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| **Study Title:**  **Protocol Number:**  **Date of protocol:**  **IRAS Number:**  **Study Design:**  **Sponsor:** | Fan Facial Airflow Recovery from Exercise Patient Trial (FANFARE-P) Protocol  Version 1.0  25.06.2021  300915  “N-of-1” Randomised Repeated Measures  Research and Development, University of Hull,  Cottingham Road,  HU6 7RX |
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**Lay Summary**

Many people with long-term lung and heart conditions suffer from persistent and disabling breathlessness despite taking the best medication for their disease. Non-drug treatments such as cool airflow from the handheld fan (fan) can help patients manage persistent breathlessness, including giving a faster recovery from shortness of breath after activity. Confidence in managing exertion-induced breathlessness is an important part of encouraging people to maintain, or even increase, physical activity – important in maintaining function and quality of life.

However, we do not know the most effective airflow rate for relief of breathlessness and as there are different types of fans available there is no guarantee that a person’s chosen fan will deliver the right airflow for maximal recovery from exertion-induced breathlessness. We also are aware that some patients do not use the fan, even though it helps, due to embarrassment because of its appearance.

The aim of our study is to find out the fan airflow rate which best speeds up recovery from exertion-induced breathlessness in people with chronic breathlessness, and which fan appearance and airflow speed is preferred.

We will recruit 10 participants (people living with chronic breathlessness). Participants will perform six short bouts of exercise each for a maximum of one minute (1 minute sit to stand test). Participants can stop the exercise before one minute if they need to for any reason before then. Following each exercise test participants will be asked to sit in a chair while they recover. During, the first 10 minutes of each recovery period, participants will have airflow from a fan directed towards their nose and mouth held approximately 10 to 15cm from their face for five of the tests and no fan airflow for a control test. We will use two different fan types (blades enclosed and blades open), with five airflow settings between them. The fans/airflow speeds/control will be administered in a random order for each participant.

We will measure the following for each test: i) how breathless the participant feels at baseline and at every minute during recovery for a maximum of 10 minutes, and ii) heart rate, oxygen levels at baseline and every 30 seconds during recovery for 10 minutes, and iii) a skin temperature “photo-map” of the participant’s face at baseline, at the end of the exercise test and after 3 and 5 minutes of recovery. Once all tests are complete, we will ask participants to tell us about their fan and flow-rate preferences.

We will use the results from this study to help design a fan with the best airflow speed for recovery from breathlessness after exercise, and the appearance of fan which patients would feel most comfortable using in everyday life.

**FAN Facial Airflow Recovery from Exercise: FANFARE Trial**

**Background**

People with progressive cardiorespiratory conditions frequently experience persistent disabling chronic breathlessness that seriously affects daily life despite optimum treatment of their underlying disease (1). Growing evidence supports the use of non-pharmacological interventions to reduce the impact of the symptom, improve quality of life and promote self-efficacy (2-7). One intervention that provides a valuable contribution to the self-management of chronic breathlessness is cool airflow delivered from the handheld battery-operated fan (fan) (2, 4, 8) Cooling of the facial skin and nasal mucosae innervated by the 2nd and 3rd branches of the trigeminal nerve, nasal mucosae and the upper airway flow receptors may modulate the central perception of breathlessness leading to decreased neural respiratory drive, thereby reducing the sensation of breathlessness. (9-13)

Studies have consistently reported patient benefit from fan use for the relief of chronic breathlessness. (2, 3, 5, 6, 14) and an exploratory SR and meta-analysis across three studies (n = 111) found the fan to provide clinical and statistically significant benefit for breathlessness intensity, mean difference -11.17 (95% confidence intervals (CI) -16.60 to -5.74), p = 0.06. (15) Moreover, a multi-methods secondary analyses of qualitative interview data from three RCTs found that over 80% patients experienced benefit of other kinds , even when breathlessness intensity did not improve (16), and that over half felt that the fan helped them increase their physical activity (17). An immediate physical sensation that reduces recovery time from exertional breathlessness, portability, low cost and ease of use and few if any side-effects are all important fan attributes that patients have identified as facilitating the implementation of the intervention for breathlessness self-management (2, 14) Indeed, some patients have reported that using the fan reduces their need for beta agonist metered dose inhalers (“reliever” inhalers) or oxygen and is useful to use between nebulizers. (2, 18-20) However, others report embarrassment at using something which may be seen as a “child’s toy”, and felt the fan lacked credibility as a medical device.

