Trial Title: Evaluation of the usefulness of adopting remote, mobile-based 6MWT among hospital outpatients (the 6-APP now Study), within the constraints imposed by the SARS-COV2 pandemic

Internal Reference Number / Short title: 6-APPnow Study

Ethics Ref: Insert

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Date and Version No: 3/5/21 Version number 1

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Funder: NIHR BRC and the Swedish Knowledge Foundation

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Statistician Signature:

No conflicts of Interests

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

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1. KEY TRIAL CONTACTS

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Funder(s)	The Swedish Knowledge Foundation
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2. LAY SUMMARY

The six-minute walk test (6MWT) is a standard method for measuring exercise capacity in patients with cardiopulmonary disease such as pulmonary hypertension (PAH) and measures how far a patient can walk in 6 minutes. The test is usually performed in the hospital, by walking along a hospital corridor. Since the outbreak of SARS-CoV-2, there has been a need to minimise patient contact with hospitals and their staff to reduce transmission of the virus. In a previous research project called 6APP, we designed, developed and evaluated a mobile phone app, to allow them to perform the 6MWT in the community. Given the current circumstances, cardiovascular outpatients including patients in the PHT clinic in Oxford are being recommended to use an app derived from that project to provide their 6MWT distance to the clinical team for assessment, in addition to their symptoms and general well-being. 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.

We would like to measure the usefulness of adopting remote, mobile-based 6MWT among hospital outpatients, within the constraints imposed by the SARS-COV2 pandemic.

3. SYNOPSIS

The Trial will review the use of a mobile-based 6MWT by hospital outpatients during the coronavirus pandemic and evaluate its use

Trial Title	Evaluation of the usefulness of adopting remote, mobile-based 6MWT among hospital outpatients (the 6-APP now Study), within the constraints imposed by the SARS-COV2 pandemic.		
Internal ref. no. (or short title)	6-APPnow Study		
Trial registration	Clinical Trials. gov		
Sponsor	Oxford University Hospitals NHS Foundation Trust Headley Way, Oxford, OX3 9DU		
Funder	NIHR BRC and the Swedish Knowledge Foundation		
Trial Design	Patient survey to evaluate their use of the 6 minute walk test smartphone app as a surrogate for regular clinic 6MWT.		
Trial Participants	Patients using 6 minute walk tests for managing cardiopulmonary function or disease management		
Sample Size	250-500 patients attending the outpatient clinics		
Planned Trial Period	Q2 2021 – Q2 2022		
Planned Recruitment period	Q2 2021 – Q2 2022		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To assess whether patients are able and willing to use a smartphone app for the 6MWT	Percentage of participants who perform at least one app-based 6MWT before patient consultation.	At 3, 6, 9 and 12 months after the start of the study.
Secondary	To assess the accuracy of the app-based measurement.	Measurement of walked distance (6MWD) measured by the app compared with a trundle wheel reference.	12 months
	To assess whether differences in distance walked altered management of patients.	Number of clinical investigations and multidisciplinary team discussion triggered by variations in app-based 6MWD.	At 3, 6, 9 and 12 months after the start of the study.

	To assess the usability and acceptance of the app.	Standard usability and acceptance questionnaires, semi-structured interviews.	12 months
	To collect raw data from phones' sensors to allow the development of future algorithms for app-guided 6MWT.	Localisation position (GPS), speed, acceleration, step count, gyroscope samples collected during 6MWT.	12 months
	To determine whether the use of the 6MWT reduces time spent and number in hospital visits.	Time spent in hospital attendances and number of hospital visits made during use of the 6MWTapp compared with previous periods.	12 months
	To compare the use of 6MWT during pandemic with pre-pandemic use.	Total number of 6MWTs performed during 2020 pandemic period compared with pre-pandemic period.	12 months

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
FC	Functional capacity
GCP	Good Clinical Practice

GP	General Practitioner
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
NYHA	New York Heart Association
OUH	Oxford University Hospitals
PAH	Pulmonary arterial hypertension
PH	Pulmonary 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
6MWD	Six minute walk distance
6MWT	Six minute walk test
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group

5. BACKGROUND AND RATIONALE

5.1. Telemedicine in the context of COVID19

Since the outbreak of SARS-CoV-2, health care systems have been subject to increased pressures. This is mainly due to infected patients being admitted to the medical wards and intensive care units, but also due to the requirement to reduce exposure of both healthcare professionals and patients to COVID by minimising contact.

