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Impact of fan therapy during exercise on breathlessness and recovery time in patients with chronic obstructive pulmonary disease: a pilot randomised controlled crossover trial

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Key words: fan therapy, exercise, chronic obstructive pulmonary disease

Conflict of interests:

Alex Long none to declare

Dr Reilly, none to declare

Dr Cartwright: none to declare

Abstract:

Background: Patients with Chronic Obstructive Pulmonary Disease (COPD) reduce physical activity to avoid the onset of breathlessness. Fan therapy (FT) can reduce breathlessness at rest, but the efficacy of FT during exercise remains unknown in this population.

Aim: To investigate **1)** the effect of FT on exercise-induced breathlessness and post-exercise recovery time in patients with COPD, **2)** the acceptability of FT during exercise **3)** to assess the reproducibility of any observed improvements in outcome measures.

Methods: A pilot single-centre randomised controlled crossover, open (non-masked) trial (NCT031375424) of FT vs no FT during 6-minute walk test (6MWT) in patients with COPD and a Modified Medical Research Council (mMRC) dyspnoea score ≥ 2. Breathlessness intensity was quantified pre and on termination of the 6MWT, using the numerical rating scale (NRS) (0-10). Post-exertional recovery time was measured; defined as the time taken to return to baseline NRS breathlessness score. Oxygen saturation and heart rate were measure pre and post the 6MWT.

Results: Fourteen patients with COPD completed the trial per protocol (4 = male, 10 = female; median age (interquartile range) = 66.50 (60.75 -73.5) years); mMRC dyspoena 3 (2-3)). Fan therapy resulted in lower exercise-induced breathlessness (Δ NRS; Δ mBORG) [within-individual differences in medians (WIDiM) = -1.00, IQR = -2.00 to -0.50, p<0.01; WIDiM = -0.25, IQR = -2.00 to 0.00, p = 0.02], greater distance walked (metres) during the 6MWT [WIDiM = 21.25, IQR = 12.75 to 31.88, p <0.01], and improved post-exertional breathlessness (NRS) recovery time [WIDiM = -10.00, IQR = -78.75 to 50.00, p <0.01]. Fan therapy was deemed to be acceptable by 92% of participants.

Conclusion: Fan therapy was acceptable and provided symptomatic relief to patients with COPD during exercise. These data will inform larger pilot studies and efficacy studies of FT during exercise.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined as 'a common and treatable disease characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gas.' [1]. COPD is progressive, associated with frequent exacerbation of symptoms including increased breathlessness, leading to increased disability and reduced Quality of Life (QofL) [1].

COPD is the fourth leading cause of death worldwide [2]. Over a million individuals in the United Kingdom (UK) have COPD, with 25,000 deaths each year [3]. COPD mortality in the UK is third in Europe [4].

The burden of chronic breathlessness is significant for patients with COPD, negatively impacting upon health-related quality of life and physical function, as patients frequently avoid activities that evoke breathlessness. This fear avoidance results disuse atrophy, which perpetuates a cycle of increasing breathlessness and disability [5, 6].

Exercise interventions such as pulmonary rehabilitation (PR) for patients with COPD, improve breathlessness, physical function, reduce exacerbation frequency and hospital admission [7]. However, PR is a brief intervention and maintaining these benefits requires patients to continue to exercise independently. Breathlessness is the main limiting factor to exercise in COPD [8], therefore any interventions to help patients to self-manage their exercise-induced breathlessness are sought.

Evidence suggests that cool facial airflow from either medical air (room air delivered under pressure via a concentrator or canister) or a fan can reduce breathlessness at rest [9,10]. The burden of chronic breathlessness is significant for patients with COPD, and their families within the UK [11,12]. Holistic Breathlessness Support Services have been shown to improve breathlessness mastery and reduce distress due to

breathlessness, where fan therapy (FT) is an integral part of these self-management interventions[13,14]. Moreover, qualitative data from patients with chronic breathlessness describe improvements in their ability to control their breathlessness at rest (self-mastery) with the use of FT [13]. The efficacy and acceptability of FT during exercise remains unknown in patients with COPD.

The aim of this study was to investigate **1)** the effect of FT on exercise-induced breathlessness and post-exercise recovery time in patients with COPD, **2)** the acceptability of FT during exercise **3)** to assess the reproducibility of any observed improvements in outcome measures.

We hypothesised that FT would reduce exercise-induced breathlessness and improve post-exercise recovery time in patients with COPD. (Null hypothesis: there would be no difference in exercise – induced breathlessness, physiological variables e.g., heart rate, oxygen saturation or recovery time between those patients using and not using FT during a six-minute walk test)

Methods

Design: A pilot single-centre randomised controlled crossover, open (non-masked) trial (NCT031375424) of FT vs no FT during 6-minute walk test (6MWT) in patients with COPD and mMRC dyspnoea score ≥ 2. There was a 30-minute washout period between 6MWT's (figure 1)

Participants

Inclusion criteria: adults with a diagnosis of COPD by a Respiratory Physician (characterised by FEV_1: FVC ratio ≤70%), with exertional breathlessness (mMRC dyspnoea score ≥ 2) and a stable smoking status were eligible.

Exclusion criteria: significant cardiovascular or peripheral disease that could influence exercise tolerance, recent change in medication or exacerbation of COPD symptoms requiring admission during the preceding 4 weeks, unable to hold a handheld fan. Unable to speak English, or not capable of providing informed consent.

Recruitment

Patients were recruited from specialist COPD out-patient clinics and Pulmonary Rehabilitation at King's College Hospital NHS Foundation Trust (KCH) (Denmark Hill site). Participants fulfilling eligibility criteria were recruited by convenience sampling. Potential participants were identified by members of the clinical teams, who gained consent for their contact details to be passed on to the researcher. Thereafter, participants were sent via the post an invitation to participate and an information letter by the researcher, given at least 1 week to read thoroughly, then re-contacted by the researcher to discuss any concerns. Interest in the study led to an assessment date being organised, at which consent forms were signed.

