancer and heart diseases	6 (254%)	7 (29%)
Others	6 (25%)	6 (25%)
MRC Dyspnea Score **AU: SHOULD THIS BE mMRC?**	3.2 (0.4)	3.4 (0.5)
Numerical Rating Scale		
Breathlessness average	5.7 (1.5)	6.0 (1.6)
Breathlessness worst	7.0 (1.7)	7.6 (1.8)
Unpleasant average	5.9 (1.9)	6.3 (2.7)
Unpleasant worst	6.9 (1.9)	7.1 (2.6)
Average steps per day	3838.3 (2171.1)	3601.0 (2023.2)
activPAL™ (steps)	26064.1 (16941.2)	24448.5 (14119.2)
6-minute walk test	229.6 (100.0)	215.4 (84.1)
Life Space total score	49.2 (22.0)	51.1 (26.5)
General Self-Efficacy Score	30.2 (5.8)	32.0 (4.4)
COPD Self-Efficacy Score	75.9 (19.6)	64.8 (28.9)

Median AKPS (IQR)	70 (7.5)	70 (10)

COPD =chronic obstructive pulmonary disease; MRC = Medical Research Council; AKPS = Australia-modified Karnofsky Performance Status; IQR = interquartile range.

Table 2. Measures for Major Outcomes at Week 4 and Comparisons for the Differences (Week 4 minus Baseline) Between Treatment and Control Groups

Study Outcomes	Treatment (*n*=24)	Control (*n*=19)	Treatment (*n*=24)	Control (*n*=19)	Results of Comparison (Week 4 minus Baseline)[a]
NRS Breathlessness					
average	6.0 (2.0)	5.0 (4.0)	0.0 (3.0)	0.0 (3.0)	*P*=0.853
worst	7.0 (3.0)	7.0 (3.0)	0.0 (4.0)	-1.0 (3.0)	*P*=0.215
average	5.5 (2.5)	6.0 (5.0)	0.0 (3.0)	-1.0 (5.0)	*P*=0.426
worst	7.5 (4.5)	48.0 (6.0)	1.0 (4.0)	-1.0 (6.0)	*P*=0.246
Average steps per day	2840 (3751)	4152 (2909)	-167.3 (1078.0)	220.0 (674.0)	*P*=0.093
activPAL™					
i) steps;	i) 20063 (27877)	i) 29064 (20366)	i) -1170.0 (7606.0);	i) 1538.0 (5030.0):	*P*=0.139
ii) % change)			ii) -9.6 (12.4)	ii) 1.5 (29.3)	*P*=0.236
6-Minute Walk	234.0 (162.5)	247.5 (110.0)	13.0 (65.0)	3.3 (73.6)	*P*=0.707
Life Space total score	47.8 (28.3)	51.7 (42.0)	0.0 (22.3)	0.7 (31.1)	*P*=0.679
General Self Efficacy Score	29.0 (7.5)	31.5 (8.0)	0.0 (4.5)	0.0 (5.0)	*P*=0.777
AKPS	70.0 (20.0)	70.0 (10.0)	0.0 (10.0)	0 (7.5)	*P*=0.816

AKPS = Australia-modified Karnofsky Performance Scale; NRS = numerical rating scale.

[a]*P*-value of Mann-Whitney *U* test for comparing the median values of the differences between treatment and control.

Table 3. Illustrative Quotes

The fan as a helpful self-management strategy

- …Oh it does (help), yeah, yeah. I don't, I don't know where I'd have been without that, without them fan, the fans, yeah (Participant 36: 77 years, male with heart failure).
- The first thing when I wake in the morning, I use the fan even though I'm not breathless, so I use that as part of my routine…I use it routinely … and then once I get upstairs, I'll sit in my seat at the kitchen table and use the fan again. And within a minute I've always settled (Participant 40: 73 years male with severe COPD).
- I might use Ventolin [beta agonist metered dose inhaler (MDI) for relief] as well, but I always reach for the fan first… I'm using both… but I would say more the fan … (Participant 49: 77 years female with COPD).
- Well I used to use Ventolin up to 30 times a day and I don't use it at all now…(Participant 40: 73 year old male with severe COPD).
- The best things were that it worked, it had a positive effect on my condition. .. now I've resumed cooking… and other things, I don't do a lot of – I can't do gardening or anything like that – but I'm more useful than I have been, and I have got no worst effects of the fan, there's only positive about the fan (Participant 40: 73 years, male with severe COPD).

Table 3 continued

The fan helps reduce their recovery time

- Well apart from knowing that after using it for about ten minutes, I know I can put it down, get up and get on with what I was doing (Participant 36: 77 years, male with Heart Failure);
- I certainly have been using it (Fan) when I get breathless, and I have a much quicker recovery than I used to…(Participant 49: 77 years, female with COPD).
- If I am somewhere where I haven't got the fan and I've got breathless then it might be ten/fifteen minutes before I've actually recovered, whereas with the fan it's usually within five minutes recovery. (Participant 27: 55 years, male with Heart Failure).

Table 3 continued.

The trial: a positive experience

- Well to this date I don't really know what COPD means. I know it's a problem but what's important to me is the fact that I now become breathless, and this study that I've been doing on breathlessness it's been great (Participant 2: 68 years, male with COPD).

- A: Yeah, I was a little bit worried about walking for six minutes…

  Q: Yeah, yeah. And when it came to it, did you feel safe, did you, you, the way it was done…?

  A: Yes, yes. Plus I found <research nurse> very good. (Participant 36, 77 years, male with heart failure)

- A: The newer doctors seem to be…well they look at my record and say "Ah I see you've been on prednisolone, try that again..." OK – thank you very much. And I've given more blood over the years than a blood donor.

  Q: So is your experience very much that when you go, it's about the disease, the condition rather than the breathing and how you cope with that breathing?

  A: Yes. Yes. Yes.

  Q: That brings us nicely on to the study, because one of things we're trying to do is tackle the breathing itself irrespective of what's causing it.

  A: Yes- that's why I was keen to do it (Participant 25; 68 years, make with COPD and wife)

Figure 1. CONSORT 2010 Flow Diagram