There are indications that reduced access to healthcare services during the pandemic is responsible for more than half of excess deaths in the United States[1]. In response to this, the CDC is advocating the use of telemedicine to keep providing a remote version of healthcare services[2]. A study of telemedicine

[1] https://jamanetwork.com/journals/jama/fullarticle/2768086

[2] https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html

services in China used during COVID-19 pandemic showed that they reduced burden on hospitals, prevented overcrowding, reduced the risk of cross-infection, and relieved patients' anxiety[3]. The use of telemedicine is also being developed in Europe, where many patients are being denied the use of clinical services, like cardiac rehabilitation[4], because of centres being closed. In the context of the NHS, an increased use of telemedicine services is being observed[5]. The NHS long-term plans do, in fact, include tele-consultations as a pillar for its sustainability[6]. Healthwatch have produced useful advice for outpatient clinicians to consider avoiding asking patients to attend physical outpatient appointments where a clinically-appropriate and accessible alternative exists. Where an appointment is clinically necessary, the national benchmark is that at least 25% could be conducted by telephone or video including 60% of all follow-up appointments. Initial promising results are being seen in the context of diabetes, where virtual clinics are recommended as mitigation to the pandemic[7].

5.2. The 6MWT

To assess patient's exercise capacity, the six-minute walk test (6MWT) is a standard method used in patients with cardiopulmonary disease such as Heart Failure (HF) or Pulmonary arterial Hypertension[8] (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[9].

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[10]. Furthermore, change in 6MWT distance correlates with VO2 max, NYHA class and mortality in those patients, 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.

5.3. Cardiovascular outpatient management during the pandemic

[3] https://mhealth.jmir.org/2020/7/e19417/

[4] https://clinowl.com/the-future-is-now-a-call-for-action-for-cardiac-telerehabilitation-in-the-covid-19-pandemic-from-the-secondary-prevention-and-rehabilitation-section-of-the-european-association-of-preventive-cardiolo/

[5] https://digital.nhs.uk/coronavirus/nhs-digital-tech-analytics

[6] https://www.bmj.com/content/364/bmj.l84.long

[7] https://www.jmir.org/2020/8/e21609/

[8] https://pubmed.ncbi.nlm.nih.gov/12890299/

[9] https://www.ahajournals.org/doi/full/10.1161/circulationaha.112.105890

[10] https://www.atsjournals.org/doi/full/10.1164/rccm.201203-0480oc

Since the outbreak of SARS-CoV-2, the standard regime of care for outpatients with cardiovascular disease has been affected.

For example, in PAH patients, the normal regime of a 6MWT, echocardiogram and face to face consultation was abandoned as those patients were felt to be extremely clinically vulnerable, and therefore were recommended to shield at home. Therefore patients needed to be assessed without having any face to face contact, unless in an emergency. This situation continued for five months until August, when shielding was initially withdrawn, however we are now back in this situation with a highly transmissible variant SARS-CoV-2. Therefore the need to reduce time spent in hospital continues as the virus continues within the community.

In cardiovascular outpatient clinics in Oxford, patients are now being regularly contacted by phone to replace face to face visits. During these phone calls, questions about the general status of the patient are asked, i.e. how far they think they can walk and whether they have noticed a change in their exercise capacity or functional capacity, but currently no objective data, like the results of the 6MWT, are available for assessment.

5.4. Telemedicine services for pulmonary hypertension

In a previous research project called 6APP, we designed, developed and evaluated a mobile-health "app" (a type of telemedicine where patients use their mobile phones), to allow them to perform the 6MWT in the community. We hypothesized that a test conducted by patients, in their environment, would reflect more the patient's functional status, would free up healthcare resources and would be less stressful and costly for the patients themselves.

The app allowed patients to perform the test both indoors, by walking back and forth along a corridor of fixed length, and outdoors, using the localization system (like the GPS). In our study with 30 PAH patients, we proved that the app is accurate when used outdoors, the measurements are reliable and repeatable and the method is well-accepted by patients[11].

After these encouraging results, the app has been simplified and made available for free for both Android and iPhones under the name of "Timed Walk". The original app was developed by Dario Salvi at the Institute of Biomedical Engineering of the Oxford University. The current app, which uses the same validated outdoors test approach, is instead maintained by the University of Malmo, Sweden, where Dr. Salvi is currently employed.