Randomisation and masking

Block randomisation was implemented using an online tool [15] to allocate participants to their initial experimental conditions (i.e. walking with a hand-held fan vs. walking without a fan) and ensure the conditions were numerically balanced. Simple 4 block randomisation was applied. On completion of the initial walking test and outcome assessments, participants were given 30 minutes to recover physiologically and then they repeated the walking test in the alternative experimental condition. Due to the nature of the intervention (FT), it was not possible to blind the researcher or patients to the allocations.

Sample size

No formal sample size calculation was performed, due to the lack of data regarding the potential impact FT may have on exercise-induced breathlessness in COPD. Therefore, this pilot study aimed to recruit 14-16 participants. The pilot data will inform subsequent efficacy studies of FT during exercise.

Ethical approval

Ethical and local research and development approval (KCH17-062) was obtained prior to commencing this research (LREC protocol number: REC 17/NE/0063). The study was registered on www.clinicaltrials.gov (NCT03137524). All participants provided written informed consent.

Intervention – fan therapy (FT)

The handheld fans used were commercially available battery operated, with 3 soft propeller blades and an on/off switched usable by participants (Marks and Spencer's Pocket-Sized Travel Fan, style number T40/8591T, cost per fan = £6.00). Patients were provided with standardised instruction as how to use the handheld fan; to hold the fan to their face throughout both the walking test, and during the recovery period until they reported breathlessness returned to baseline.

Primary Outcome Measure

Breathlessness change: the magnitude of exercise-induced breathlessness during a 6MWT; defined as the change (Δ) in breathlessness scores from rest (immediately pre-exercise) to immediately post-exercise, quantified using the numerical rating scale (NRS). The NRS breathlessness is a validated, self-reported, unidimensional scale to rate chronic breathlessness intensity. It is simple to use across a variety of everyday activities, and adjustable to specific time points [16]. NRS anchors were; 0 = "not breathless at all", 10 = "worst possible breathlessness".

Secondary outcome measures:

Breathlessness intensity: self-reported level or intensity of breathlessness as indicated on the NRS

Perceived breathing difficulty / effort: perceived breathing difficulty / effort was quantified using the modified Borg breathlessness (mBORG) scale at rest and at end exercise. The mBORG is quantifies perceived breathing difficulty / effort on a 0 - 10 scale, with descriptors e.g. 0 = nothing at all, 5 = severe, 10 =maximal. It was developed for use during exertion [17]. It has a minimal clinically important difference (MICD) of one point, with larger changes more likely at the higher end of the scale due to larger numerical intervals between descriptive markers [18]. Reliability and validity of mBORG breathlessness measurement during 6MWT is accepted (ICC from 0.59 to 0.92 and mean difference of <1 point) [19].

Distance walked (meters) during the 6MWT: The 6MWT is a self-paced walking test. It measures walking capacity by measuring total distance covered around a flat 30 metre course covered in 6 minutes. Standardized instructions are given throughout the test. It is a robust test of functional exercise capacity [19].

Post-exertional recovery time (seconds): post-exertional recovery time was measured; defined as the time taken to return to baseline NRS breathlessness score, oxygen saturation ($Sp0_2$) and heart rate (HR). Participants were asked to report when their NRS breathlessness score had returned to base levels. $Sp0_2$ and HR were measured using a pulse oximetry (Onyx ®9500 Fingertip Pulse OximeterTM, Nonin Medical Inc, Plymouth, MN, USA). Sp02 and HR was measured at rest, during and post the 6MWT.

Acceptability of using the handheld fan: acceptability was assessed via a Likert Scale Questionnaire (range 1-5) based on the Theoretical Framework of Acceptability (TFA) [20]. Participants were asked to respond to specific questions reflecting the overall acceptability of FT and five sub-constructs from the TFA (affective attitude, burden, perceived effectiveness, intervention coherence, and self-efficacy).

Experimental protocol

The study was conducted at the Clinical Research Facility at King's College Hospital NHS Foundation Trust. Baseline demographic data included; age, sex, spirometry, smoking history, body mass index (BMI), mMRC dyspnea score, chronic obstructive disease assessment test (CAT).

Participants performed 3 six-minute walk tests; one practice to account for potential learning effect, following by 2 as per protocol (figure1). The 6MWT was performed in accordance with technical procedures described by the American Thoracic Society (ATS) [21]. Participants were given a 30-minute period between the practice 6MWT and commencing the RCT experimental protocol figure 1. Outcome measures recorded pre-and post-all 6MWTs included; NRS breathlessness, mBORG, Heart Rate (HR), Pulse Oxygen Saturations (SpO2). The distance walked and number of rest period / stops the patient required was recorded for all 6MWT's completed. Recovery time (RT) for NRS and HR to return to baseline post 6MWT was timed (in seconds) immediately from the end of the 6MWT. Recovery was recorded in standardised seated position. The self-reported acceptability questionnaire was completed at the end the RCT (figure 1).

Reproducibility: to assess the reproducibility / consistency of any observed improvements in outcome measures, patients were invited to complete the above described experimental protocol again, a week later (Trial 2). To reduce the chance that any imbalances between allocation sequence groups (AB vs BA) following the initial randomisation in Trial 1 being carried forward to Trial 2, participants were re-randomised to allocation sequences for Trial 2.

