

**Diagnostic accuracy of WEARable TECHnology single-lead ECG in detecting cardiac arrhythmias: WEAR-TECH ECG**

**Short title: WEAR-TECH ECG**

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**Potential Conflicts of Interest:** None

**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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<b>Clinical Trials Unit</b>	N/A
<b>Committees</b>	N/A

## 2. LAY SUMMARY

Over 2 million people in the UK suffer from cardiac arrhythmias (heart rhythm problems). The most common type of arrhythmia is atrial fibrillation (AF), the heart beats irregularly and usually rapidly. Other arrhythmias may cause the heart to beat slower or faster than normal. Heart rhythm problems can range from being an inconvenience to a serious health problem. Although patients may complain of palpitations, dizziness, chest discomfort or even shortness of breath, many don't experience any symptoms.

An electrocardiogram (ECG) uses sensors placed on the skin to record the heart's electrical activity. A 12-lead ECG uses 10 sensors (one in each limb and 6 on the chest) and is the gold-standard (best available test) to detect any abnormal heart rhythm disturbances. However, some arrhythmias, such as AF, may be short and unpredictable, and may not be captured when a 12-lead ECG is undertaken. Therefore, a small (non-intrusive) device that continuously tracks your heartbeat and record a 1-lead ECG could make the diagnosis of cardiac arrhythmias much quicker and easier.

Accessories such as watches, bands or rings — referred to as wearable devices — have extremely good sensors that measure pulse rate by detecting small changes in skin colour during each heartbeat. More advanced wearable devices, such as the Apple Watch and the Skylab CART-I ring, can also perform a 1-lead ECG which is sent directly to your doctor.

These commercially available wearable devices do not go through the same rigorous testing as hospital equipment. Robust tests are essential before they are used in patients as an 'abnormal' finding may not represent a true heart rhythm problem but may lead to significant anxiety and trigger unnecessary tests or treatments, which can be harmful.

The purpose of this study is to test how well two commonly used innovative wearable devices — the SkyLabs CART-I ring and the Apple Watch — detect different cardiac arrhythmias. We plan to recruit 500 patients attending Cardiology Departments in several hospitals in the UK and will have a 12-lead ECG as part of their care. Participants will first have a simultaneous 12-lead ECG with a 1-lead ECG from one of the two wearable devices. This will be followed by a second (extra) 12-lead ECG with a 1-lead ECG from the remaining wearable device. Therefore, in addition to their usual 12-lead ECG, participants will have one extra 12-lead ECG and two extra 1-lead ECGs. No extra follow-up visits are required. At the end of the study, we will compare interpretation by heart rhythm specialists of the 1-lead ECGs recorded by the wearable devices and the 12-lead ECG.

### 3. SYNOPSIS

Trial Title	<b>Diagnostic accuracy of <u>WEAR</u>able <u>TECH</u>nology single-lead <u>ECG</u> in detecting cardiac arrhythmias: WEAR-TECH ECG</b>		
Internal ref. no. (or short title)	<b>WEAR-TECH ECG</b>		
Trial registration	Intended register – Clinicaltrials.gov		
Sponsor	Oxford University Hospitals NHS Foundation Trust		
Funder	Abbott Educational Grant/CRM research Hub fund/ SkyLabs		
Clinical Phase	Observational study		
Trial Design	Prospective multicenter observational study.		
Trial Participants	Male and female participants who are 18 or older.		
Sample Size	500 participants		
Planned Trial Period	12 months		
Planned Recruitment period	9 months		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Compare the accuracy of physician rhythm interpretation of 1-lead ECG generated by SkyLabs CART-I ring and Apple Watch versus 12-lead ECG (gold-standard)	Sensitivity, specificity, positive and negative predictive value of the SkyLabs CART-I ring and Apple Watch 1-lead ECGs interpretation for different cardiac arrhythmias compared with a 12-lead ECG (gold-standard)	At the time of ECG acquisition
Secondary	1. Compare the accuracy of automatic AF detection of the SkyLabs CART-I Ring and Apple Watch compared to a cardiologist interpretation of a 12-lead ECG (gold-standard)	1. Sensitivity, specificity, positive and negative predictive value of the AF detection algorithm of the Skylab CART-I ring and Apple Watch compared to a 12-lead ECG (gold-standard)	At the time of ECG acquisition