Given the current circumstances, the PH clinic in Oxford and other cardiovascular outpatient clinics are recommending patients to use the Timed Walk app, the results of which are being used by the clinical team to assess patients in addition to their symptoms and general well-being. 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 app only allows outdoor tests (as these proved to be more reliable and practical) and to share 6MWT data via email if patients want to.

[11] https://mhealth.jmir.org/2020/1/e13756/ and https://preprints.jmir.org/preprint/22748

It has to be noted that the app is only used to identify trends and, when deterioration is detected, for example reduction in 6MWT distance walked or change in Borg score, patients are invited to the clinic for further assessment.

6. OBJECTIVES AND OUTCOME MEASURES

The population to be studied is composed of hospital outpatients who have conditions where the 6MWT is routinely used in clinical care, and/or are using the 6APP as an alternative.

The objective is: To evaluate the usefulness of adopting remote, mobile-based 6MWT among hospital outpatients, within the constraints imposed by the SARS-COV2 pandemic.

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To assess whether patients are able and willing to use a smartphone app for the 6MWT	Percentage of participants who perform at least one app-based 6MWT before patient consultation.	At 3, 6, 9 and 12 months after the start of the study.
Secondary Objectives To assess the accuracy of the app-based measurement.	Comparison of walked distance (6MWD) measured by the app versus a trundle wheel reference.	12 months.
To assess whether differences in distance walked according to the app altered management of patients.	Number of clinical investigations and multidisciplinary team discussion triggered by variations in app-based 6MWD.	At 3, 6, 9 and 12 months after the start of the study.

To assess the usability and acceptance of the app.	Standard usability and acceptance questionnaires, semi-structured interviews.	12 months.
To collect raw data from phones' sensors to allow the development of future algorithms for app-guided 6MWT.	Localisation position (GPS), speed, acceleration, step count, gyroscope samples collected during 6MWT.	12 months.
To determine whether the use of the 6MWT reduces time spent and number in hospital visits.	Time spent in hospital attendances and number of hospital visits made during use of the 6MWT compared with previous periods.	12 months.
To compare the use of 6MWT during pandemic with pre-pandemic use.	Total number of 6MWTs performed during 2020 pandemic period compared with pre-pandemic period.	12 months.

7. TRIAL DESIGN

The study consists of 2 parts. The first consists of collecting data about the use of an app for phone-based 6MWT, the "Timed Walk" app, during the outpatient consultations (via phone or in clinic). These data will be used to understand if patients are using the app and if the measurements produced by the app are being used for clinical decisions. The data will be collected on an electronic spreadsheet, using a coding schema, which will be analysed every 3 months for quality assurance and at the end of the study for the final statistics.

The second part of the study will involve a sample of 15 patients who will be sent a trundle wheel and will be invited to perform 10 6MWT using the app and the trundle wheel simultaneously. The data collected in this way will be used to A) assess the accuracy of the app measurement and B) create a public anonymised dataset for the development of future algorithms for the 6MWT. The same group of patients will also be invited to answer a questionnaire about the usability and acceptance of the app and will be interviewed about the same topics.

This study is a collaboration between the Oxford University Hospital (OUH) Trust and Malmo University, Sweden. Malmo University is the main developer and maintainer of the Timed Walk app, and their interest focuses on the accuracy and usability of the app. The OUH Trust is, on the other hand, interested in using the app to remotely monitor their cardiac patients and assessing its impact on the management of those patients. Malmo University will therefore offer engineering work both in terms of the app and data analysis and OUH will recruit patients and collect data.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

All patients under the care of the cardiovascular clinics in Oxford, who are able to walk and use a smartphone.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 years or above.
- Under the care of the cardiovascular clinic at OUH Owning or having access to a smartphone with either Android or iOS
- Being able to use a smartphone app
- Being able to walk

A subgroup of 15 patients will be identified among those who are more willing to use the app to perform the additional measurements with the trundle wheel and to answer the questionnaire. This group should include a balanced representation of age groups and sexes.

8.3. Exclusion Criteria

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

- Long term oxygen therapy
- Cognitive impairments
- Cannot use a smartphone
- Pregnancy
- Not able to complete a 6MW

- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

9. TRIAL PROCEDURES

9.1. Recruitment

Outpatients undergoing follow up in the cardiovascular outpatient clinics in Oxford will be eligible for participation. Some of these patients are already using the app, regardless of the study, for example in the case of the pulmonary hypertension clinic. They will be approached by a member of the clinical team for consideration and recruited during a regular consultation either via phone call or during a visit in the clinic. They will be asked to download the app over the Internet.

