Comparison of the standard Maximal 6-Minute Walk Test against a Normal-speed 6-Minute Walk Test as an alternative and accurate assessment for ambulatory oxygen requirement

Version 2.0

February 2023

This protocol has regard for the HRA guidance

Hampshire Hospitals
NHS Foundation Trust

TITLE OF THE STUDY

Comparison of the standard 6-Minute maximal speed Walk Test against a 6-Minute normal speed Walk Test as an alternative and more accurate assessment for ambulatory oxygen requirement.

SHORT STUDY TITLE

Comparing 6-Minute Walk Tests for Ambulatory Oxygen Assessment V1

PROTOCOL VERSION NUMBER AND DATE

Version Number	Date	Summary of changes
1.0	19.08.2022	Initial full study protocol.
1.1	26.09.2022	Adjustment of titles and description of maximal 6MWT to ensure compliance with international guidelines. Addition of outline of performing 6MWT.
1.2	02.11.2022	Revisions based on provisional opinion from the REC, including clarification of data protection and academic collaborations.
2.0	01.02.2023	Amendment of 6MWT instruction to match most recent published guidance. Amendment of exclusion criteria

RESEARCH REFERENCE NUMBERS

IRAS Number: 306758

SPONSORS Number: 2022 SPON-HG-0922

FUNDERS Number: 2022 SPON-HG-0922

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Internal Conference on Harmonisation Good Clinical Practice (ICH GCP) standards, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

Siobhan Laws

Date:
02/09/2022

Name (please print):

Siobhan Laws

Position: R&D Director

Chief Investigator:

Signature:

Date:
05/09/2022

Name: (please print):

Harry Griffin

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KEY STUDY CONTACTS

Chief Investigator	**Dr Harry Griffin** Lead Respiratory Physiologist Hampshire Hospitals NHS Foundation Trust Basingstoke RG24 9NA Email: harry.griffin@hhft.nhs.uk
Principle Investigator	**Dr Michael Hughes** Trainee Clinical Scientist Hampshire Hospitals NHS Foundation Trust Basingstoke RG24 9NA Email: michael.hughes@hhft.nhs.uk
Academic Supervisor (MSc Project for Dr Michael Hughes)	Professor Dilwyn Marple-Horvat Professor of Motor Neuroscience Faculty of Science and Engineering John Dalton Building Manchester Metropolitan University M15 6BH Email: D.E.Marple-Horvat@mmu.ac.uk
Academic advisor	**Professor James Faulkner** Faculty Head of Research and Knowledge Exchange, Health and Wellbeing University of Winchester Sparkford Road, SO22 4NR Email: James.Faulkner@winchester.ac.uk
Study Co-ordinator	Victoria Corner
Sponsor	Hampshire Hospitals NHS Foundation Trust Basingstoke RG24 9NA
Funder(s)	Hampshire Hospitals NHS Foundation Trust Basingstoke RG24 9NA

STUDY SUMMARY

Study Title	Comparison of the standard Maximal 6-Minute Walk Test against a Normal-speed 6-Minute Walk Test as an alternative and accurate assessment for ambulatory oxygen requirement.
Internal ref. no. (or short title)	Maximal-speed vs Normal-speed 6MWT for ambulatory oxygen assessment.
Study Design	Randomised crossover trial of patients referred for a standard Maximal 6-Minute Walk Test (Max_6MWT) where half of patients will perform the standard Max_6MWT followed by a Normal-speed 6-Minute Walk Test (Nor_6MWT) and the other half a Nor_6MWT followed by Max_6MWT.

Study Participants	Any patient referred for a Max_6MWT with capacity to consent, >18 years of age and able to perform a Max_6MWT.
Planned Size of Sample (if applicable)	82
Follow up duration (if applicable)	N/A
Planned Study Period	18 – 24 months
Research Question/Aim(s)	Does Nor_6MWT provide a better indicator for ambulatory oxygen requirement than the standard Max_6MWT

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Hampshire Hospitals NHS Foundation Trust	Use of facilities and personnel for the study

ROLE OF STUDY SPONSOR AND FUNDER

The study sponsor and funder is Hampshire Hospitals NHS Foundation Trust (HHFT). As such, HHFT will oversee the study and its implementation and will store any patient and study information on site in either paper form (within the Respiratory Physiology Department) or electronically on internal NHS Trust systems.

PROTOCOL CONTRIBUTORS

Harry Griffin as CI for the study has conceptualised and drafted the study protocol, along with its aims and primary and secondary outcomes.

