Study Title: Evaluation of a new 6 minute walk test smartphone app in patients with pulmonary hypertension (the 6-APP Study)

Internal Reference Number / Short title: 6-APP Study

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Funder:	NHIR BRC
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No conflicts of Interest

Confidentiality Statement

TABLE OF CONTENTS

1. SYNOPSIS

Study Title	Evaluation of a new 6 minute walk test smartphone app in patients with pulmonary arterial hypertension (the 6-APP Study)	
Internal ref. no. / short title	6-APP Study	
Study Design	Comparison of standard 6 minute walk test with 6 minute walk test smartphone app	
Study Participants	Patients with, or being assessed for, pulmonary hypertension	
Planned Sample Size	30	
Planned Study Period	Q4 2017- Q4 2019	
	Objectives	**Outcome Measures**
Primary	To demonstrate that patients are able and willing to use the app for the 6MWT	Percentage of participants who perform app-based home 6MWT
Secondary	To validate app 6MWT measurements against the hospital 6MWT	Average and standard deviation of the difference in distance as measured by physiologists and the app
	To compare the outdoor 6MWT app with the hospital based 6MWT	Correlation of outdoor 6MWT app parameters with the hospital 6MWT test.
	To assess the usability and acceptance of the app and the physicians' website	Standard usability and acceptance questionnaires, semi structured interviews, analysis of technical logs

2. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice

GP	General Practitioner
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
NYHA class	New York Heart Association class
PAH	Pulmonary arterial hypertension
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
VO2 Max	Maximal oxygen consumption on exercise test
6MWT	Six minute walk test

3. BACKGROUND AND RATIONALE

Pulmonary Arterial Hypertension (PAH) is a progressive illness that; if not diagnosed early or left untreated, can be a severe life limiting condition (1). It is a chronic disease of the pulmonary vasculature, with vascular proliferation and remodelling of the small pulmonary arteries leading to a progressive increase in pulmonary vascular resistance (PVR). This can ultimately lead to right heart failure and premature death (2). The predominant symptom of PAH is dyspnoea on exertion, with a decrease in exercise capacity, and most patients present with this symptom (2).

PAH is an uncommon condition, affecting about 6000 patients in the United Kingdom (3), and due to its rarity, the NHS commissions 7 centres to care for patients with PAH (4). Oxford University Hospital works closely with the Royal Brompton Hospital to provide care for patients with PAH in Oxfordshire and the surrounding region.

The six-minute walk test (6MWT) is a standard method for measuring exercise capacity in patients with cardiopulmonary disease such as PAH. The 6MWT measures how far a patient can walk in 6 minutes. Walking is an activity performed every day, by most patients except for those most severely limited. By assessing patients' ability to exercise, the 6MWT provides a global assessment of respiratory, cardiovascular, neuromuscular and cognitive function. The 6MWT does not differentiate what limits the patient, nor does it assess maximal exercise capacity. Instead, the 6MWT allows the patient to exercise at a daily functional level, and is a useful tool for assessing changes after a therapeutic intervention, and correlates with a subjective improvement in dyspnoea (5).

In PAH the 6MWT is used to evaluate patients' response to treatment, with an increase in 6MWT distance of greater than 42 m being considered a clinically significant improvement (6). Furthermore,

change in 6MWT distance correlates with VO2 max, NYHA class and mortality in PAH patients, (7) providing an objective assessment of disease progression, prognosis and response to treatment. It is a universally accepted test as it is safe and easily performed by the patient.

The 6MWT has become the primary end-point for many trials, and as a surrogate invalidated survival outcome for all placebo controlled trials of PAH therapy (8). It is used by regulatory bodies to determine whether a treatment should be approved. However, there is much discrepancy between whether it is the total distance walked at baseline prior to treatment, a decrease in total distance walked over time or a percentage increase in walking distance that correlates best with survival outcome. We hypothesize that it is all 3 of these measures, and that having a validated and more reproducible 6MWT would help assess patients and guide treatment strategies better.