9.2. Screening and Eligibility Assessment

Patients will be screened every week according to the scheduled clinic phone calls or visits. A list of candidates who match inclusion and exclusion criteria (except use of smartphone) will be prepared before consultation.

During the consultation, patients will be asked about their access and fluency with smartphones to further verify compliance with the criteria.

The subgroup of 15 patients will be chosen among those using the app depending on the frequency of their use of the app and general willingness to participate in the study.

9.3. Informed Consent

Patients to be recruited will be sent a study information sheet and consent form by post before being recruited. The information sheet will explain how to download and use the app and will introduce the study. Informed consent forms will have to be signed and sent by post (a pre-stamped folder will be prepared). For those patients attending the clinic physically, the information sheet and the informed consent will be given and signed during the day of the clinic.

Signed informed consents will be collected by the research team, either on the day of their appointment or if a tele-medicine appointment, it will be sent back to the research team. If any patient denies consent or withdraws, the reason will be recorded on the spreadsheet.

The subgroup of 15 patients selected for part 2 of the study will be sent an additional leaflet with instructions and further consent will be sought with a different consent form.

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial 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 trial; 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 trial 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 trial. 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. This consent will be obtained at the time of either their clinic appointment, either face to face or by telephone and the consent form returned by post. 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 trial site, and a copy to be filed in medical records.

9.1. Enrolment

All eligible patients will be enrolled from outpatient clinics. They will be recruited to the trial and not randomised .

9.2. Baseline Assessments

There is no baseline assessment of each patient, however, we will request baseline statistics about 6MWT performed during 5 years previous to the pandemic. These data will be pulled from the electronic health record. Only the patient ID and the date of the 6MWT are needed for this analysis.

9.3. Subsequent Visits

Part 1: logging of events

At each consultation, either through phone or face to face visit, the clinician who contacts the patient will log on the spreadsheet the distance walked and a series of study-related events, marked with a code. Coding is needed to simplify and automate later analysis. The following is an example of the structure of the spreadsheet:

Patient hospital number	Date	Event	Comments

Events codes are explained in the following table:

Event	Code	Example comments
The patient accepts to join the study and provides consent.	RECRUIT-ACCEPT	Patient has accepted to join the study.
The patient denies consent and does not join the study.	RECRUIT-DENY	Patient denies consent because of lack of time.
The patient has decided to withdraw from the study.	RECRUIT-WITHDRAW	Patient's conditions have worsened and she cannot walk 6 minutes any more.
The patient declares to have the app installed on a phone he/she can use.	APP-OK	Patient has downloaded the app, everything works as expected.
The patient declares that he/she is having technical issues with the app.	APP-ISSUE	The app crashes when started on iPhone 11.
The patient shares a 6MWT not older than 2 weeks either through email or by telephone.	APP-6MWT	Date: 3/5/2021, distance: 420 m
The patient needs further evaluation because of changed medical conditions. The role of the app-based 6MWT is also coded depending on whether it was irrelevant to the decision, partially involved or fundamental for the decision. The event is logged once per decision (further contacts with the patient resulting from the decision should not include the tag).	NEW-EVAL-NO-6MWT NEW-EVAL-PART-6MWT NEW-EVAL-FULL-6MWT	The patient shows a general deterioration, last 6MWT was below 300m. An MDT is required.
The patient needs a change in the treatment. The role of the app-based 6MWT is specified as above.	NEW-TREAT-NO-6MWT NEW-TREAT-PART-6MWT NEW-TREAT-FULL-6MWT	Medication regime increased because of a lower 6MWD in the last 4 weeks.

Regular clinic 6MWT	CLINIC-6MWT	Date: 23/4/2021, distance: 450m
Additional observations	EXTRA-OBS	Because of reduced risk of corona infection, patient is invited to the clinic.

A list of possible codes with their explanation will be included in a tab of the spreadsheet.

Part 2: accuracy, usability and acceptance assessment

Fifteen patients will be selected based on their ability and engagement and invited to perform 10 additional 6MWT using the app and a trundle wheel simultaneously. An additional informed consent form will be sent to these patients. To those who accept, the research team will send a pre-packaged trundle wheel.