Michael Hughes as PI for the study has reviewed the study protocol and drafted the necessary documents for the study.

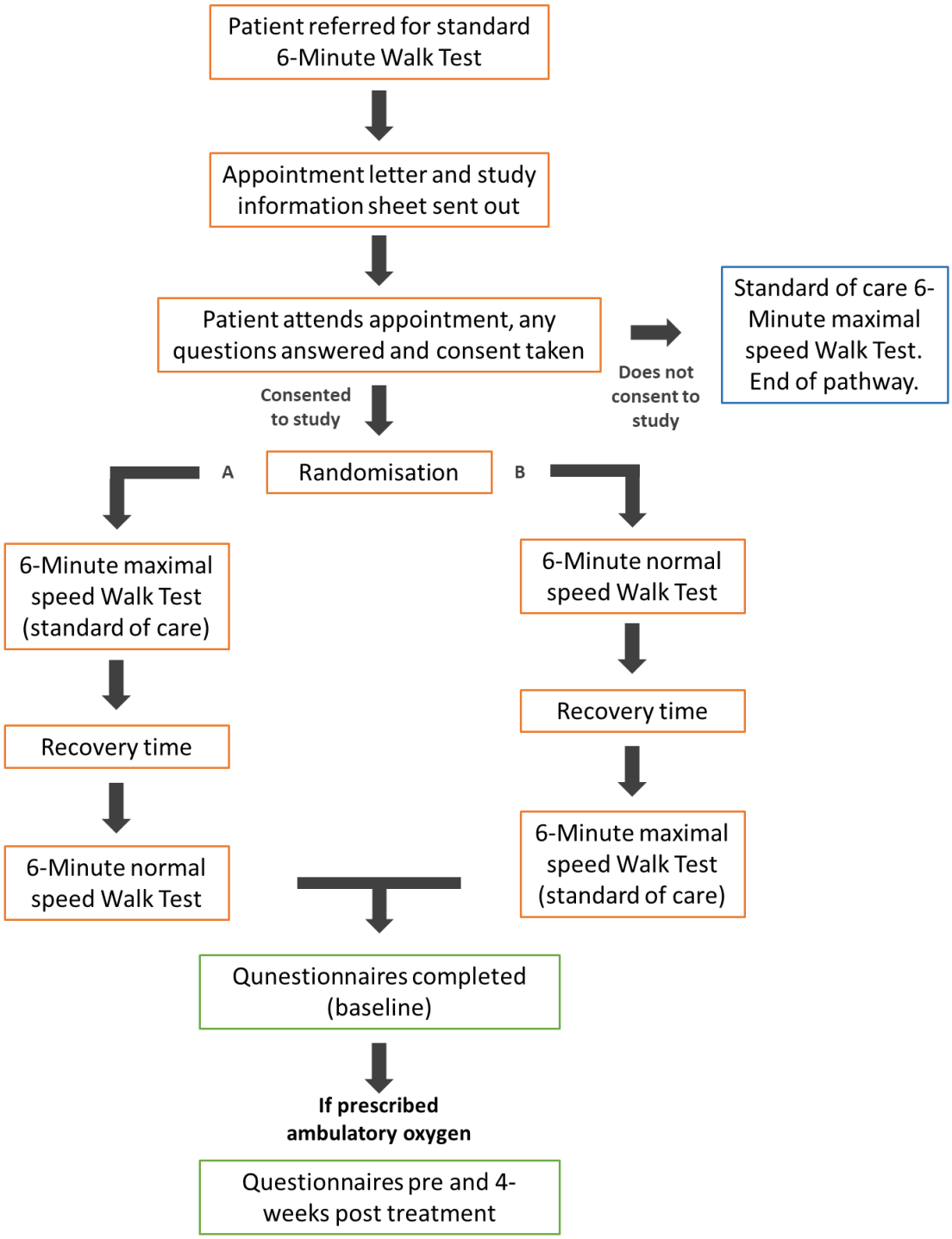
Dr Alison Grove advised on the protocol development.

Professor James Faulkner has reviewed the study protocol.

Study aims and protocol discussed with Andover Breathe Easy group at their January 2022 meeting (14:00 pm, 20/01/2022, Andover). Please see Appendix IV for key points from meeting.

KEY WORDS: 6MWT, exercise-induced hypoxaemia, ambulatory oxygen, oxygen assessment, field exercise test

STUDY FLOW CHART



STUDY PROTOCOL

Comparison of the standard 6-Minute maximal speed Walk Test against a 6-Minute normal speed Walk Test as an alternative and more accurate assessment for ambulatory oxygen requirement.