The test is usually performed in hospital, by walking along a hospital corridor, where many factors on the day of the test can affect patients' performance, including tiredness, unfamiliarity with the environment or anxiety. The test typically requires 2 physiologists to monitor the distance walked by the patient, their oxygen saturations by pulse oximetry, and to record symptoms felt during the test. To improve the assessment of a patient's exercise capacity using a 6MWT, we hypothesized that the test would reflect more the patient's functional status, if it were undertaken prior to the hospital outpatient appointment. We have designed a mobile-phone "app" that allows patients to perform the 6MWT within the patient's home environment. This is felt to be more appealing to the patients, and would reduce the time spent in hospital on the day of their outpatient appointment.

The 6MWT app is categorised as mobile-health (m-health) system, a form of telehealth whereby healthcare is delivered at a distance using smartphones. By utilizing biometric collection devices such as a pulse oximeter monitor with Bluetooth capability, m-health can be used to measure the oxygen saturation levels in the blood from patients, and transmit them to a secure server, allowing them to be reviewed by cardiologists and other healthcare professionals.

The evidence-base for m-health as a tool for assessing physical fitness is increasingly established (9, 10). This new approach not only offers the opportunity for reliable collection of data, but provides the infrastructure to do this at scale and will allow decisions on patient's health to be based on more frequent and more accurate information.

There are no known risks to undertaking a 6MWT in the community as walking is an activity of daily living, and all patients are encouraged to walk daily.

The population to be studied would be those with PAH who are currently assessed with a 6MWT. Once the app has been validated, patients with any type of cardiorespiratory disease who are assessed with a 6MWT could use the app, for example patients with chronic obstructive airways disease, heart failure, renal failure, pre-transplantation work up.

The 6MWT results form part of the NHS data set collected by NHS England for patients with PAH, and it would be beneficial to have a more reproducible assessment, whose results can be compared between the 7 centres providing care for these patients. At present, there is much variability in how 6MWTs are performed between units, and the app would reduce this variability.

The 6MWT has been undertaken at the JR for 5 years and we would like to retrospectively analyse the data from the 6MWT that have previously been undertaken. The data on patients will be pseudo-anonymised, i.e. no personal information like name, surname or address, will be used, but we will keep date of birth, gender, diagnosis, dates and results of the 6MWT, date and causes of death. As part of the clinical care team reviewing the data is part of the normal standard of care for patients with PHT. The data is collected on the Solus cardiac reporting system and can be extracted from this database and the data will be pseudo-anonymised by the PI for analysis, and then shared with the wider research team. The data would be analysed to look at distance walked, and change in Oxygen saturation and heart rate during the test. We would analyse the data over time, to look for changes in these parameters and correlate these with outcome data, ie mortality. The data would be anonymised when reviewed.