Data analysis and reporting

Inferential statistical analysis of outcomes was completed, with a significance level of $p<0.05$ using the Statistical Package IMB SPSS v26 (Armonk, NY: IBM Corp). Normality of the data was determined by skewness and Shapiro-Wilk test. The data was non-normally distributed, hence central tendencies are described using medians and inter-quartile ranges (IQRs) calculated in Microsoft Excel (version 2106). Within-individual differences in the medians (WIDiM) and IQRs (Fan vs No Fan) were calculated by, first, subtracting a participant's score in the No Fan condition from their score in the Fan condition, and then calculating the median (IQR) of these within-individual differences. WIDiMs retain the repeated nature of the crossover design at the level of the individual and are used to assess treatment effects [22], in our case using non-parametric tests (Wilcoxon Matched-Pairs Signed-Rank Tests, with 2-sided Exact Significance). In tables 2 and 3 we also report group level medians. For example, for participants allocated to the sequence Fan-then-No-Fan (n=7), we report the group level medians for each outcome in the Fan condition and in the No Fan condition. These group level medians do not retain the repeated nature of the crossover design at the level of the individual, so they cannot legitimately be used to estimate treatment effects, however they are helpful in understanding the likelihood of carryover effects and period (order) effects, as well as the amount of missing data [22]. WIDiMs and group level medians are not directly related as they are generated from independent calculations.

Results:

Recruitment and engagement: Recruitment took place over 10 weeks (May to July 2017). Twenty-six patients were screened, three (12%) were ineligible. Of the 23

eligible patients; 8 (35%) declined to participate and 14 (61%) agreed to participate and were randomised. Fourteen participants (100%) completed the trial per protocol (see table 1). Thirteen out of the fourteen patients (92%) completed the reproducibility study. One patient declined due to unforeseeable personal circumstances.

Patient characteristics:

Fourteen patients with COPD completed the trial per protocol (4 = male, 10 = female; median age (interquartile range) = 66.50 (60.75 -773.50) years); mMRC dyspoena 3 (2-3), summarised in Table 1.

Outcomes: Prior to exercise there were no differences between the experimental conditions for resting NRS Breathlessness, mBORG, heart rate or SpO2. Following exercise, change scores for the primary outcome (Δ NRS) showed that low-level physical activity under the Fan condition resulted in lower exercise induced breathlessness i.e., smaller increases in breathlessness compared to the No Fan condition [within-individual differences in the medians = -1.00, IQR = -2.00 to -0.50, p<0.01]. For the secondary outcomes, the Fan condition resulted in a smaller increases in perceived breathing difficulty / effort (Δ mBorg) [WIDiM = -0.25, IQR = -2.00 to 0.00, p = 0.02], greater distance walked (metres) during the 6MWT [WIDiM = 21.25, IQR = 12.75 to 31.88, p <0.01], and a shorter post-exertional breathlessness recovery time (seconds) (NRS) [WIDiM = -10.00, IQR = -78.75 to 50.00, p <0.01] (Table 2). However, there were no overall treatment effects for heart rate, saturated oxygen or the number of stops taken during the 6MWT.

The reproducibility RCT (Trial 2), demonstrated consistent findings of benefits for the Fan condition: smaller increases in breathlessness (Δ NRS) [WIDiM = -1.00, IQR -1.00 to 0.00, , p <0.01], smaller increases in perceived breathing difficulty / effort (Δ mBorg) [WIDiM = -1.00, IQR = -2.00 to 0.00, p <0.01], greater distance walked (metres) during the 6MWT [WIDiM = 28.00, IQR = 17.50 to 45.00, p<0.01] and a shorter post-exertional breathlessness recovery time (seconds) (NRS) [WIDiM = -65.00, IQR = -

130.00 to -20.00, p <0.01] (Table 3). Again, there were no overall treatment effects for heart rate, saturated oxygen or the number of stops taken during the 6MWT.

FT was acceptable to 92% of participants (Table 4), median (IQR) acceptability score of 4 (4-5) out of 5. Fifty-three percent reported no additional burden of FT during the 6MWT. Patients reported they liked the handheld fan (median 4, 3-5), it was of minimal burden (median 1, 1-3). Patients were confident to use the handheld fan (median 5, 4-5) and understood how it was supposed to help them (median 4, 3-5).
In keeping with the observed improvements in breathlessness scores and exercise performance, patients perceived the handheld fan to be effective during exercise (median 4 ,3-4) and to help to resolve breathlessness post exertion (median 4,3-4). Moreover, these patients who had not used a fan before reported that they would use a handheld fan during everyday life (median 5, 4-5), which reinforces the acceptability of this intervention. One person commented that using (holding) the fan negatively affected their walking style. Free text comments, were limited, but supported the use of the handheld fan:

"*very useful during exercising"* *(male, FEV_1 0.59 L)*,

"*I think it worked… it helped my breathing,"* (female, *FEV_1 1.4 L)*

"it acts as a distraction from my breathing which I find useful." *(female, FEV_1 1.55 L).*

Table 1: Patient characteristics of the fourteen patients that completed the randomised controlled crossover trial of FT vs no FT during 6-minute walk test (6MWT).

	Median	**Interquartile range**
Age (years)	66.50	60.75 – 73.50
BMI	25.85	20.60 – 30.25
SEX **Male: Female**	 4:10	
Smoking status **Current smoker** **Ex-smoker**	 6.00 8.00	
Smoking pack years	48.00	25.75 – 82.60
MRC Dysponea score	3.00	2.00 – 3.00
FEV_1 (L)	1.30	0.94 – 1.59
FEV_1 (%)	63.00	38.75 – 74.0
FVC (L)	2.30	1.90– 2.75
FVC (%)	82.00	71.00– 93.25
FEV_1/ VC ratio	56.75	47.43 – 63.50
CAT score	21.00	12.25 – 29.75

BMI = body mass index, MRC = medical research council, FEV_1 = forced expiratory volume in the first second, L = litres, % = percentage, VC = Vital capacity, CAT = chronic obstructive disease assessment test.

Table 2: Results observed in the primary randomised controlled crossover trial of FT vs no FT during 6-minute walk test (6MWT) in patients with chronic obstructive pulmonary disease (COPD).