	<p>2. Compare the accuracy of ECG interval measurement for the SkyLabs CART-I Ring and Apple Watch to a 12-lead ECG (gold-standard)</p> <p>3. Compare the accuracy of heart rate detection of the SkyLabs CART-I ring and Apple Watch 1-lead ECG to a 30-second 12-lead ECG</p> <p>4. Compare the accuracy of rhythm interpretation of SkyLabs CART-I ring 1-lead ECG to combined plethosmography (PPG) signal and 1-lead ECG.</p>	<p>2. Level of agreement of measured interval duration between the SkyLabs CART-I ring, Apple Watch 1-lead ECG and a 12-lead ECG.</p> <p>3. Correlation coefficient between the mean heart rate from simultaneous single lead and 12 lead ECG acquisitions</p> <p>4. Compare sensitivity, specificity, positive and negative predictive value of the Skylab CART-I ring if a PPG signal is added</p>	
Intervention(s)	<p>Wearable devices</p> <ul style="list-style-type: none"> <li>• SkyLabs CART-I Ring</li> <li>• Apple Watch Series 6</li> </ul>		
Comparator	Standard 12-lead Electrocardiogram		

#### 4. ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
AR	Adverse Reaction
AT	Atrial Tachycardia
CI	Chief Investigator
CRF	Case Report Form
ECG	Electrocardiogram
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICM	Implanted Cardiac Monitor
ICF	Informed Consent Form
IRB	Independent Review Board
NHS	National Health Service
OUHFT	Oxford University Hospital NHS Foundation Trust
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PPG	Photoplethysmography
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event

## 5. BACKGROUND AND RATIONALE

Clinical significance: Cardiac arrhythmias are associated with morbidity and economic cost. Rhythm abnormalities increase in frequency with age and approximately 5% of those aged between 65-73 years will have a cardiac arrhythmia but many patients remain unaware. The most prevalent arrhythmias are atrial fibrillation (AF), bradycardia and conduction disorders. A 12-lead electrocardiogram (ECG) is the gold-standard test to identify heart rhythm disorders.

Atrial fibrillation (AF) affects millions of people worldwide; its prevalence is projected to almost double in the next decades.<sup>(1-3)</sup> AF is associated with significant morbidity and mortality.<sup>(4)</sup> AF results in a 5-fold increased risk of ischaemic stroke<sup>(5)</sup>, accounting for 20-25% of all strokes, which are generally more severe and disabling, more likely to recur and associated with higher-healthcare costs.<sup>(1)</sup>

Symptoms alone are unreliable in identifying the presence or absence of AF. Early diagnosis allows institution of therapies, such as oral anticoagulation and catheter ablation, which have the potential to reduce arrhythmia burden, improve quality of life and reduce the risk of cardioembolic strokes.<sup>(6, 7)</sup> Indeed, asymptomatic AF is associated with higher mortality than symptomatic AF.<sup>(8)</sup> As the prevalence of AF increases, opportunistic screening with pulse palpation followed by a 12-lead ECG is cost-effective and recommend in patients over 65 years of age.<sup>(1)</sup>

Mobile Health Technology: In the last decade, there has been an exponential growth in mobile health technologies (mHealth) with more than 400 brands and models of wearable activity monitors, including smartwatches, smartbands, rings and vests.<sup>(9, 10)</sup> Initially designed to track activity and heart rate, many devices now notify users of bradycardia, tachycardia and AF episodes. Most devices use very sensitive optical sensors and photoplethysmography (PPG) to analyse changes in skin colour, light intensity, and absorption to measure heart rate.<sup>(11)</sup> In addition, advanced proprietary algorithms assess heart rate variability to diagnose AF. PPG technology has several inherent limitations that increase the number of false positive detections of AF, such as noise and artefact from changes in pressure, motion, skin tone and ambient light.<sup>(12)</sup> More recently, an ECG sensor unit incorporated into smartwatches and rings generates a standard lead I (left arm to right arm vector) ECG which is transmitted to a smartphone app and can be exported in PDF format for further review by physicians. Wearable devices able to record 1-lead ECG can potentially identify other arrhythmias in addition to AF.