4. OBJECTIVES AND OUTCOME MEASURES

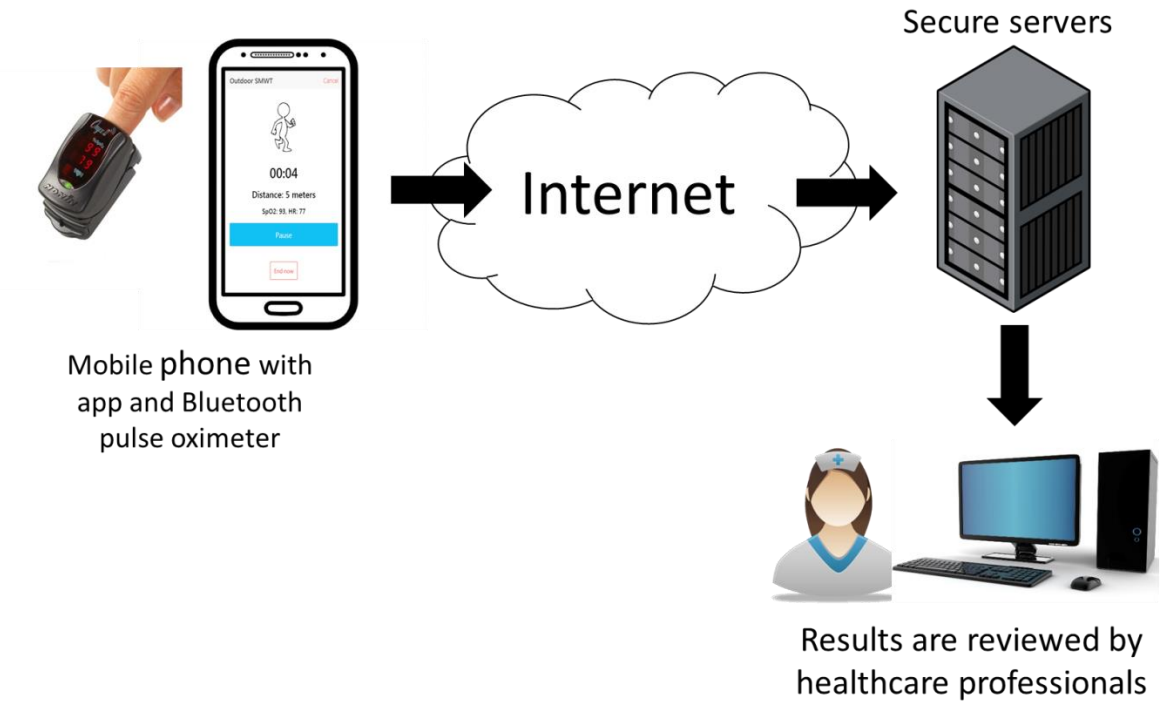
Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective O1: To demonstrate that patients are able and willing to use the app for the 6MWT	Percentage of participants who perform app-based home 6MWT	TP 1: 3 months after baseline visit TP 2: 6 months after baseline visit
Secondary Objectives O2: To validate app 6MWT measurements against the hospital 6MWT.	Average and variability of the difference in distance as measured by physiologists and the app.	TP 1: at baseline visit TP 2: at 3-month visit TP 3: at 6-month visit
O3: To compare the outdoor 6MWT app with the hospital based 6MWT.	Correlation of outdoor 6MWT app parameters with the hospital 6MWT test.	TP 1: baseline visit 6MWT compared with following home test TP 2: 3-month visit 6MWT compared with closer home test before or after TP 3: 6-month visit 6MWT compared with closer home test before or after

O4: To assess the usability and acceptance of the app and the physicians' website.	Standard usability and acceptance questionnaire to users assessing their use of the app and website, semi structured interviews, analysis of technical logs.	TP 1: at 6 months after baseline visit
Tertiary Objectives O5: To test whether the 6MWT app can detect changes in 6MWT distance more effectively than the hospital 6MWT, in patients starting advanced therapies.	Comparison of change in 6MWT app measurement with hospital 6MWT measurement, measured before and after initiation of new therapies.	TP 1: at baseline visit TP 2: at 3-month visit TP 3: at 6-month visit

5. STUDY DESIGN

We propose to evaluate a novel approach to service delivery by monitoring PAH patients using an established m-health system to send 6MWT results to a central server where they can be accessed by the clinical team (Figure 1). The system includes a mobile phone "app" to allow participants to comfortably perform the 6MWT at home (indoors or outdoors). In the outdoor scenario, the app makes use of GPS to track the user's position. In the indoor scenario it uses the phone's accelerometer and magnetometer (compass) to count the number of laps over a fixed-length walkway.

Figure 1. Diagram of the system



Undertaking a 6MWT test within the participant's home environment, using mobile technology to transmit the results via a software application on a mobile phone is appealing as it is likely to be more acceptable to the participant, may provide more consistent and functionally relevant data, and may reduce hospital attendances and healthcare costs. By utilizing biometric collection devices such as a pulse oximeter monitor with Bluetooth capability, telehealth can be used to capture the oxygen saturation levels in the blood from participants and transmit them to a secure server, allowing them to be reviewed by cardiologists and other healthcare professionals.

This study aims to compare the indoor 6MWT, with the hospital performed 6MWT. It will assess the feasibility and acceptance of a mobile phone app as an instrument to measure the 6MWT.

The 6MWT is currently undertaken at every Outpatient appointment, normally at 0- 3-, 6- and 12-month outpatient reviews. The participant would perform a hospital based 6MWT, whilst simultaneously using the indoor version of the app on their own mobile phone at baseline, 3- and 6-month follow up. This will demonstrate to the participant how to use the app, and we will be able to understand whether they are able to use it correctly. It will also allow direct comparison of the standard 6MWT distance measurement with the measurement provided by the app.

The participant will be then invited to use the app in their local environment, preferably in the outdoor scenario, and the collected information would then be transmitted to the hospital servers where it could be reviewed. The app could be used many times prior to attendance in outpatients, giving the clinicians more detailed information as to the overall functional status of the patient. Participants will be required to perform a test before and after their follow up appointments so that home-based measurements can be compared to hospital-based ones. They will be allowed to do as many tests as they are willing to, preferably once per week and at least each month.