	Allocation Sequence AB (Fan → No Fan)				**Allocation sequence BA (No Fan → Fan)**				**Overall treatment effect**	
	Group-level medians (+IQR)		**Within-individual difference in medians (+IQR)**		**Group-level medians (+IQR)**		**Within-individual difference in medians (+IQR)**		**Within-individual difference in medians (+IQR)**	
	Period 1 Fan (n=7)	Period 2 No fan (n=7)	WIDiM (n=7)*	Wilcoxon Signed Ranks Test†	Period 1 No fan (n=7)	Period 2 Fan (n=7)	WIDiM (n=7)*	Wilcoxon Signed Ranks Test†	WIDiM (n=14)*	Wilcoxon Signed Ranks Test†
Subjective measures of breathlessness										
NRS‡	5.00 (3.75, 6.25)	7.00 (6.25, 8.25)	-2.00 (-2.00, -1.00)	0.02	4.00 (2.50, 5.75)	3.00 (2.00, 4.75)	-0.50 (-1.25. 0.00)	0.25	-1.00 (-2.00, -0.50)	<0.01
Δ NRS§	3.00 (1.25, 4.25)	5.00 (3.00, 6.75)	-1.50 (-2.00, -1.00)	0.02	3.50 (2.25, 4.75)	3.00 (1.75, 3.25)	-0.50 (-1.25, 0.00)	0.25	-1.00 (-2.00, -0.50)	<0.01
NRS recovery time‡	110.00 (15.00,135.00)	210.00 (160.00, 295.00)	-90.00 (-205.00, -32.50)	0.03	150.00 (75.00, 195.00)	210.00 (165.00, 227.50)	60.00 (10.00, 65.00)	0.09	-10.00 (-78.75, 50.00)	<0.01
mBORG‡	3.00 (0.75, 3.50)	4.00 (4.00, 5.00)	-1.00 (-2.50, 0.25)	0.06	3.00 (2.00, 4.50)	3.00 (1.00, 3.50)	0.00 (-1.00, 0.00)	0.50	-0.25 (-2.00, 0.00)	0.02
Δ mBORG§	2.00 (0.25, 3.00)	3.50 (3.50, 4.00)	-1.00 (-2.50, -0.25)	0.06	3.00 (1.75, 3.50)	2.00 (0.75, 3.00)	0.00 (-1.00, 0.00)	0.50	-0.25 (-2.00. 0.00)	0.02
Objective measures of physiology										
HR‡	84.00 (74.00, 89.50)	82.00 (79.00, 96.00)	-4.00 (-12.00, 4.00)	0.38	96.00 (94.00, 106.50)	92.00 (85.50, 97.50)	-3.00 (-5.50, -2.00)	0.14	-3.50 (-7.50, 1.00)	0.11
Δ HR§	11.00 (5.50,14.00)	12.00 (8.50, 19.00)	-3.00 (-5.50, -1.00)	0.20	15.00 (4.00, 18.00)	2.00 (0.50, 14.00)	-3.00 (-5.50, -1.00)	0.47	-3.00 (-5.75, -0.25)	0.13
$Sp0_2$‡	96.00 (94.50, 98.50)	97.00 (96.50, 98.00)	0.00 (-1.00, 1.00)	1.00	96.00 (95.00, 96.50)	97.00 (95.00, 97.00)	0.00 (-1.00, 1.00)	0.94	0.00 (-1.00, 1.00)	0.70
Δ $Sp0_2$§	0.00 (-1.00, 1.50)	0.00 (-1.00, 1.00)	0.00 (-0.50, 1.00)	1.00	0.00 (-1.50, 0.50)	0.00 (-1.50, 1.00)	0.00 (-1.00, 1.00)	1.00	0.00 (-0.75, 1.00)	1.00
Objective measures of functional response										
6-MWT distance¶	404.00 (336.25, 465.00)	400.00 (312.50, 420.00)	25.00 (17.50, 30.00)	0.02	330.00 (223.75, 517.50)	383.00 (247.50, 561.25)	15.00 (11.00, 42.75)	0.02	21.25 (12.75, 31.88)	<0.01
6-MWT stops¶	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	0.00 (-0.50, 0.00)	1.00	0.00 (0.00, 2.00)	0.00 (0.00, 1.50)	0.00 (0.00, 0.00)	1.000	0.00 (0.00, 0.00)	0.63

NRS = numerical rating scale, mBORG = modified Borg scale for breathlessness, HR = heart rate, SpO_2 = oxygen saturation measured from a pulse oximeter, 6MWT= 6-minute walk test, **Δ =** change. *Calculated so that positive values indicate higher scores for the Fan condition and negative values indicate higher scores for the No Fan condition; †Exact Sig, 2-tailed; ‡assessed post exercise; §change from pre to post exercise; ¶assessed during the exercise period. Note: Only within-individual differences in the medians are used for estimating treatment effects; group-level medians are helpful in assessing carryover and order effects (see Methods).

Table 3: Results observed in the repeated randomised controlled crossover trial of FT vs no FT during 6-minute walk test (6MWT) in patients with chronic obstructive pulmonary disease (COPD).