Clinical practice guidelines recommend the fan not only for everyday breathlessness but also for managing episodes of acute-on-chronic breathlessness (21). These episodes often lead to unplanned emergency acute care attendance and/or hospitalisation a substantial proportion of which might be preventable by better supporting patients to self-manage their breathlessness using strategies like the fan (22).

However, patients report that airflow speed may vary in the fans that are commercially available to buy and they are unable to optimise the airflow delivery to their breathlessness needs. Work by Smith *et al* that tested the physical properties of five different fans reported COPD patient preferences in terms of increased intensity and pleasantness of airflow and reduced noise. (23) This is in keeping with qualitative analysis that suggests the need to design a fan with the optimal flow rate range that can be tailored to personal preference and has the model specifications to address technical problems such as ease of battery change/rechargeable batteries, operability, robustness, safety, and noise. (8) Therefore, the aim of this study is to investigate the optimal airflow rate from the fan for relief of exertional breathlessness after an exercise test in people with chronic breathlessness. These results will be used to help design a fan with the optimal airflow speed, and ease of use, for recovery from exertion-induced breathlessness which then can be tested in a larger study.

Lastly, as there are few data regarding any learning or fatigability effects with repeated 1-STS in this population, we will also assess this as an exploratory sub-analysis.

**Aims and objectives**

**Aim.** To investigate whether cool facial airflow improves recovery from exertion-induced breathlessness in patients with chronic breathlessness due to medical conditions, and identify the optimal airflow rate.

**Objective 1 (primary)**

To determine whether five different airflow speeds (lower air speeds being delivered via a fan model with enclosed blades, higher air speeds being delivered via a fan model with external blades) vs. control (no airflow) result in differences in NRS breathlessness recovery over time.

**Objectives 2 to 3 (secondary)**

To determine whether five different airflow speeds (lower air speeds being delivered via a fan model with enclosed blades, higher air speeds being delivered via a fan model with external blades) vs. control (no airflow) result in differences in i) oxygen saturation, and ii) heart rate recovery over time.

**Objective 4**

To determine whether there is a dose-response relationship for airflow speed in terms of NRS breathlessness recovery over time.

**Objective 5**

To assess patient preferences for different airflow rates, the perceived pleasantness of airflow and for fan model appearance

**Objective 6**

To explore and describe a possible learning or fatiguability effect with repeated one-minute sit to stand tests for each participant

**Objective 7**

To determine whether five different airflow speeds (lower air speeds being delivered via a fan model with enclosed blades, higher air speeds being delivered via a fan model with external blades) vs. control (no airflow) result in differences in facial skin temperature over time that correlate with NRS breathlessness scores

**Design and methods**

**Summary design:**

This is a prospective, experimental, two-factorial, within-subjects design. Since all factors (Fan Speed and Time) are nested within participants, this is a complete cross-over design with replication on all factors. Ten participants are randomly allocated to different orders of the main experimental factors Fan Speed (Factor A) with outcomes measured at a different number of Time points per outcome (Factor B).