1 BACKGROUND

Patients with lung disease who report breathlessness on exertion are often referred for a Max_6MWT. During this test patients are asked to walk up and down a corridor (or other flat area) for six minutes whilst their blood oxygen levels and heart rate are non-invasively measured using a pulse oximeter (finger probe) and the distance walked is measured. In addition, a questionnaire that obtains a Borg Score measures the patients' perceived breathlessness and leg muscle fatigue both before and immediately following the test.

A Max_6MWT provides clinicians with two primary results. Firstly, they determine whether the patient's blood oxygen levels decline whilst they walk which is used to help determine whether they could benefit from ambulatory oxygen therapy. Ambulatory oxygen therapy involves walking with a cylinder of compressed oxygen or a portable oxygen concentrator which the patient breathes from via a face mask or nasal cannula. Secondly, they provide a total distance walked which provides a measurement of functional capacity and physical impairment.

The standardised approach for a Max_6MWT as recommended by international and UK respiratory bodies and used by our department is to ask the patient to walk as far as possible during the six minutes and thus essentially walk as fast as possible[1]. A Max_6MWT is therefore appropriate to assess the patient's maximal walking distance and thus functional capacity which is useful for assessing the impact of a patient's lung disease on their quality of life and is also used by surgeons and anaesthetics to assess surgical risk. However, it would seem likely that a significant number of patients will demonstrate a decline in blood oxygen levels that they may never experience in their daily life when they walk at their normal and slower pace. Subsequently they may be incorrectly prescribed ambulatory oxygen therapy or prescribed ambulatory oxygen at a flow rate exceeding what is required and possibly safe.

We are aware that many oxygen services across the UK, including some in Hampshire, will assess patients for ambulatory oxygen by having them perform their normal day-to-day activities whilst measuring their oxygen levels, rather than performing a Max_6MWT. These include activities such as walking up and down the stairs, walking around their house/garden etc. This seems a far more appropriate assessment for ambulatory oxygen, but a thorough literature review was unable to find any studies that had investigated whether a Max_6MWT caused a greater reduction in blood oxygen levels than occurs during these normal day-to-day activities. Until the current guidelines are challenged with evidence to show a Max_6MWT may not be an appropriate tool to assess patients for

ambulatory oxygen most departments will continue to follow national and international recommendations and use a Max_6MWT.

In this study, patients who are routinely referred for a Max_6MWT to investigate possible exercise-induced hypoxaemia will be invited to perform an additional walking test which is performed at their normal walking speed, referred here on in as a Nor_6MWT. This additional test will utilise the exact same medical equipment to record their blood oxygen levels as that of the Max_6MWT and be performed at the same location (i.e. flat hospital corridor). The order of performing these tests will be randomised with half performing the Max_6MWT first and the other half performing the Nor_6MWT first. Patients will be given 20 minutes to rest between each test in line with the British Thoracic Society guidelines, or a minimum of 10 minutes with a return to baseline of SpO2, HR and Borg Scores.

2 RATIONALE

- The routinely used and internationally recognised diagnostic test for assessing the requirement of ambulatory oxygen, Max_6MWT may not correspond to the degree of exercise that patients actually perform when they would use their prescribed ambulatory oxygen (i.e. normal walking speed).

- It is possible that a significant proportion of patients prescribed ambulatory oxygen cannot physiologically benefit from using it as they do not experience a decline in oxygen levels during their normal physical exercise.

- Prescribing of ambulatory oxygen to patients that cannot benefit from it carries additional burdens for the patient, and costs for the NHS, without improving the patient's quality of life.

- If this study shows that a normal walking speed test is a more appropriate assessment for ambulatory oxygen, a higher proportion of patients prescribed ambulatory oxygen will benefit from the therapy and reduce incorrect prescribing of ambulatory oxygen.

- Max_6MWT is a maximal exercise test for most patients with notable respiratory disease and is not always well tolerated (e.g. becoming very breathless). Furthermore, it carries a small but not insignificant risk of acute heart issues and falls. A 6 minute or shorter test at normal walking speed would be safer and easier for a patient to perform.

- Patients' wellbeing could be harmed by misdiagnosing exercise-induced hypoxaemia. Anecdotal evidence suggests some patients become less active after being prescribed ambulatory oxygen for a variety of reasons, including feeling self-conscious or struggling to carry the oxygen cylinder.