	Allocation Sequence AB (Fan → No Fan)				**Allocation sequence BA (No Fan → Fan)**				**Overall treatment effect**	
	Group-level medians (+IQR)		**Within-individual difference in medians (+IQR)**		**Group-level medians (+IQR)**		**Within-individual difference in medians (+IQR)**		**Within-individual difference in medians (+IQR)**	
	Period 1 Fan (n=7)	Period 2 No fan (n=7)	WIDiM (n=7)*	Wilcoxon Signed Ranks Test†	Period 1 No fan (n=7)	Period 2 Fan (n=7)	WIDiM (n=7)*	Wilcoxon Signed Ranks Test†	WIDiM (n=14)*	Wilcoxon Signed Ranks Test†
Subjective measures of breathlessness										
NRS‡	5.00 (3.50, 5.50)	5.50 (4.25, 7.00)	-1.00 (-1.00, -0.75)	0.03	3.80 (0.75, 6.00)	1.80 (0.38, 5.00)	-0.25 (-0.88. 0.00)	0.25	-1.00 (-1.00, 0.00)	<0.01
Δ NRS§	3.50 (2.25, 3.75)	4.00 (2.75, 4.75)	-1.00 (-1.00, -0.75)	0.03	1.80 (0.75, 2.75)	1.80 (0.38, 2.00)	-0.25 (-0.88, 0.00)	0.25	-1.00 (-1.00, 0.00)	<0.01
NRS recovery time‡	120.00 (75.00, 180.00)	185.00 (152.50, 277.50)	-110.00 (-127.00, -62.50)	0.02	175.00 (43.75, 227.50)	105.00 (25.75, 185.00)	-17.00 (-102.50, -11.00)	0.06	-65.00 (-130.00, -20.00)	<0.01
mBORG‡	3.00 (2.00, 4.00)	4.00 (3.00, 4.50)	-1.00 (-2.00, -0.50)	0.06	2.50 (0.88, 5.25)	1.50 (0.25, 5.00)	-0.25 (-0.88, 0.00)	0.250	-1.00 (-2.00, 0.00)	<0.01
Δ mBORG§	3.00 (1.00, 3.00)	3.00 (2.50, 3.50)	-1.00 (-2.00, -0.50)	0.06	2.50 (0.88, 3.00)	1.50 (0.25, 2.00)	-0.25 (-0.88, 0.00)	0.25	-1.00 (-2.00, 0.00)	<0.08
Objective measures of physiology										
HR‡	89.00 (84.50, 99.50)	87.00 (85.00, 99.50)	0.00 (-4.50, 1.50)	0.69	89.50 (86.75, 91.50)	84.50 (81.75, 90.25)	-1.50 (-6.50, 2.75)	0.69	0.00 (-6.00, 2.00)	0.49
Δ HR§	10.00 (5.00, 15.00)	10.00 (10.00, 12.00)	0.00 (-6.00, 4.00)	0.88	6.00 (2.50, 12.50)	5.50 (2.75, 12.75)	1.00 (-2.00, 2.50)	0.85	1.00 (-3.00, 3.00)	0.96
$Sp0_2$‡	94.00 (92.50, 95.50)	94.00 (93.00, 97.00)	0.00 (-3.00, 0.00)	0.25	98.0 (96.50, 98.00)	96.50 (96.00, 97.75)	0.00 (-0.75, 0.00)	0.75	0.00 (-2.00, 0.00)	0.16
Δ $Sp0_2$§	0.00 (-3.50, 1.00)	-1.00 (-1.50 - 0.50)	-1.00 (-2.50, 1.50)	0.52	0.50 (-1.50, 2.50)	-0.50 (-1.00, 0.00)	-1.00 (-1.75, 0.50)	0.53	-1.00 (-2.00, 1.00)	0.29
Objective measures of functional response										
6-MWT distance¶	282.50 (233.75, 470.25)	265.00 (209.75, 430.00)	28.00 (20.00, 38.75)	0.06	432.50 (399.38, 516.25)	531.30 (421.25, 560.63)	22.50 (11.25, 71.25)	0.06	28.00 (17.50, 45.00)	<0.01
6-MWT stops¶	0.00 (0.00, 2.00)	1.00 (0.00, 1.50)	0.00 (0.00, 0.00)	1.00	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.00	0.00 (0.00, 0.00)	0.75

NRS = numerical rating scale, mBORG = modified Borg scale for breathlessness, HR = heart rate, SpO_2 = oxygen saturation measured from a pulse oximeter, 6MWT= 6-minute walk test, **Δ =** change. *Calculated so that positive values indicate higher scores for the Fan condition and negative values indicate higher scores for the No Fan condition; †Exact Sig, 2-tailed; ‡assessed post exercise; §change from pre to post exercise; ¶assessed during the exercise period. Note: Only within-individual differences in the medians are used for estimating treatment effects; group-level medians are helpful in assessing carryover and order effects (see Methods).

Table 4: Patient reported acceptability of fan therapy during exercise

Acceptability domain	Question	Median (IQR)	Range (min – max)
Overall acceptability	How acceptable was it to use the HHF during the exercise test? (1=completely unacceptable, 5= completely acceptable	4 (4-5)	3 – 5
Affective attitude	How much did you like using the HHF during the walking test? (1=strongly dislike, 5=strongly like)	4(3-5)	3 – 5
Burden	How much additional effort was required to use the HHF during the walking test? (1=no additional effort, 5= a huge additional effort)	1(1-3)	1 – 4
Self-efficacy	How confident were you about using the HHF as instructed during the walking test? (1= Very unconfident, 5 = very confident)	5(4-5)	1 - 5
Intervention coherence	Do you understand how the HHFT was supposed to work? (1= definitely do not understand, 5 completely understand)	4(3-5)	2 – 5
Perceived Effectiveness	How effective was the HHF in reducing breathlessness when walking? (1= very ineffective, 5=very effective)	4(3-4)	3 – 5
	How effective was the HHFT in helping you to recover your breathing after you finished walking? (1=very ineffective, 5=very effective)	4(3-4)	3 – 5
	Would you use a HHF to help with breathlessness in your everyday life? (1= I definitely would not use it, 5= I definitely would use it)	5(4-5)	2 – 5

Discussion

This study aimed to investigate the effect of FT on exercise-induced breathlessness and post-exercise recovery time in patients with COPD, and the acceptability of using FT during exercise in controlled circumstances. Findings across two pilot trials with the same participants suggest that using a hand-held fan during low level exercise has no impact on physiological measures (heart rate, SpO2) but reduces subjective feelings of exercise-induced breathlessness, increases walking distance and speeds post-exertional recovery time. FT was deemed to be acceptable by 92% of participants.

This is the first paper to report an improvement in recovery time post exertion due to FT in patients with COPD. The reduction in exercise-induced breathlessness was similar to Marchetti [23] who reported significance between median (range) mBORG at maximal exercise of 6.50 (0-10) with fan directed to leg versus 5.00 (0-10) with fan directed to face (p=0.03). Our data extend these findings and show that using a handheld fan during exercise was perceived to be acceptable to participants and provided symptomatic relief to patients with COPD during exercise. These data will inform larger efficacy studies of FT during exercise.