**Setting**

Single site; Respiratory Clinical Trials Unit, Castle Hill hospital, Hull

**Participants**

10 patients with moderate to severe chronic breathlessness attending respiratory out-patient clinics/support groups at Castle Hill Hospital, Hull

**Eligibility criteria**

**Inclusion**

* Chronic breathlessness; due to chronic non-malignant lung disease such as Chronic Obstructive Pulmonary Disease,(COPD), any Interstitial Lung Disease (ILD), or other respiratory diseases
* Modified Medical Research Council (mMRC) breathlessness 3 or 4
* Able to provide informed written – or witnessed verbal - consent, complete study exercise tests and outcome measures
* Patients may have current or prior, or no, fan use experience

**Exclusion**

* Unable to provide informed consent,
* Unable to complete study measures
* Unable to perform the sit to stands tests due to musculoskeletal problems, or currently advised by a usual care clinician to avoid such physical activity for any other reason
* Unable to tolerate fan or trigeminal nerve damage
* Patients using ambulatory oxygen for confirmed exercise-related oxygen desaturation, or long-term oxygen therapy

**Withdrawal**

Participants will be withdrawn if i) not fit to continue in the opinion of the research clinical team conducting the tests e.g. > 15 minutes to recover from any of the one-minute sit to stand tests in terms of breathlessness or other discomfort, ii) participant withdrawal of consent.

**Recruitment**

Patients will be identified and invited to participate by a member of their clinical team, such as their respiratory doctor or nurse, or the researcher if the patient is on the research database (list of patients who have given permission for direct contact by researchers) in the Respiratory Trials Unit (Castle Hill Hospital, Hull). The patient will be invited to participate in the study when they attend for a hospital visit such as an outpatient appointment, or by phone as above if on the research database. Interested patients will be given a participant information sheet and permission obtained to be contacted by a member of the research team. The researchers will contact interested participants (phone or video-call, or in person) to talk about the study, check eligibility, answer any questions and see if they want to take part.

If they agree to take part then they will arrange a date/time to attend the Respiratory Clinical Trials Unit at Castle Hill Hospital.

**Consent**

All patient participants will sign a written consent form, or have a witnessed verbal consent completed, before taking part in the study. Patient participants will have as much time as they wish to consider the study, in practice this will be more than a day. As this is a low risk trial, consent could be signed immediately prior to participation if the participant would prefer in order to save the inconvenience of repeated visits.

All participants will be assured that their participation is entirely voluntary, of confidentiality, anonymity and the right to withdraw at any stage without the need to provide a reason, and without detriment to their clinical care.

All signed consent forms will be completed by a Good Clinical Practice trained member of the research team and documented and stored in accordance with ethical requirements.

• the original copy will be given to the participant,

• one copy will be inserted into the medical file

• one copy will be filed in study file.

**Verbal witnessed consent process**

The study setting Hull is associated with a relatively high illiteracy rate therefore to prevent unnecessary study exclusion, verbal consent will be used in the event of a participant who wants to take part, but has insufficient literacy skills or any other reason making written consent not possible. Participants unable to read for any reason will have the Participant Study Information leaflet read to them and be given adequate opportunity to ask any questions. Consent will verbally be given if needed and witnessed by a non-research team person.

**Study outcomes**

Primary outcome:

* Change in exertion-induced breathlessness over time

Secondary outcomes:

* Change in HR, oxygen saturation over time
* Dose-response relationship for airflow speed in terms of NRS breathlessness recovery over time.
* Patient preferred airflow rates
* Patient preferred fan type
* Pleasant/unpleasant airflow sensation
* Facial skin temperature

**Baseline measures**

Demographic

* Age
* Sex

Clinical characteristics

* mMRC breathlessness scale; a 5-point categorical scale that is a reliable descriptive measure of functional impairment due to breathlessness (24).
* Diagnostic group e.g. Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD)
* Lung function: most recent FEV1, FVC (with date) and TLCO (if available) expressed as absolute and percent predicted values.
* Number of sit-to-stands in one minute: the first test 1-STS (23) will be used to describe the study population.

**Outcome measures**

See Schedule of assessments (Table 1)

1. Numerical Rating Scale (NRS) 0-10 breathlessness intensity, a validated and recommended measure for the assessment of chronic breathlessness (25, 26) \*
2. Oxygen saturation levels (pulse oximetry)\*\*
3. Heart Rate\*\*
4. Facial temperature measured by the thermal video camera image of cheek trigeminal nerve area of face\*\*\*
5. Patient preferences for different flow rate, NRS perceived pleasantness of airflow (0 – 10 pleasant/unpleasant) and visual appearance of the fan\*\*\*\*
6. Number of sit-to-stands in one minute for each test.