- Furthermore, patients may be worried about exercising without ambulatory oxygen if prescribed this therapy due to the perception of risk due to exercise-induced hypoxaemia and potentially incorrect requirement for supplemental oxygen.

- Patients who demonstrate exercise-induced hypoxaemia during a Max_6MWT are required to repeat the Max_6MWT at least once in order to identify the required flow rate of ambulatory oxygen. Titrating the flow of ambulatory oxygen is required to ensure it is sufficient to prevent the exercise-induced hypoxaemia but not too high that could induce hypoventilation and subsequent CO2 retention. It is plausible that prescribing a flow rate shown to prevent hypoxaemia during a Max_6MWT could far exceed that required to prevent

hypoxaemia during a patients' normal day to day exercise activities and lead to CO2 retention. Furthermore, prescribing at a higher than required flow rate will lead to reduced cylinder duration or reduced battery life of portable concentrators which in turn could lead to restraints in the duration patients could exercise for.

- In some cases, sub-maximal 6MWT are reported to be performed [2] without rationale or comparison with the internationally recognised guidelines for a maximal-effort 6MWT [3]. There is no published literature adapting the Max_6MWT to improve the suitability for ambulatory oxygen assessment.

3 THEORETICAL FRAMEWORK

Due to the nature of the Max_6MWT, patients are required to walk as far as they can in 6 minutes. This may lead to an inaccurate assessment of their requirement for ambulatory oxygen as this form of exercise may not correspond to their normal daily activities (such as walking to the shops, walking up the stairs, gardening). It may also not accurately measure the normal changes in oxygen saturation (or desaturation) that occurs in these patients during their normal daily activities.

These two problems could lead to the prescribing of ambulatory oxygen that does not assist patients in their normal daily activities and, therefore, is a burdensome and ineffective therapy for some individuals [4]. Several studies have also shown that ambulatory oxygen is often prescribed with no measurable benefit to patients due to a variety of factors, including potentially inaccurate indications from investigations like 6MWTs. This appears to be exaggerated in patients with milder symptoms in diseases such as COPD, and potential benefits were negated when patients had to carry their supplemental oxygen supply [4,5].

4 RESEARCH QUESTION/AIM(S)

To compare the nadir in oxygen saturation reached whilst performing a standard Max_6MWT compared with a Nor_6MWT.

To compare the average oxygen saturation and average drop in oxygen saturation from baseline to the nadir whilst performing a standard Max_6MWT compared with a Nor_6MWT.

To measure when the nadir in oxygen saturation occurs during a Nor_6MWT.

To assess in patients prescribed ambulatory oxygen, what benefit in their symptoms do they report and how does this compare to their Max_6MWT and Nor_6MWT results.

4.1 Objectives

Primary objective:

1. Average drop in SpO_2 from baseline to nadir

Secondary objectives:

1. Average SpO_2 during the 6 minutes walking
2. Nadir in oxygen saturation (SpO_2)
3. At what time does the nadir in SpO_2 occur during a Nor_6MWT

Other objectives:

1. Walking speed: Distance walked divided by 6 minutes
2. Average HR during the 6 minutes walking
3. Peak HR
5. Borg Scores
6. Results from questionnaires (for patient's prescribed ambulatory oxygen)

4.2 Outcome

A greater drop in oxygen saturation during a Max_6MWT compared with Nor_6MWT may indicate over-prescribing of ambulatory oxygen as during normal activity, patients' requirement for oxygen may be lower than indicated by a Max_6MWT. Whilst ambulatory oxygen can improve patients' quality of life, it is not without drawbacks and, therefore, prescribing only to patients that will benefit is important.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

Patients attending a routine appointment for a Max_6MWT will be identified and approached to be invited to participate in the research study.

Along with a basic clinical history, the patient's blood pressure, Borg score for dyspnoea and leg fatigue, oxygen saturation and heart rate will be recorded before the walk tests – their baseline measurement.

The order of the tests will be randomised using a random number generator on the day where odd numbers will perform a Max_6MWT followed by a Nor_6MWT and even numbers the reverse. For each test, clear instructions will be provided along with continuous monitoring of their oxygen saturation heart rate and distance walked for the 6 minutes of the test using a using a Bluetooth enabled device that transmits this data to a medically approved monitoring device with manual lap counting. Should this equipment fail, manual readings will be taken every minute during the test.

Between each test, ample time (usually 20 minutes) will be provided for a patient's degree of dyspnoea and leg fatigue, and objective measurements of heart rate and oxygen saturation to return to baseline.