Relevance of findings

The United Kingdom's Medical Research Council (MRC) produced a series of guidelines from 2000 onwards to help researchers develop and evaluate of complex health interventions. These MRC guidelines explicitly recommend that developers assess the acceptability of prototype interventions at an early stage and throughout the development process [24-26]. There is now a growing consensus that developers need to optimise interventions to ensure acceptability to those delivering and receiving them [27]. Evidence shows that the acceptability of interventions impacts on their implementation, uptake, adherence and effectiveness [26, 28-30]. The Theoretical Framework of Acceptability (TFA) [20] identifies underlying constructs presumed to contribute to evaluations of intervention acceptability and offers suggestions on how to assess acceptability. The current study used the TFA to guide the assessment of the retrospective acceptability of FT to intervention recipients. The findings provide preliminary support for the acceptability of the FT to patients with

COPD suggesting that not only was FT was acceptability overall but that the intervention required low effort, was liked, that participants understood how the fan was supposed to help them during exertion. Participants were confident as how to use the fan as directed. Participants perceived the fan to be effective at reducing breathlessness, helping them return to normal breathing post-exertion and would be useful during everyday tasks (Table 4). This is in line with the observation by Bausewein et al,[31] that at two months post completion, 50 % of participants continued to use the fan. Findings relating to acceptability were positive for all TFA constructs assessed, suggesting there is no need adapt the intervention prior to further evaluation. However, acceptability can change with exposure to an intervention, therefore future studies should assess the acceptability of FT for people with COPD and other respiratory conditions at multiple time point during longer exposures. Studies should also use the full range of TFA constructs (we did not assessed the perceived opportunity costs or ethicality of FT) and assess acceptability of FT to intervention deliverers.

In keeping with our observations, Johnson *et al.* [32] used magnetoencephalography to scan the brains of participants (n=8) with chronic lung disease (50% diagnosed with COPD) during post-exertional recovery following exercise with or without airflow. Time (median (range)) in seconds to recovery was 270 (range 60-360) with airflow versus 330 (range 210-390) which is longer than our cohort, indicating our sample recovered quicker, although our sample did not achieve such a high breathlessness intensity. Preliminary imaging suggested that facial airflow might result in different areas of lobar activity being identified, potentially altering central processing and perception of neural respiratory drive and breathlessness. The insular cortex, anterior cingulate cortex and amydala contribute towards this [33].

Brain imaging in healthy participants suggest that affective experiences (e.g. distress, anxiety, fear) and the sensory experiences (e.g. pain, difficulty breathing) of breathlessness are processed by different neural pathways [34].

Physiological studies in healthy volunteers propose that cool air stimulates facial receptors connected to the trigeminal nerve, altering input to sensory processing areas of the brain [35], whilst oral mucosal stimulation can affect afferent information [36], thereby altering and reducing the perception and intensity of breathlessness. Morelot-Panzini [37] describes this as “fooling the brain” into the perception that the respiratory system is more efficient than it is. These physiological observations are supported by qualitative accounts of patients’ coping strategies used to manage acute breathlessness e.g. *opening windows, letting cold air into the room* [38].

Lansing, Gracely and Banzett [39] proposed a multi-dimensional model of dyspnea based on the pain literature, where unpleasant sensations of breathlessness lead to withdrawal from physical activity, whilst an emotional component then leads to lifestyle changes to avoid dyspnea . Avoiding dyspnea triggers such as physical activity, resulting in deconditioning which lowers the threshold for dyspnea and causes further decline.

Patients with COPD frequently feel helpless or not in control of their breathlessness which is distressing for both the patient and their significant others [38, 40]. This can lead to them avoiding activities that make them breathless. An intervention that could reduce the extent of exertion-induced breathlessness and improve the recovery time could be important in breaking the cycle of avoidance behaviours commonly seen in patients with COPD and potentially lead to improvements in health-related quality of life.

Significant differences in favour of FT were observed for two measures of breathlessness (NRS; mBorg) and distance on the 6-minute walk test (Tables 2 and 3). Based on the overall treatment effect, NRS scores were 1 unit lower in Fan condition (Trial 1 and Trial 2), mBorg scores were between 0.25 units (Trial 1) and 1 unit (Trial 2) lower in the Fan condition, and distance walked was between 21 (Trial 1) and 28metres (Trials 2) greater in the Fan Condition. Of these outcomes, only the NRS demonstrated consistent benefits (across both Trials) for the Fan condition that reached the respective MCID (1 unit for NRS).[41]

Benefits for the Fan condition as assessed by mBorg breathlessness and distance on the 6MWT failed to consistently meet the MCIDs of 1-unit and 30 metres [19,21,41]. Nevertheless, the findings for NRS suggest that the use of a Fan during low level physical activity may lead to clinically meaningful improvements in breathlessness and functional response. However, these improvements need to be contextualised as they were observed in a controlled situation on a flat indoor surface and were transitory. Taken at face value, the findings suggest there could be a role for Fan Therapy in helping individuals with COPD cope with physical exertion (e.g., walking upstairs) or participation in patient exercise/ rehabilitation programmes.

All outcomes were assessed over a very short period of time, and we cannot comment on the longer-term potential benefits of FT. Future studies need to validate these acute findings and look at the acceptability and feasibility of sustained use of FT and potential long-term benefits. Different roles for FT should also be explored. For example, fans can be used for temporary symptomatic relief during day-to-day activities or in a more therapeutic way as an adjunct to exercise interventions and / or breathlessness self- management interventions; both approaches may be useful. Studies should explore benefits across a wider range of patient reported outcomes such as breathlessness mastery, health related quality of life and illness perception, as these are potentially modifiable factors.