At the end of each of these tests, patients will need to share the raw data collected by the phone during the test through the app's "share" button. When prompted, users will choose to share the data through email and send them to a special address that will be set up for the purpose in Malmo. The app will automatically attach to these emails the data it used to compute the distance including the patient's geographical position (longitude, latitude, altitude, speed) and inertial sensors data (acceleration, inclination, detected steps). Patients will be instructed to also add the distance measured by the trundle wheel to the message for reference.

In order to study the accuracy under different conditions, patients will be instructed to perform 5 tests walking along paths the shape of which is known to obtain the best distance estimation (straight or gently curved paths). Patients will also perform 5 more tests walking over paths that may be more "challenging" for the app, for example those including narrow curves, U-turns or in confined spaces.

If less than 15 trundle wheels are purchased for the study, patients will be asked to send the meters back to the clinical centre once the 10 tests are completed. Trundle wheels will be then cleaned and disinfected and sent to another batch of patients until covering 15 subjects.

Towards the end of the study, patients of the subgroup will be sent an online questionnaire related to usability and acceptance to be filled in electronically. The questionnaire will be based on the validated and widely used uMARS questionnaire[12] and the Mobile Health Technology Acceptance Model (MoHTAM) questionnaire[13].

Five to ten patients will be selected for an additional phone-based short interview. Notes from the interview will be taken and voice will be recorded if technically possible. The interview will aim at

[12] https://mhealth.jmir.org/2016/2/e72/

[13] https://ieeexplore.ieee.org/abstract/document/6149947

understanding causes and motivations for use or non-use of the app, based on a technology acceptance model. Patients will have to sign an authorization to allow the registration of their voice. This will be sent together with the informed consent.

9.4. Sample Handling

No samples will be taken.

9.5. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with trial procedures
- Participant decision

Participants may choose to stop study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. Patients are allowed to withdraw at any time. In case of withdrawal, they will communicate it to the staff who will log the withdrawal on the spreadsheet together with the reason. The patients will remain under regular active follow up

1) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
2) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

9.6. Definition of End of Trial

The study ends 12 months after the first patient has been recruited or when restrictions to clinical practice due to the pandemic are lifted.

10. TRIAL INTERVENTIONS

Not applicable

11. 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 as per the below.

11.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
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 labelling. 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.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

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.

11.2. Assessment results outside of normal parameters as AEs and SAEs

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.

Issues with the device will also be logged on the study spreadsheet using the APP-ISSUE code.

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 the study. A participant may also voluntarily withdraw from the study 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.

11.3. Assessment of Causality

The relationship of each adverse event to the trial must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

11.4. Procedures for Reporting Adverse Events

All AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be reported on the trial CRF,

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial device and action taken. Follow-up information should be provided as necessary.

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

Non-serious AEs considered related to the trial as judged by a medically qualified investigator or the Sponsor will be followed up until the event is stable.

11.5. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.6. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

12. STATISTICS

12.1. Description of Statistical Methods

The analysis of the data involves reviewing the spreadsheet. The use of the labels will simplify analysis and will avoid manual coding. The R programming environment will be used to compute statistics.

To assess whether patients are able and willing to use a smartphone app for the 6MWT.

For each recruited patient, we will compute the number of app-based 6MWT results available since they confirmed that they have downloaded the app. From this number, we will compute a histogram of the number of available app-based 6MWT per patient and the percentage of participants who perform at least one app-based 6MWT prior to every consultation.

To assess the accuracy of the app-based measurement.

We will compare the walked distance measured by the app with the distance measured by the trundle wheel for those tests that provide both information. We will compute descriptive statistics (mean, standard deviation, percentiles) of the difference and BlandAltman plots.

To assess whether differences in distance walked according to the app altered management of patients.

We will use the codes related to clinical evaluations to compute descriptive statistics about the frequency of those evaluations and about how many of them were triggered by observed changes of the 6MWD.

To assess the usability and acceptance of the app.

We will compute descriptive statistics of the results of the usability and acceptance questionnaires. We will use thematic content analysis to analyse the interview transcripts.

To collect raw data from phones' sensors to allow the development of future algorithms for app-guided 6MWT.

We will also use the sensors data sent from patients involved in part 2 of the study to identify strategies to improve the algorithm that computes the distance. The availability of this type of data would be unique and would open interesting research in computer science and biomedical engineering. The University of Malmo is planning to experiment signal processing (Kalman filters, FIR filters) and machine learning (LSTM RNN) techniques to improve the accuracy of the current GPS-based algorithm and to explore the possibility to develop an indoor version of the algorithm based purely on the inertial sensors (acceleration).