From these tests it is possible to determine the distance walked, the degree of dyspnoea and leg fatigue, the time to nadir in oxygen saturation, the average drop in oxygen saturation and the average and peak heart rate. These data can be compared using paired tests to determine differences between Max_6MWT and Nor_6MWT.

Only the results of the clinical standard Max_6MWT will be relayed back to the referring member of the clinical care team – they will not see the outcome of the Nor_6MWT. A copy of the IPAQ Elderly Short questionnaire will be provided to fill out during the appointment – this forms the baseline assessment. If they decide to prescribe ambulatory oxygen, questionnaires will be provided to complete either in physical form, or over the phone with a member of the research team. These patients will be identified from the hospital digital patient record. These will include two identical copies of the IPAQ Elderly Short questionnaire – one before they begin ambulatory oxygen and one to complete after four weeks of using ambulatory oxygen – and an Ambulatory Oxygen Questionnaire four weeks after starting ambulatory oxygen. These will provide a surrogate for clinical benefit achieved by the use of ambulatory oxygen. The questionnaires will contain patient identifiable information to enable linking of the data to their test results and, therefore, will be stored securely on a NHS shared drive within HHFT. A secure nhs.net email will be used to receive the completed questionnaires if physical copies are not returned. These data, as a metric of clinical improvement, can then be compared with the outcomes of both the Max_6MWT and Nor_6MWT to determine if these tests can predict patients that will benefit from ambulatory oxygen.

The data from these tests will be stored on the clinical software used in routine testing (SentrySuite, Vyaire) and this may be exported to numerical handling software such as Excel (Microsoft) and stored internally on an NHS shared drive. Follow up will be limited to questionnaire data for those prescribed ambulatory oxygen and this will be arranged either by the physiology team or by the consultants prescribing ambulatory oxygen.

In the event a patient be randomised to the Nor_6MWT and declines to proceed to the Max_6MWT, the results from the Nor_6MWT will be passed on to the medical team and the patient will be withdrawn from the study.

5.1 6-minute walk test protocol

Steps for carrying out the walk test are outlined below:

Group 1: Maximal speed walking test (Max_6MWT) followed by normal speed walking test (Nor_6MWT).

Step 1: Wait at least 10 minutes in a seated position from any previous breathing tests. Baseline blood pressure, heart rate and oxygen saturation obtained. Borg score completed.

Step 2: Instructions provided: "

The aim of this test is to walk as far as possible for 6 minutes. You will walk along this hallway between the markers, as many times as you can in 6 minutes.

I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are. 6 minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able.

Remember that the objective is to walk as far as possible for 6 minutes, but don't run or jog. "

Step 3: Very slow walk to the start line and then perform the walk test.

Step 4: Perform post-test Borg score immediately after the test. Twenty minutes of rest, or a minimum of 10 minutes sitting rest/recovery with a return to baseline of SpO2, HR and Borg Score

Step 5: Proceed to perform Nor_6MWT as above but with the following instructions: “

The aim of this test is to walk at your normal walking speed for 6 minutes. This could be the speed that you walk a dog if you have one, or the speed you would walk around town shopping. You will walk along this hallway between the markers for 6 minutes.

I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are. 6 minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able.

Remember that the objective is to walk at your normal walking speed for 6 minutes, but don't run or jog.”

Step 6: Perform post-test Borg score immediately after the test. Allow the patient to rest for at least 10 minutes or until SpO2 and HR back to baseline.

……

Group 2: Nor_6MWT followed by Max_6MWT.

Step 1: Wait at least 10 minutes in a seated position from any previous breathing tests. Baseline blood pressure, heart rate and oxygen saturation obtained. Borg score completed.

Step 2: Instructions provided: “

The aim of this test is to walk at your normal walking speed for 6 minutes. This could be the speed that you walk a dog if you have one, or the speed you would walk around town shopping. You will walk along this hallway between the markers for 6 minutes.

I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are. 6 minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able.

Remember that the objective is to walk at your normal walking speed for 6 minutes, but don't run or jog."

Step 3: Very slow walk to the start line and then perform the walk test.

Step 4: Perform post-test Borg score immediately after the test. Twenty minutes of rest, or a minimum of 10 minutes sitting rest/recovery with a return to baseline of SpO2, HR and Borg Score

Step 5: Proceed to perform Max_6MWT with the following instructions: “

The aim of this test is to walk as far as possible for 6 minutes. You will walk along this hallway between the markers, as many times as you can in 6 minutes.