We report some positive preliminary findings, along with some null results, that suggest FT merits further investigation in larger and more methodologically rigorous studies. The current study raises important practical considerations such as how will people use handheld fans in their day-to-day life (is it just an aid while they try to improve their respiratory fitness on a treadmill, or will they find it useful while walking to the park/ shop/ friend's house etc.). There is also a question of whether people will use a fan on an ongoing basis, either as a rehabilitation aid or as a practical day-to-day aid for going to shops etc.). Does the use of a fan translate into quality of life benefits? The low cost and scalability of FT could increase the potential impact, although the real world practicalities of FT also need to be examined.

Strengths and Limitations

A strength of the study was the use of a practice walk with the 6WMT. There is known learning effect with the 6MWT, with the second test usually performing better [19]. Internal validity was enhanced by a randomised crossover study design, which is suitable in chronic disease for evaluating the temporary effect of an intervention [42]. This study achieved a 53.8% recruitment rate from screening, similar to previous breathlessness literature [43]. This suggests the generalisability of the current findings may be limited to only those people willing to engage with the intervention. Future studies could usefully embed an assessment of the reasons for refusal to participate as has been done in other challenging clinical areas e.g. Occupational Therapy intervention for individuals with Dementia [44].

We must acknowledge the potential fatigue impact of undertaking three, six-minute walk tests in a day. We ensured that there was sufficient time between walk tests and that patients remained at their symptomatic baseline prior to each test. However, we did not account for the potential effect fatigue may have on the observed outcomes, a point that warrants consideration when planning the subsequent randomised controlled trial.

Washout periods aim to reduce the potential of carry over effects of the "intervention" being studied. There is no census on the optimal duration of wash out periods. Pharmacological studies often calculate their washout period based on five or more times the half-life of the drug under investigation [45]. For non – pharmacological interventions deciding the optimal duration of the wash out period is challenging. Galbraith et al., [46] reported that a 10-minute wash out after use of HHFT at rest was insufficient. In this study, we choose a 30-minute washout period as we believe that this would provide sufficient time for patients to physiological recover from the 6MWT and for the acute potential effects of the fan therapy to have diminished. It must be acknowledged, that a longer washout period of an hour maybe more appropriate, in subsequent studies, especially if including patients advanced

disease (MRC >3). Moreover, it is important to factor in the overall time burden of the study design on participants, an important factor when estimating recruitment rates.

Commercially purchased, pocket-sized travel fans (Marks and Spencer's) were used [43], however a limitation of this, and most other FT literature is that that airflow generated by each fan used, either static or hand-held appears generally unknown. Marchetti *et al.* [23] reported peak airflow generated by their static fan was 840Ft/min. Airflow studies describe a ranging flow rates. What remains to be ascertained is whether there is a minimal or optimum flow rate that should be used in these studies to allow for greater comparison and transparency of results.

Conclusion:

Fan therapy using a low cost, readily available hand-held fan was acceptable and provided symptomatic relief to patients with COPD during a short period low-level exercise (walking). Our positive preliminary findings suggest FT merits further investigation in larger and more methodologically rigorous studies. The current study raises important practical considerations such as (how) would people use handheld fans in their day-to-day life

Author contributions: Conception and design: C.C. Reilly. Data acquisition: A. Long. Statistical analysis and interpretation: M. Cartwright. Drafting the manuscript for important intellectual content: A. Long & C.C. Reilly. Final review of manuscript: all authors.