In total, we aim to collect 3 indoor hospital-based measurements (baseline, 3- and 6-month) and at least 5 outdoor home measurements, one close to each hospital visit plus one between two visits. The data collected will allow us to understand the usage of the app by participants, validate the indoor measurements and correlate the home measurements with the hospital-based ones.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants with pulmonary arterial hypertension due to any cause who are able to perform a 6MWT. Patients on long term oxygen therapy will not be included as it will be difficult to perform the outside 6MWT whilst on oxygen. Also patients with cognitive impairments, even if able to use a smartphone, will be excluded as they would possibly introduce noise for not being able to use the app correctly.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study
- Male or Female, aged 18 years or above
- Diagnosed with PAH who are able to undertake 6MWT off-oxygen
- Being of PAH group 1 or 4
- Participant owns a compatible smartphone (Android or iPhone) and is able to use it.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Long term oxygen therapy
- Cognitive impairments
- Rheumatological diseases that limit the measurement of finger Oxygen saturations
- PAH groups 2, 3 or 5
- Cannot use a smartphone
- Pregnancy.

7. STUDY PROCEDURES

7.1. Recruitment

Patients undergoing follow up in the PAH clinic will be eligible for participation. They will be approached by a member of the clinical team for consideration and recruited. We will recruit 30 compliant patients to enrol in the study.

7.2. Screening and Eligibility Assessment

The patients attending the PHT outpatient clinics will be screened to assess whether they have pulmonary arterial hypertension and assessed as to whether they will be able to undertake a 6MWT using the App and then recruited

7.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site and a copy filed in participants medical notes.

7.4. Baseline Assessments

The baseline assessment will be a standard 6MWT which measures resting heart rate and oxygen level at rest, the distance walked over 6 minutes, then the oxygen saturations and heart rate at end of the 6MWT. Prior to the initiation of the test, participants will be asked to download the app onto their personal mobile phones. Participants will also be asked to use the app in its indoor mode, while performing the test in hospital. Participants who are not able to either download the app or use it correctly will be unable to participate. We will be using the BORG questionnaire at the end of both the app test and the hospital 6MWT. The Borg Rating of Perceived Exertion (RPE) is a way of measuring physical activity intensity level. Perceived exertion is how hard a patient feels they are working. It is based on the physical sensations a person experiences during physical activity, including increased heart rate increased breathing rate, increased sweating, and muscle fatigue. Although this is a subjective measure, a person's exertion rating may provide a fairly good estimate of the actual heart rate during physical activity (11). During activity, the patient uses the Borg Scale to assign numbers as to how hard they think they are working. Participants will be provided with the questionnaire at the end of their

6MWT and are encouraged to complete the questionnaire by the app or by the hospital physiologist. The physiologists undertaking the test will measure the distance walked using the system website to record the measurement. This way all measurements will be digitally available in one place. At the end of the assessment, participants will be asked to perform a home-based 6MWT within 3 days of the visit and 1 home test per week, or, at least, one per month.

7.5. Subsequent Visits

The participants will be followed up as per the normal outpatient protocol at 3 and 6 months. At all the appointments they will perform a standard hospital based 6MWT, which will again document resting heart rate and oxygen saturations, the distance the participant walks in 6 minutes and their heart rate and oxygen saturations at the end. Participants will be asked to use the app while performing the test. The BORG questionnaire will be also presented at the end of the test.

After the test, if no home 6MWT was performed within 3 days before the visit, participants will be reminded to perform a home test within the following 3 days. In addition, participants will be reminded to perform 6MWTs at home once per week, or at least once per month. At the end of the study, all participants will be asked to complete a usability and technology acceptance questionnaire and a group of randomly chosen 5 to 10 patients will be asked to attend a short interview about the use of the app.

7.6. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of Consent
- Loss to follow up

If participants withdraw from the study, their data until that point will still be analysed, unless deletion of data is requested by the participant (e.g., by withdrawing consent). Any participant that withdraws from the study will be replaced with a new participant. The reason for withdrawal will be recorded in the CRF.

7.7. Definition of End of Study

The end of study is the date of the 6-month follow up appointment for the last participant.