I will let you know as each minute goes past, and then at 6 minutes I will ask you to stop where you are. 6 minutes is a long time to walk, so you will be exerting yourself. You are permitted to slow down, to stop, and to rest as necessary, but please resume walking as soon as you are able.

Remember that the objective is to walk as far as possible for 6 minutes, but don't run or jog.”

Step 6: Perform post-test Borg score immediately after the test. Allow the patient to rest for at least 10 minutes or until SpO2 and HR back to baseline.

6 STUDY SETTING

This is a single centre study, taking place at two locations within HHFT: the Royal Hampshire County Hospital, Cardiac Measurement Department and at Basingstoke and North Hampshire Hospital, Cardiac Investigations. These locations are current sites for standard Max_6MWT and are suitable for carrying out the additional Nor_6MWT with access to the required space and equipment for this research.

Patients will be assessed during a routine clinic appointment and the tests performed in a corridor within the respective departments.

Each location will perform the same activity.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Patients must be attending a respiratory outpatient clinic at Hampshire Hospitals NHS Foundation Trust to be eligible for the study and meet the following criteria:

7.1.1 Inclusion criteria

1. Referred for a Max_6MWT
2. Provision of informed written consent
3. Aged 18 years or over

7.1.2 Exclusion criteria

1. Lack of capacity to provide informed consent
2. Poor peripheral perfusion that prevents an accurate measurement of SpO_2
3. Contraindicated to perform a Max_6MWT as indicated in the standard HHFT 6MWT SOP
4. Already prescribed ambulatory oxygen

7.2 Sampling

All patients referred for a diagnostic 6MWT will be informed of the study and asked if they wish to participate following reading and understanding the patient information leaflet and providing informed consent.

7.2.1 Size of sample

A sufficient number of patients will be recruited in order to assess any differences between the Max_6MWT and Nor_6MWT. The study is to establish whether there is any significant difference of the continuous variable, SpO_2, at rest and at end of 6 minute-walk. Prior data, from the HHFT pilot study, yielded an effect size of 0.30 and this study will need 82 subjects to be able to reject the null hypothesis that this response difference is null with a power of 80%. The Type I error probability associated with this test for null hypothesis is 0.05.

7.2.2 Sampling technique

As the proposed study will assess a novel test against standard of care, convenience sampling will be utilised to capture any patient referred for the standard of care test.

7.3 Recruitment

Once patients are referred for a standard Max_6MWT by a doctor at HHFT, patients will be made aware of the study by a covering letter and Patient Information Leaflet (PIL) alongside their routine appointment letter. At their outpatient appointment, the patient will again have the opportunity to review the PIL and ask any questions to the researcher(s) conducting the study. If they are willing to participate, informed consent will be taken during their appointment prior to testing. Accepting or refusing to participate in the study will have no impact on the care provided to the patient, or their ongoing clinical investigations and treatment.

If a patient is unable to complete both the Max_6MWT and Nor_6MWT, they will be subsequently removed from the study.

7.3.1 Sample identification

The CI or named individuals on the delegation log will screen for patients who meet the eligibility criteria based on the referral information provided on the digital bookings system. Patients will not be actively recruited by either Patient Identification Centres or by public advertising.

Any person identifying patients will already have access to this information as part of the patient's ongoing clinical care. As such, no arrangements are required to pass this information on to anyone outside the patients' existing clinical care team. Additionally, as the study will be conducted within a patients' existing outpatient appointment, there is no reimbursements for travel or time to participate in this research.

7.3.2 Consent

Informed consent will be taken on the day of the outpatient appointment after the patient has had time to review the supporting information in the Patient Information Leaflet, either prior to the appointment or at the beginning of the appointment if the patient has not done so prior. The researcher taking informed consent will outline the nature of the study; confirm the patient has capacity to provide consent (using the below criteria) and has had an opportunity to ask any questions. A patient will be told they may abort the study at any point without reason and that this will not affect the care provided by the clinical care team.

Assessing capacity to provide informed consent - a patient must:

- understand the purpose and nature of the research

- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

8 ETHICAL AND REGULATORY CONSIDERATIONS

This research aligns with both ethical and regulatory framework, aiming to improve the quality of care for patients and providing better diagnostic tools. The research poses very low risk to patients participating as they are only required to walk at their normal walking pace on a flat surface and whilst there may be no immediate direct benefit, there is a direct implication for future clinical decision making based on the outcomes of this study.