To determine whether the use of the 6MWT reduces time spent and number in hospital visits.

We will estimate the time spent in hospital attendances and the number of hospital visits made during the study period and compare it with previous 5 years.

Compare the use of 6MWT during pandemic with standard care.

We will compute statistics regarding the number of 6MWT available per patient over the last 5 years and compare them with the number of available 6MWT results within the study period. This will help identify the difference between the number of 6MWT per patient per year before the pandemic (standard 6MWT in clinic) and after the pandemic (using the app).

12.2. Sample Size Estimation

For part 1, we will not use sampling as we aim to involve all patients in the cardiovascular clinics who require a 6MWT and are able to use the app.

With regards to part 2, our 15 patients cohort is in agreement with typical usability studies.

12.3. Analysis Populations

All participants.

13. DATA MANAGEMENT

13.1. Data Recording and Record Keeping

Part1

The data will be collected using an electronic spreadsheet shared by the team at OUH. Patients will be asked about their recent app-based 6MWTs during visits or phone calls and will be invited to share the log of their app-based 6MWTs by email or telephone with the clinician. If patients have technical problems and need assistance, they can contact the team in Sweden, who are responsible for the development of the Timed Walk app. In this case, the patient can disclose their identity to the team in Sweden if they wish.

Every 3 months, the spreadsheet will be anonymised by substituting the patient hospital number with an internal ID and sent to Malmo University for analysis in an encrypted email.

Part 2

Results of the additional 6MWTs performed by the subgroup of 15 patients will be shared by email with the team in Malmo. We will seek explicit consent to share these data, both as identifiable information for the researchers in Sweden and in an anonymous format publicly.

In order to anonymise the data before publication, the following strategy will be used:

- Email addresses will be removed and an internal patient ID will be used to group tests belonging to the same user.
- Timestamps will be formatted only in relation to the start of the test.
- Location data will be anonymised using a random offset on both longitude and latitude (resulting in the trace to keep its original shape, but the position to be placed in a random place).
- Any unique identifier of the phone will be removed, but the make and model may be kept in order to compare different phones characteristics.

Electronic questionnaires for usability and acceptance will be set up using Microsoft Forms. Malmo University has an agreement with Microsoft to use the product for research purposes and guarantees

that data is protected according to the GDPR. The questionnaire will not require personal information to be collected and will be deleted after analysis.

Audio recording of the interviews will be collected by OUH and sent electronically to Malmo University for analysis. These files will not be linked to the identity of the patient, they will be transcribed and deleted immediately after. All files containing patients' anonymised data exchanged between Malmo and OUH will be encrypted using a password which will be communicated verbally during a phone call.

Paper forms will be kept by the Principal Investigator at OUH.

Identifiable patients data will be kept by OUH for up to 10 years after study completion or until ethical approval terminates, whichever is sooner.

13.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

13.2. 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

Malmo University will access data collected in part 1 of the study only in an anonymised format, while data collected in phase 2 will be sent using patients' emails, and therefore will be identifiable. Direct contact with patients may be allowed, with patients consent, for solving technical issues, via email or phone.

After anonymisation, data collected in phase 2 will be made public through websites used for the sharing of research data like Physionet. Anonymised data will be made available with a permissive license like Creative Commons BY-SA 4.0[14].

13.3. Data Recording and Record Keeping

[14] https://creativecommons.org/licenses/by-sa/4.0/

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

Spreadsheets with logs of part 1 will be stored on computers at the John Radcliffe Hospital, in offices normally locked when not in use and on computers that require authorised personnel login to be used.

Before being sent to Malmo, spreadsheets will be pseudonymised with a study-specific participant and encrypted using a password shared verbally during a call.

Data collected during the 6MWT (acceleration, distance, location) in part 2 will be sent by participants, using their emails, to a specific email account setup by Malmo University and accessible only by researchers involved in the study. The files in attachment will be anonymised and made public.

Data sent to Malmo in both parts 1 and 2 will be kept on Malmo's researcher's computers. These are encrypted and only accessible by authorised personnel. The data will be kept by Malmo until the publication of the results and no longer than 5 years after the end of the project.