\* Baseline, maximal exertion, then every minute for 10 minutes or until recovery to baseline breathlessness (whichever is first)

\*\* Baseline, maximal exertion, then every 30 seconds for 10 minutes

\*\*\* Baseline, maximal exertion and after 3 and 5 minutes recovery

\*\*\*\* On completion of all tests

**Table 1. Schedule of assessments**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | **Time Minutes/seconds** | | | | | | | | | | | | | | | | | | | |
|  | Baseline | Maximal  Exertion | 0.30 | 1.00 | 1.30 | 2.00 | 2.30 | 3.00 | 3.30 | 4.00 | 4.30 | 5.00 | 5.30 | 6.00 | 6.30 | 7.00 | 7.30 | 8.00 | 8.30 | 9.00 | 9.30 | 10.00 |
| NRS breathlessness | **\*** | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |  | **\*** |
| Oxygen saturation | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** |
| Heart rate | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** | **\*** |
| Facial skin temperature | **\*** | **\*** |  |  |  |  |  | **\*** |  |  |  | **\*** |  |  |  |  |  |  |  |  |  |  |

**Study Procedures**

The study requires participants to attend for a single visit (about 3 hours) to the Respiratory Clinical Trials Unit, Castle Hill Hospital, Hull. At the visit, each participant will be asked to complete 6 short bouts of exertion (1 minute), each followed by a recovery period. The one-minute sit to stand (1-STS) test will be used to induce maximal exertional breathlessness; it is a reliable, valid and responsive test for measuring functional exercise capacity in patients with chronic respiratory disease and has a physiological response comparable to that of the 6MWT.(27)

**Randomisation**

Each participant will have the order of each test (which flow rate, or none) determined by a randomisation sequence generated by an online randomisation calculator (remotely by MJ). The order for all participants will be generated at the same time, and the sequences taken in order of participation.

**Study fans**

In order to provide standardised flow rates that are consistent (the rate does not fall off as battery power reduces) we will use commercially available fans, with their batteries replaced by a motor and a dial to change to set flow rates. This has been completed, tested and calibrated by the Department of Engineering, University of Hull, funded by an Impact Acceleration Fund grant).

**1-Sit To Stand test**

The participant will perform the 1- STS test using a standard chair (height 46–48 cm) with a flat seat and no armrests, stabilised against a wall. Participants will be asked to sit with their legs hip-width apart and flexed to 90°, with their hands stationary on the hips without using the hands or arms to assist movement. They will be instructed to stand completely straight and touch the chair with their bottom when sitting, but that they need not sit fully back on the chair. Participants will be asked to perform as many repetitions as they feel comfortable in 1 minute and after 45 seconds will be told “you have 15 seconds left until the test is over”. The participant will be informed that they can stop the 1 minute STS test earlier if they perceive their maximal exertional breathlessness or for any other reason.

**Recovery period**

There will be up to 20 minutes recovery between each 1- STS test. From previous research experience (12, 14, 28), we anticipate most patients will have recovered to baseline values within 5 minutes and all by 10 minutes. During the first 10 minutes the participant will direct randomly allocated different airflow rates from two types of handheld fan (blades enclosed and external) or control ( no airflow) towards the face, nose and mouth area held 10 to 15cm from the face. Flow rates will be delivered in a randomised order to each participants. The randomisation order will be generated using an online generator by MJ (geographically remote from the Respiratory Trials Unit in CHH) and provided to the research nurses.

For each test, the researcher will measure ,i) NRS breathlessness at baseline, maximal exertion, and every minute during recovery for 10 minutes or until return to baseline breathlessness level, whichever occurs first, and ii) heart rate, oxygen saturation levels at baseline, maximal exertion, and every 30 seconds during recovery for 10 minutes. A thermal camera image of the participant’s cheek trigeminal nerve area will be recorded at baseline, maximal exertion and after 3 and 5 minutes recovery. On completion of each test, NRS airflow pleasantness of sensation will be measured.