8. IDENTIFICATION & DESCRIPTION OF THE DEVICE

8.1. Description of the Device

The app used in the study, called “SMWT” is a smartphone "app", and is a software device. Its main purpose is to measure the walked distance in a timed walk. In the "outdoor mode", the app makes use of GPS to track the user's position and compute the distance. In the "indoor mode" it uses the phone's compass to count the number of laps over a fixed-length walkway. The app also collects blood saturation and pulse samples from commercially available pulse-oximeters, connected to the phone via a wireless link. The app is available, free of charges, on common "app stores" (Google Play Store and Apple iTunes) and is currently not distributed as a medical device but as a research prototype.

The app is able to retrieve data from two commercial pulse-oximeters: Creative Medical PC-68B and Nonin Onyx II, both certified as medical devices in Europe and United States. The validation of the pulse-oximeters is not object of this research.

8.2. Device Safety

The app is being tested in relation to its reliability and the accuracy of distance estimation.

In the "indoor mode", from 46 tests in lab and with actual patients, the app has an average absolute error of 5.58 m and a maximum of of 21.46 m, which is below the threshold that is considered clinically relevant. In the "outdoor" mode, from 24 tests performed in lab, the average error is 11.23 m and the maximum 27.19 m, both still not clinically significant.

There are no safety risks associated to use of the app.

Volunteers are also being involved in technical testing and assessing usability and long-term acceptance.

8.3. Device Accountability

The production of the software app is responsibility of the Department of Engineering Science of the University of Oxford.

9. SAFETY REPORTING

The study is low risk however, in the event of an adverse event (AE) or serious adverse event (SAE) occurring to a participant this would be reported to the REC and MHRA in the annual report.

9.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in participants, users or other persons whether or not related to the

	investigational medical device. This includes events related to the investigational device or comparator, events related to the procedures involved (any procedure in the protocol). For users or other persons this is restricted to events related to the investigational medical device.
Adverse Device effect (ADE)	An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or form intentional misuse of the investigational device.
Serious Adverse Event (SAE)	An adverse event that: • Led to death • Resulted in serious deterioration in the health of the subject that: o resulted in a life-threatening illness or injury o resulted in a permanent impairment of a body structure or a body function o required in-patient care or prolongation of hospitalisation o resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. This includes device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) circumstances had been less fortunate. These are handled under the SAE reporting system. Planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above. *Unanticipated Serious Adverse Device Effects (USADE)*

	Any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been identified
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate
User error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

Severity definitions

The following definitions will be used to determine the severity rating for all adverse events:

Mild: awareness of signs or symptoms, that does not interfere with the subject's usual activity or is transient that resolved without treatment and with no sequelae.

Moderate: a sign or symptom, which interferes with the subject's usual activity.

Severe: incapacity with inability to do work or perform usual activities.

9.2. Causality

The relationship of each adverse event to the trial device may be determined by the manufacturer and/or a medically qualified Investigator according to the following definitions:

Not related: The event is clearly related to other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication.

Unlikely: The event is probably produced by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication and does not follow a known response pattern to the device

Possibly: The event follows a reasonable temporal relationship form the time of placement/administration and/or follows a known response pattern to the device but could have been caused by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication.

Most probable: The event follows a reasonable temporal relationship form the time of placement/administration and/or follows a known response pattern to the device and could not have been caused by other factors such as the patients/participants clinical condition, therapeutic intervention, concomitant medication. Further the event immediately follows the administration/placement of the device and improves on stopping or removing the device.

9.3. Procedures for Recording Adverse Events

All adverse events (including ADEs) and device deficiencies occurring during the course of the study will be recorded on the CRF whether or not attributed to the trial device. The information recorded will include but not be limited to:

- A description of the event
- The dates of the onset and resolution
- Action taken
- Outcome
- Assessment of relatedness to the device
- Whether the AE is serious or not
- Whether the AE arises from device deficiency
- Whether the AE arises from user error

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs/ADEs considered related to the device as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE/ADE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE/ADE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.4. Reporting Procedures for Serious Adverse Events

Reporting of all Serious Adverse Events will be done in accordance with the European Commission Guidelines on Medical Devices Serious Adverse Event Reporting (MEDDEV 2.7/3; December 2010).