Data	**Identifiable?**		**Transmission**	**Storage**		**Retention**	
	OUH	Malmo		OUH	Malmo	OUH	Malmo
Part 1 logs	Yes	Study IDs	Encrypted emails from OUH to Malmo	Computers in locked rooms	Encrypted computers	10 years	Until publication or 5 years
Part 2 6MWT raw data	NA	Temporarily, until anonymised	Email from participants to Malmo	NA	Encrypted computers	NA	Forever after anonymization
Part 2 interviews audio files	Yes	Study IDs	Encrypted emails from OUH to Malmo	Computers in locked rooms	Encrypted computers	10 years	Until publication or 5 years
Part 2 questionnaires	NA	No	Participants fill web forms	NA	Microsoft forms managed by Malmo	NA	Until publication or 5 years

14. QUALITY ASSURANCE PROCEDURES

Data produced on the electronic health record will be analysed every 3 months to assess their quality by the research team. Assessment will focus on the presence of the keywords, their correct spelling and the consistency of the data.

Upon suspicion of the app not being able to produce accurate data, or of misuse of the app, the clinical team may request patients to share the details of a test. These data can then be used on a web tool to visualise the path walked, altitude and statistics that may help the clinician to identify the problem. The web tool retains the data locally in the browser and does not share them with any server or third party over the Internet.

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

14.1. Risk assessment

A risk assessment has not been undertaken.

14.2. Monitoring

Monitoring will not be undertaken for this study.

14.3. Trial committees

Not applicable

14.4. Safety Monitoring Committee

Not applicable

15. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

16. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. 6MWT

6MWT 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 require medical attention. The participants undergoing the app-based 6MWT will be provided with a checklist for them to assess themselves with, and would not undertake a test if they fail this.

17.2. Sars-Cov-2

The study will follow the general recommendations of the NHS, particularly the advice from Healthwatch to consider avoiding asking patients to attend physical outpatient appointments where a clinically-appropriate and accessible alternative exists. In this regard, the study aims to significantly lower the number of patients needing visits to the PH clinic and in itself does not require patients to do so.

17.3. Declaration of Helsinki

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

17.4. Guidelines for Good Clinical Practice

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

17.5. Approvals

Following Sponsor approval the protocol, informed consent form, participant information will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), 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.

17.6. Other Ethical Considerations

Not applicable

17.7. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.8. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), . All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

17.9. Expenses and Benefits

Not applicable

18. FINANCE AND INSURANCE

18.1. Funding

The study will be partially funded by: the Swedish Knowledge Foundation, KK stiftelsen, through the Internet of Things and People research profile. Their contribution will support the involvement of the research team at Malmo University.

18.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If any patient is 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.

18.3. Contractual arrangements

A collaboration or data sharing agreement will be required between the trust and The University in Sweden.

19. PUBLICATION POLICY

The research team will be involved in editing and reviewing manuscripts, abstracts, press releases and any other publications arising from the study. All involved researchers and clinical staff will be invited to co-author the papers.

Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

21. ARCHIVING

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

[1] https://jamanetwork.com/journals/jama/fullarticle/2768086

[2] https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html

[3] https://mhealth.jmir.org/2020/7/e19417/

[4] https://clinowl.com/the-future-is-now-a-call-for-action-for-cardiac-telerehabilitation-in-the-covid-19-pandemic-from-the-secondary-prevention-and-rehabilitation-section-of-the-european-association-of-preventive-cardiolo/

[5] https://digital.nhs.uk/coronavirus/nhs-digital-tech-analytics

[6]https://www.bmj.com/content/364/bmj.l84.long

[7] https://www.jmir.org/2020/8/e21609/

[8] https://pubmed.ncbi.nlm.nih.gov/12890299/

[9] https://www.ahajournals.org/doi/full/10.1161/circulationaha.112.105890

[10] https://www.atsjournals.org/doi/full/10.1164/rccm.201203-0480oc

[11] https://mhealth.jmir.org/2020/1/e13756/ and https://preprints.jmir.org/preprint/22748

[12] https://mhealth.jmir.org/2016/2/e72/

[13] https://ieeexplore.ieee.org/abstract/document/6149947

[14] https://creativecommons.org/licenses/by-sa/4.0/

[15] https://creativecommons.org/licenses/by-sa/4.0/

23. APPENDIX B: SCHEDULE OF PROCEDURES

Procedures	**Visit timing Day 1**	**Phase 1**	**Phase 2**	**End of study**
Informed consent	X			
6MWT using app		X	X	
6MWT using app + raw data			X	
Questionnaire				X
Interview				X

24. APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, or HRA (where required).