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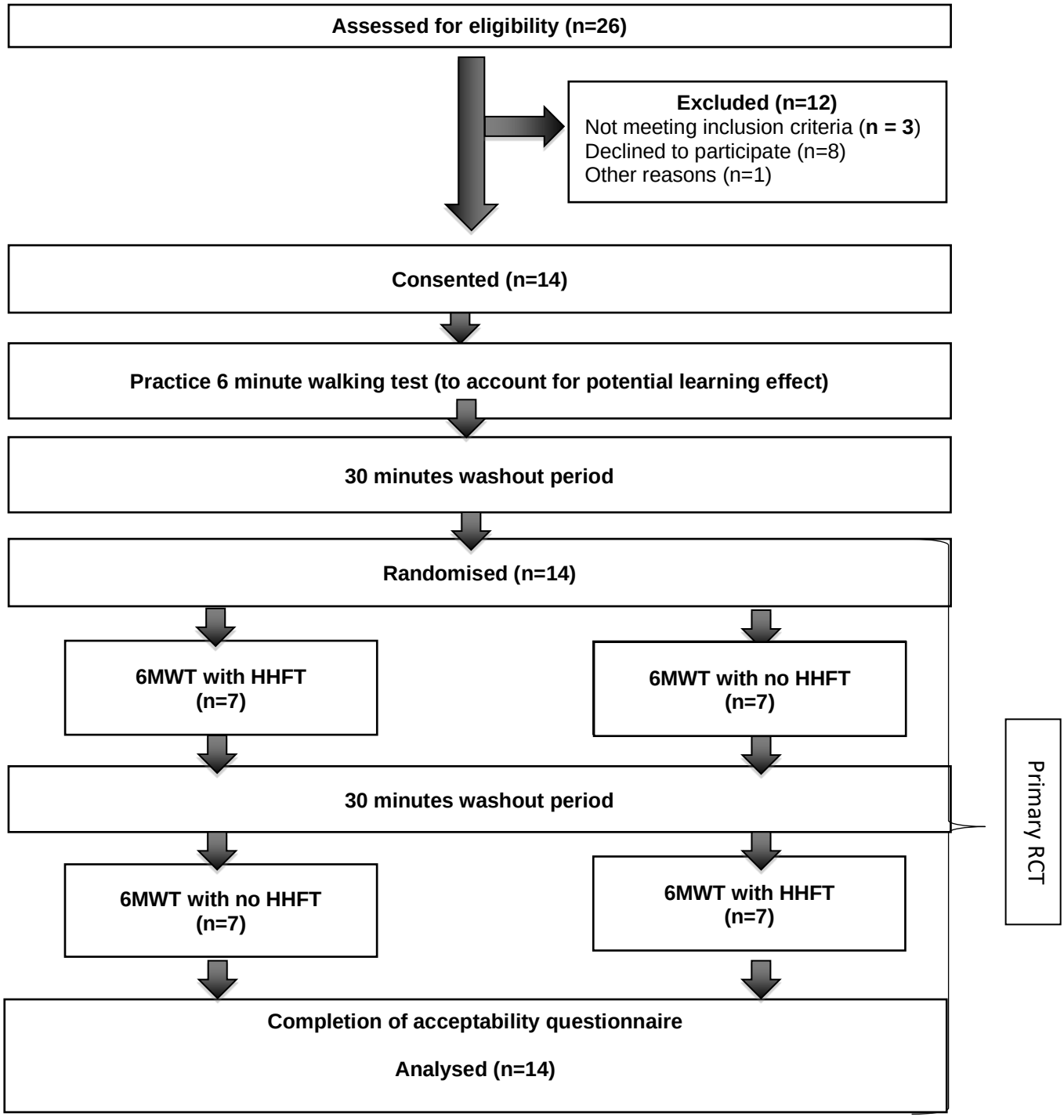
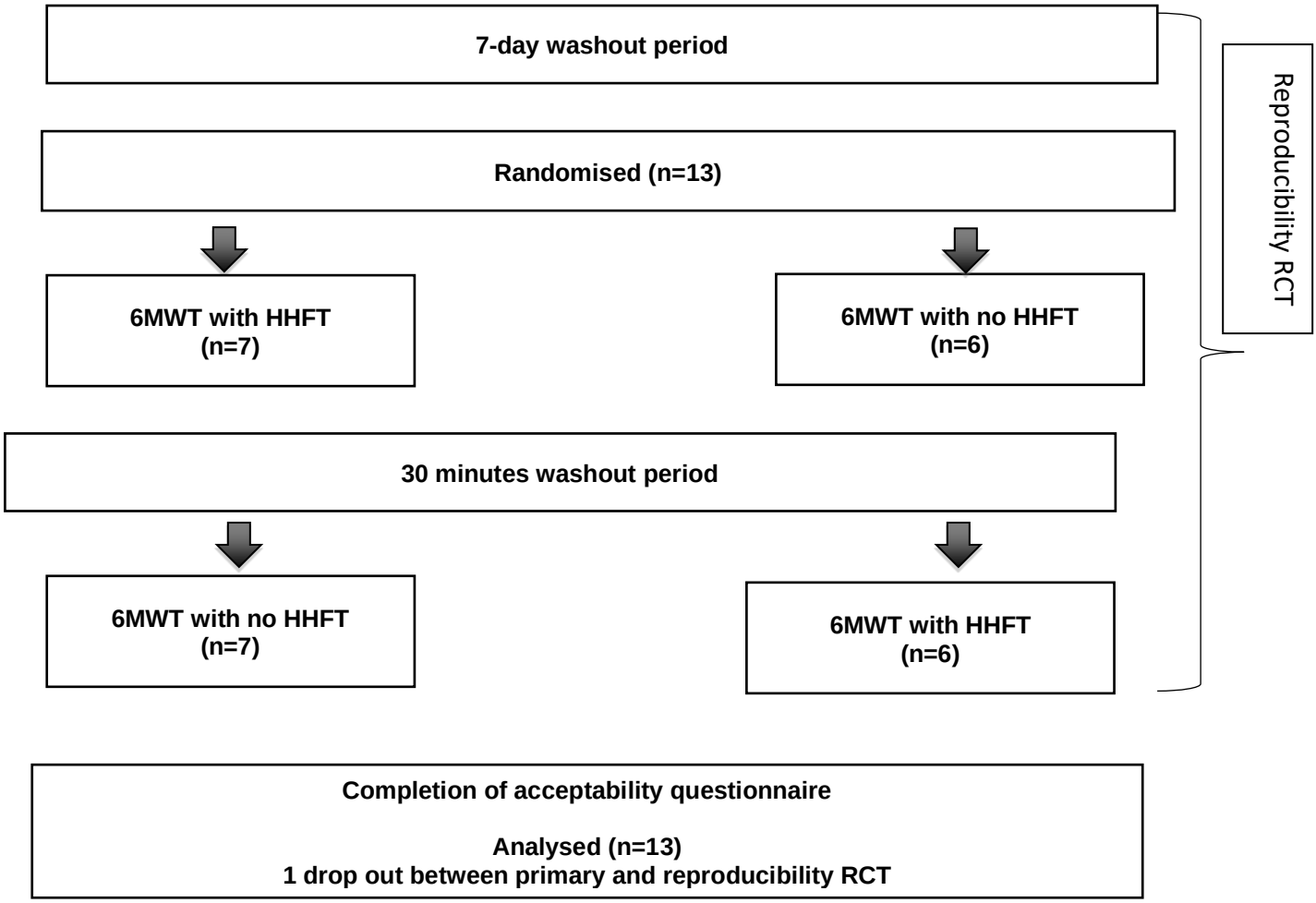
Figure 1: Study design and flow of patient through the study protocol: A pilot single-centre randomised controlled crossover, open (non-masked) trial of FT vs no FT during 6-minute walk test (6MWT) in patients with COPD and mMRC dyspnoea score ≥ 2.


Assessed for eligibility (n=26)
Excluded (n=12)
Not meeting inclusion criteria (n = 3)
Declined to participate (n=8)
Other reasons (n=1)
Consented (n=14)
Practice 6 minute walking test (to account for potential learning effect)
30 minutes washout period
Randomised (n=14)
6MWT with HHFT (n=7)
6MWT with no HHFT (n=7)
30 minutes washout period
6MWT with no HHFT (n=7)
6MWT with HHFT (n=7)
Completion of acceptability questionnaire
Analysed (n=14)
Primary RCT



Completion of acceptability questionnaire

Analysed (n=13)
1 drop out between primary and reproducibility RCT