SADEs/USADEs that pose an immediate risk to patient health or safety, will be reported to the OUH R&D team immediately or no later than 24 hours after the Investigator is aware. All information must be recorded on an SAE form and emailed to R&D at ouhsae.reports@ouh.nhs.uk.

R&D will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. It will also be reviewed at the next Trial Safety Group meeting.
This information will also be reported to the device manufacturer, competent authority and the REC within 2 calendar days of the Chief Investigator becoming aware of the event.

SAEs/SADEs will be recorded for a 24 hour period following the use of the device. All SAEs will be followed up to resolution.

9.5. Safety Monitoring Committee

The Oxford University Hospitals Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs/SADEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

Data will be analysed when the study is completed.

Statistical methods that will be employed to analyse and validate the results of the study are:

- Descriptive statistics (mean, standard deviation, median, interquartile range)
- Pearson correlation coefficients
- Distribution plots
- Scatter plots
- Bland Altman charts
- Error bars and confidence intervals

10.2. Number of Participants

This is an exploratory observational study and therefore no sample size calculation is provided, we propose collecting data on 30 participants.

10.3. Analysis of Outcome Measures

All participants' data will be used excluding those who withdrew consent.

Primary Objective:

O1: We will measure the percentage of participants who perform at least one home 6MWT between baseline visit and 3-month visit and the percentage of participants who perform at least one home 6MWT between baseline visit and 6-month visit. These two percentages will be used as the main measure of the success of this study.

In addition, the distribution over time of when home performed tests will be computed.

Secondary Objectives

O2: We will compute the mean and standard deviation of the difference in distance as measured by the physiologists and the app. To evaluate the agreement between the two approaches, a Bland Altman graph will be also prepared.

O3: We will compute the correlation of the distance as computed by the app when used at home within 3 days from the hospital visit with the one gathered in the hospital 6MWT test.

O4: Ease of use, acceptance and mobile phone affinity will be measured with standard questionnaires. Compliance with the use of the app will be measured by counting the frequency of use of the app. Simple descriptive statistics will be computed and correlations among quantities will be explored. A selected number of participants will be chosen for semi-structured interviews in order to gain a deeper understanding of their usage of the app.

Tertiary Objectives

O5: Descriptive statistics about the walked distance, blood oxygen saturation and heart rate, BORG scale and number of steps will be used to compare changes before and after initiation of new therapies.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. All authorised representatives will be employed by the Oxford University Hospitals Trusts (OUH), hold honorary contracts with OUH, or hold a valid NHS Research Passport.

11.2. Data Recording and Record Keeping

Participants' data will be recorded on an ad-hoc system developed by the Institute of Biomedical Engineering of the University of Oxford. The data will be collected in two ways: by the app and through forms submission on a website. The app will be used by participants, the website will be used by physicians.

All the communication between the patients' apps and / or the physicians' browsers and the server is encrypted though state-of-the-art web technology. The web interface and the database are hosted on computers within the OUH network and protected by the NHS firewall. Access to the server from both patients' apps and physicians is allowed only through the submission of personal, private user credentials.

The data will be pseudo-anonymised, therefore no directly identifiable information will be stored. Participants will be given pseudonyms (e.g. participant1, participant2 etc.) that will be used to log into the app. Only study staff and authorised personnel will be given credentials for reviewing participants' data.

A paper form will be kept by the principal investigator

Data will be kept for up to 10 years after study completion or until ethical approval terminates, whichever is sooner.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

13.7. Other Ethical Considerations

6MWTs

6MW testing is very safe and is used in many conditions including in people with heart failure. However, as can occur with all forms of exercise, very occasionally some people have significant changes in their heart rate and rhythm that requires medical attention. Although the risk of this happening is small, the test is carried out in hospital in with physiologists monitoring the patients. The participants undergoing the home or outdoor 6MWT will be provided with a checklist for them to assess themselves with, and would not undertake a test if they fail this.

Participants will be provided with all necessary information and can access their right to make a decision regarding participation.

14. FINANCE AND INSURANCE

14.1. Funding

The NIHR Oxford Biomedical Research Centre will fund involvement of a research engineer and the electronic equipment (pulse oximeters).

14.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR Oxford Biomedical Research Centre. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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17. APPENDIX A: STUDY FLOW CHART