In addition, for each participant, on completion of all tests, patient preferences for high, medium or low airflow rate and the type of fan will be sought.

The participant will also assess their personal preferred flow rate on each fan by “free-hand” adjusting the dial to vary the flow rate. This will be recorded along with a NRS 0 to 10 score for perceived pleasantness of the airflow rates.

The minimum participant time required to complete six 1- STS tests with up to 20 minutes recovery between each test will be 2 hours 10 minutes. It is anticipated that the length of the visit to the Respiratory Trials Unit for each participant will therefore be about 3 hours. Participants may have comfort or rest breaks as they wish. This allows time for the participant to complete written informed consent, familiarisation with the 1- STS test, the two fan types and the NRS scoring as well as collection of baseline demographic data. The researcher will teach, explain and demonstrate:

1. the correct use of the fan in relation to the direction of airflow and distance from the face.
2. the correct performance of the 1 - STS test including reasons for stopping
3. how to score their breathlessness and airflow sensation using the NRS
4. a comfortable sitting position to be adopted during recovery from the 1-STS.

**Research Governance**

The sponsor of the study will be the University of Hull. The study will be governed by the requirements of the Research Ethics Governance. Recruitment will not start in the centre until the necessary research governance is in place (Hull York Medical School ethics approval, Health Research Authority approval, NHS REC and site Capacity and Capability approvals).

**Safety and Adverse Events**

This is a low risk study, and in previous studies of the battery-operated hand-held fans, there have been no serious adverse reactions related to the use of the fan. This is in keeping with a device that is in widespread community use, available for unmonitored purchase by the lay population including many elderly people with serious medical conditions.

The safety of the adapted commercial fans (battery replacement with a motor and a dial to change the flow rates) has been assessed and the fans PAT tested by the Department of Engineering, University of Hull. The external motor is covered to minimise potential risk. All participants will be taught correct use of the fan and closely supervised by the researcher during fan use.

The study will be conducted by trained clinicians on hospital premises with full resuscitation facilities.

Adverse events will be directly observed and documented contemporaneously. Events will be immediately assessed for seriousness, relatedness and expectedness.

Definitions

AE (Adverse event): An adverse event is any untoward medical occurrence in a subject to whom a research intervention or procedure has been administered, including occurrences which are not necessarily caused by or related to that intervention or procedure.

AR (Adverse Reaction):  An adverse reaction is any untoward and unintended response in a subject which is caused by or related to a research intervention or procedure.

Serious Adverse Event (SAE): An adverse event becomes serious if it:

- results in death

- is life-threatening

- requires hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability or incapacity

- is a congenital anomaly or birth defect

- is otherwise considered medically significant by the investigator

Reporting adverse events

The AE reporting period for this study begins at the start of test 1 and finishes following completion of all study procedures. The investigator will record all directly observed AEs and all AEs spontaneously reported by the trial subject. A pre-existing condition (i.e. a disorder present before the AE reporting period started and noted on the pre-study medical notes), is not to be reported as an AE unless the condition worsens during the AE-reporting period. Only adverse events assessed as related and unexpected (see section on SAEs below) will be recorded in patients data collection forms (CRFs). All adverse events will be recorded in patients’ medical records. All AEs will be followed-up until the event has resolved or a decision has been taken for no further follow-up.

Reporting serious adverse events

Consistent with Health Research Authority requirements for clinical trials that do NOT involved medicinal products, only reports of Serious Adverse Events (SAEs) that are, in the opinion of the chief investigator:

* **related**to the study (ie they resulted from administration of any of the research procedures) and
* **unexpected**(ie not listed in the protocol as an expected occurrence – see Table 1 below)

will be reported. SAEs will be emailed to the REC using the [Non-CTIMP safety report to REC form](https://www.hra.nhs.uk/documents/1087/safety-report-form-non-ctimp.docx) within 15 days of the chief investigator becoming aware of the event.