Collection of physiological data is done with non-invasive methods and respects the dignity of patients participating in the study. These collection techniques are internationally recognised and conform to all local and national legislation.

8.1 Assessment and management of risk

The study will be conducted according to the principles of the Declaration of Helsinki (9.10.2008) and Good Clinical Practice and in accordance with the Medical Research Involving Human Participants Act (WMO) and other guidelines, regulations and acts. All members of the research team will have up to date safeguarding training provided by HHFT and be aware of dealing with safeguarding concerns in line with local Trust policies.

There is minimal additional risk to patients involved in this study. Walking for 6 minutes in a controlled environment has a small risk of falls and syncope. These risks are managed by visually monitoring patients continuously, ensuring a seat is available by the testing site and assessing baseline blood pressure and SpO_2.

8.1.1 Adverse and Serious Adverse Events

As the study only involves walking down a corridor, it is not envisaged any adverse and serious adverse events are not expected, however procedures will be place in case of an event.

Adverse events (AE) are defined as any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease. Occurrence of possible AEs will be registered by the principal investigator.

All adverse events reported spontaneously by the participant or observed by the principal investigator or their staff will be recorded. On a study day, Adverse Events (AEs) may be established by asking the participants: “How are you feeling?” before and after the experimental procedures.

A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing in patients’ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a new event of the trial likely to affect the safety of the participants, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life-threatening disease or a major safety finding from a newly completed animal study.

Any Serious Adverse Event, with a possible relation to the study will be reported by the medical investigator upon hearing (within 24 hrs) to the sponsor, and the general practitioner and the study participant will be informed. Any SAE not or unlikely to be related to the study will be reported to the sponsor and ethical committee by the Chief Investigator within three working days.

As this is a single-day study with no lasting intervention or therapy, reporting and recording of AEs and SAEs will only happen if they occur during the study visit itself. It is not deemed that completing a questionnaire carries any risk and will not be monitored under the AE/SAE criteria.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Appropriate ethical approval from both local R&D and REC will be sought prior to the study commencing. Any amendments to the protocol or related documents will also receive appropriate approvals prior to implementation. The CI along with the sponsor will determine if an amendment is substantial or non-substantial and amendments will then be drafted and then reviewed by the CI before submission to the sponsor and the REC where required. All amendments will be noted at the beginning of the protocol in the relevant section and relevant parties notified by email, including when these changes can be implemented following approval from the relevant bodies and or committees.

These approvals and correspondences will be stored in the site file and appropriate annual reports such as the annual progress review will be submitted by the named CI. The REC will be notified at the end of the study and a subsequent final report will be submitted within 12 months, along with any publications from the study.

8.3 Peer review

This protocol has been peer reviewed externally by three independent external reviewers, each of whom has experience of working directly with the standard 6-minute walk test or with research projects that use similar measurements and patient groups to those described within this protocol. Each reviewer was provided a copy of the protocol, information leaflet and associated questionnaires for review using a standard reviewers form supplied by the R&D department at HHFT.

8.4 Protocol compliance

Accidental protocol deviations can happen at any time. If a protocol deviation is identified, the CI and sponsor will be made aware immediately and the exact deviation documented and stored in the site file. Appropriate action will be taken to avoid repeating the protocol deviation. If frequent recurring

deviations are identified, the protocol will be reviewed by the CI and amended to prevent future deviations. Recurring deviations may be classed as a serious breach and may be treated as such.

8.5 Data protection and patient confidentiality

All (personal) data will be handled confidentially in accordance with the Data Protection Act 1998 and General Data Protection Regulation (GDPR). Personal data are stored on the HHFT secure digital electronic patient records (EPR) on an internal network, which is protected by usernames and passwords. All personal data will remain within HHFT and there will be no transmission of this data to third parties.

All personal source data will be kept on the NHS clinical server and in medical records as part of normal medical care. A copy of the consent form and patient information sheet will also be stored in the medical records where possible and within the site file. In case of withdrawal from the study, the participant can decide whether the data already acquired shall be destroyed or can be used.

In the event of a data protection breach or serious breach of GCP, all HHFT protocols will be followed to ensure proper reporting and management of such an incident.

Participants will be given a study ID upon consenting to the study allowing for pseudo-anonymisation of any data collected. The link connecting patient names to the pseudo-anonymised research data will be kept in an encrypted file held on NHS servers to which only the CI and those delegated by the PI will have access to (all paper documents will be stored in a specific site file within HHFT). Clinical information collected and any test results that may be useful to a patients' ongoing clinical care may be stored alongside routine test results and treated as confidential patient information as part of their healthcare record and exempt from the archiving and deletion policies as part of this research.