**Table 1.** **Expected SAEs due to causative medical condition exempt from SAE reporting**

|  |
| --- |
| * Admission to hospital or prolongation of existing hospitalisation for acute exacerbation/complication of causative medical condition or known co-morbidities (e.g. decompensation of heart failure, infective exacerbation of COPD, angina, arrhythmia) |
| * Death due to causative medical condition or known co-morbidities |
| * Life-threatening complication of causative medical condition or known co-morbidities not resulting in hospital admission |
| * Exacerbation/complication of causative medical condition or known co-morbidities resulting in persistent disability |
| * Worsening of symptoms of causative medical condition or known co-morbidities resulting in persistent disability |
| * Treatment on an emergency, outpatient basis for an event due to causative medical condition **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission. |

**Data management**

Source data will be captured in the case report form (CRF).

Paper consent forms and the study master index linking study ID number and participant names and contact details will be kept in a locked metal cabinet in a locked office in the Respiratory Trials Unit at CHH.

The electronic study file will be stored on the private channel of the Hull York Medical School Microsoft Teams folder. Anonymised data will be entered into a Microsoft excel database, that will be password protected, and stored on the private channel of the Hull York Medical School Microsoft Teams folder. Access will be restricted to authorised study personnel involved in data input and analysis only.

Confidentiality will be observed at all times and data managed compliant with GDPR.

**Data Analysis**

Since this is a randomized crossover two-factorial design with replication on all factors, repeated measures analyses of variance (rmANOVA) will be used for analysing the different hypotheses. For descriptive statistics, all continuous variables will be summarized using means, medians as measures of location and standard deviations as well interquartile ranges as measures of spread. Categorical data will be described using absolute frequencies and percentages.

We do not plan imputation methods for missing data.

Assumptions of rmANOVA will be tested before and after fitting the statistical models to the data. The normality of residuals assumption will be tested by graphing and testing the standardized Pearson residuals after fitting the model. This will be done via histograms, boxplots and the Shapiro-Wilk test for normality. The assumption of homogeneity of variance/sphericity will be tested using Mauchly’s test of sphericity and by using Barlett’s Fmax test. (29) Since there is no non-parametric alternative to the two-factorial rmANOVA in SPSS, data will be transformed to achieve a normal distribution of residuals and variance homogeneity over time if assumptions of rmANOVA are violated. Since there might be a learning/order effect present in the cross-over experiment, we consider log-transforming data to combat increasing variance over time. However, the optimum transformation factor will be explored via Box-Cox transformation and assessing lambda. (30, 31)

Results per outcome of all study participants will be graphed to assess effects visually.

Objectives 1 to 3 explore interaction effects and contrasts. One repeated measures ANOVA per outcome will be fitted. Each rmANOVA will be followed by a contrast hypothesis test. The interaction effect will be tested in addition to the main effects for airflow speed and time. The partial eta² will be interpreted according to Jacob Cohen’s guidelines ( small effect, medium effect, small effect) (32) . In addition, effects will be explored graphically by constructing interaction diagrams of means with 95% confidence intervals with Factor A fan speed and Factor B time on the x-axis, respectively. Tests will be Bonferroni-corrected as appropriate.

All analyses will be repeated for objectives 2 and 3. For objective 4, a repeated-measures ANOVA with trend analysis will be used to discern a possible dose-response relationship. Factor levels of the factor fan speed represent increasing levels of speed and thus will be explored using a test of trend. We will determine the trend in NRS breathlessness as well as heart rate and oxygen saturation across time points. Different functions for the trend (linear, quadratic or other) will be fitted via trend coefficients. The trend analysis via contrasts will be fitted following a two-way rmANOVA.

Objective 5 will be analysed using descriptive statistics and parametric or non-parametric hypothesis tests (paired t tests or Wilcoxon tests). The appropriate test will be determined based on the nature of the variable and its distribution. Differences between airflow rates and fan model will be graphically displayed via boxplots and line graphs.

Objective 6 will be determined by analysing whether NRS breathlessness and secondary outcomes show a significant interaction effect of the experimental factor order (number of experimental procedure per patient) x time point. Since not all possible sequences of fan speed/conditions are realised in the sample of n = 10 patients, the fatiguability effect will only be determined graphically by plotting means and 95% confidence intervals across sequence numbers and time points for patients.

Objective 7 will be analysed by fitting change scores of facial skin temperature as two separate covariates into the rmANOVA of objective 1.

All analyses will be done in SPSS v27 (IBM, Armonk, NY, 2020) (33). All analyses will be based on a significance level of 5% except for contrast and trend analyses which will be adjusted for type I error rate using the Bonferroni correction (34)

**Ethical considerations**

**Benefits, burdens and risks of study measures**

The symptoms of breathlessness are distressing; therefore this study has been carefully designed using measures that cause as little additional burden as possible, while still ensuring that the study outcomes can be met. The study involves one visit to hospital and there are no invasive procedures as part of the study. In an effort to minimise participant burden, the demographics and the clinical data case report form will be kept intentionally short.

At all stages of the design we have sought to minimise the participant burden by using simple outcome measures and keeping study assessments to a minimum. For example, the participant will use the simple numerical rating scores (NRS) to rate their breathlessness during recovery from the 1 minute sit to stand (1-STS) test

The 1-STS test has been selected as this is a validated and acceptable exercise test for patients with COPD and is unlikely to cause further psychological burden or distress as it allows the patient to stop at any time reducing the chance of any unnecessary physical burden. The 1-STS test will be conducted at the hospital where there is immediate access to clinical support if needed and it will be performed according to validated guidelines to ensure patient safety and minimise any risk.

The researchers are aware of the potential reasons for stopping the 1-STS test and have completed regular clinical up-dates of CPR training in the unlikely event of a problem. All measurements are chosen with both validity/reliability and ease of completion in mind.

It is not anticipated that participants will experience any physical or psychological stress from taking part in the exercise tests or completing the study measures. The participants will be informed that they can stop the 1-STS test early if they perceive their maximal exertional breathlessness or if they feel unable to continue for any other reason. The participant will be closely monitored by the researcher during the 1-STS tests for any signs of distress or physical problems. The researcher will ask the participant to stop if they believe it is not in their best interests to continue with the exercise test. e.g. > 15 minutes to recover from any of the one-minute sit to stand tests in terms of breathlessness or other discomfort

The researcher will have close contact with the clinical team, therefore in the unlikely event of any distress in the participant this can be reported to the clinical team, once confirmed by the participant, in order that clinical care of the participant can take place. There will be no deception of participants at any stage of the project. Each participant interaction will be undertaken by carefully selected and trained researchers who have undertaken Good Clinical Practice training, to ensure that they are able to detect and monitor participant distress.

**Potential conflict of interest**

The nature of clinical-participant relationships dictates that participants may feel that they are in the dependent position. The researchers will work to eliminate any concern of inappropriate influence—the presentation of the study will be as unbiased as possible, the information sheet and consent forms will be clear, and participants will be able to withdraw from the study at any time. This will be made clear before consent.

Breathlessness is a distressing symptom faced by people with life limiting illnesses, however research is essential to help clinicians improve the management of breathlessness. Therefore, although research in this area poses its own unique dilemmas, the ethics of not conducting research to design the best interventions to manage breathlessness for people with life limiting illnesses is untenable. Importantly, participants will be cared for as individuals with specific needs; the needs of research will come second.

**Consent**

Again, because we are aware of the nature of this population, the consenting process will be carefully followed and the researchers taking consent will be GCP trained. The participant information sheet will be used as a basis for the discussion. In compliance with the recommendations of the Declaration of Helsinki and the ICH-GCP guidance, each participant will be adequately informed of aims, methods, anticipated benefits, potential hazards and discomforts the study may entail. All participants will be assured that their participation is entirely voluntary, of confidentiality, anonymity and the right to withdraw at any stage without the need to provide a reason, and without detriment to their clinical care.

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