Any information shared with academic collaborators at the University of Winchester and Manchester Metropolitan University (for the purposes of completion of a part-time MSc by the study PI) will only use the study ID and no personal identifiable information.

Questionnaires returned by email will be sent to a secure NHS account (respphysresearch@hhft.nhs.uk) accessible by researchers involved in the study and on the study delegation log.

8.6 Indemnity

The study will be conducted within an NHS Trust and by NHS employees and, therefore, the NHS indemnity scheme will cover all activities under this study. As the study will be carried out during a normal procedure referred for by a medical professional, it is not expected any compensation would be required as a result of this study.

8.7 Access to the final study dataset

The CI and individuals involved in the routine care for patients participating in the study will have access to the final dataset, including physiologists and clinical scientists. In addition, any medical professionals involved in the routine care of the patients involved in the study will also have access to the final dataset – although their access to the full dataset during the study will be restricted as outlined in the study design and methods.

A final report, that does not allow identification of individuals' participating in the research, will also be published on a public domain and freely available to participants and members of the public.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The data arising from the study remains the ownership of HHFT. Upon completion, anonymised data will be formulated into a written report with the aim of publication either as a journal article or conference proceedings. These data may also be presented at conferences verbally and/or a poster.

The full dataset will also be made available to the medical team involved in the routine care of the study participants once the study has completed or for an individual participant once their involvement in the study is complete (they have reached the end of the study protocol).

A final report will also be generated for study participants to inform them of any findings from the study in the form of a leaflet, poster or patient feedback session. The required information will be submitted to the public-facing database where the clinical trial is registered. The CI and PI will aim to share this with participants via email where this information is accessible.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be reserved for those directly involved in the collection of study data and the presentation of these data in written form or presented at conferences.

10 REFERENCES

1. Crapo, R. O. *et al.* ATS statement: Guidelines for the six-minute walk test. *Am. J. Respir. Crit. Care Med.* **166**, 111–117 (2002).
2. Lewko, A., Marshall, J. & Garrod, R. Ambulatory oxygen therapy assessment: A comparative study of incremental shuttle and six-minute walking tests. *Kingst. Univ. Res. Repos.*
3. ATS. ATS Statement: Guidelines for the Six-Minute walk test. *Am. J. Respir. Crit. Care Med.* **166**, 111–117 (2002).
4. Whitty, J. A. *et al.* Cost-effectiveness of ambulatory oxygen in improving quality of life in fibrotic lung disease: preliminary evidence from the AmbOx Trial. *Eur. Respir. J.* **55**, 1901157 (2020).
5. Criner, G. J. Ambulatory Home Oxygen: What Is the Evidence for Benefit, and Who Does It Help? *Respir. Care* **58**, 48–64 (2013).

11 APPENDICIES

11.1 Appendix 1- Required documentation

Researchers involved in the study:

- CV
- GCP Certificate
- Present on the delegation log

At the study site:

- Copy of PIL
- Consent forms
- Site file containing study protocol
- Approvals and correspondence relating to the study
- Delegation Log
- All correspondence with relevant regulatory bodies

11.2 Appendix 2 – Schedule of Procedures

All procedures will be performed in a single visit during a routine outpatient appointment. Collection of questionnaire data will occur after this appointment if subsequently a patient is prescribed ambulatory oxygen either by posting the physical questionnaire to the research team, or by email. In addition, a separate Schedule of Events document has been attached for convenience.

11.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	Pending	Michael Hughes	Amendment of 6MWT instruction to match most recent published guidance. Amendment of exclusion criteria.

11.4 Appendix 4 – Meeting notes from the Breathe Easy group

Attendees at the Breathe Easy group (Andover) discussed the research study. Attendees all agreed that “a six-minute walk test is not the normal thing that any one of them would do, in their own situations, so not a good test as to whether they need oxygen in their day to day lives.”

Attendees highlighted the need for adequate rest between the two walk tests, which we will encompass into the study design. Attendees that had previously performed six-minute walk tests commented on the varying protocols depending on who asked them to do the tests (including physiotherapists, nurses, rehabilitation practitioners, pre-op assessments): sometimes they were asked to walk at normal speed, sometimes at maximal speed and there was quite a lot of confusion over the purpose of the tests. They were very happy with the idea of the study and felt if it could reduce the need for them to do these maximal tests which they found very hard then they would appreciate it.