The European Society of Cardiology (ESC) recognises the pitfalls of wearable technologies in their recent guidance and recommends caution when interpreting published accuracy data from wearable devices. The guidelines state that AF diagnosis should not be based on PPG signals but can be diagnosed by physician interpretation of a single-lead ECG from a mobile or wearable device.<sup>(1)</sup> Lastly, it highlights the need for robust validation studies prior to adopting wearable technology and 1-lead ECGs in routine clinical practice.

Undoubtedly, mHealth technology has many potential applications in healthcare, from monitoring cardiovascular risk factors and improving engagement and compliance to screening and monitoring of cardiac arrhythmias. However, the ubiquitous use of mHealth technologies— many without rigorous validation studies — will generate vast amounts of biometric data of uncertain quality and significance and will have several implications for both patients and physicians and for health economics. For patients, an ‘abnormal’ hearth rhythm detection may create significant anxiety and prompt them to take

medications which may not be indicated and potentially cause harm. For physicians, this will likely translate in a steep increase in GP and Cardiology clinic referrals to review mHealth data and perform further investigations, with significant associated healthcare costs.

Devices being investigated:

Apple Watch Series 6: The Apple Watch collects PPG waveforms to measure heart rate during periods of minimal arm motion and creates a tachogram (heart rate over time). If the tachogram identifies an irregular heart rate it will trigger further tachograms to confirm if the irregular heart rate persists. An AF notification will be sent to its user if the next 4 confirmatory tachograms also detect an irregular pulse (5 consecutive tachograms with irregular heart rate in total).<sup>(13, 14)</sup> The diagnostic accuracy of AF detection was investigated in the Apple Heart Study which recruited almost 420,000 participants without prior AF diagnosis. The positive predictive value of an individual tachogram in detecting atrial fibrillation was 0.71 (95% CI: 0.69-0.74) but increased to 0.84 (95% CI: 0.69-0.74) for AF notification which combined 5 tachograms.<sup>(14)</sup> The single-lead ECG performance was not evaluated in this study.

The Apple Watch Series 6 can generate a high quality 30-second single-lead ECG by placing a finger on the metal crown. Analysis of this recording has 3 possible outcomes: “sinus rhythm”, “atrial fibrillation” and “inconclusive”. Each 30 second recording can be exported as a PDF for further analysis. In a small study of 50 patients following cardiac surgery, the diagnostic yield of the Apple Watch 1-lead PDF interpretation in detecting AF had a 96% sensitivity and 100% specificity.<sup>(15)</sup> Data on the diagnostic accuracy of other arrhythmias is limited.

SkyLabs CART-I Ring: The CART-I ring was designed to collect PPG signals from the proximal finger. The potential benefits of this strategy include increased user long-term compliance and, as the fingers are more vascular than the wrist, the PPG signal may have a better signal-to-noise ratio and therefore improve diagnostic accuracy. Its AF detection validation study included 100 participants undergoing elective direct current cardioversion and showed a 99% sensitivity and a positive predictive value of 94.3% for AF episodes longer than 20 seconds.<sup>(16)</sup>

By placing a finger in the metal portion of the ring, a high quality 30-second single-lead ECG and PPG signal is created in its smartphone app. The automatic analysis will classify the recording as sinus rhythm, atrial fibrillation or uninterpretable.

Rationale: Wearable technologies have the potential to improve the management of patients with atrial fibrillation and other cardiac arrhythmias. Their utility is dependent on having an accurate, reproducible 1-Lead ECG and very sensitive (and reasonably specific) detection of cardiac arrhythmias, including atrial fibrillation. This observational study will investigate the accuracy of two contrasting wearable devices: the Apple Watch Series 6 and the SkyLabs CART-I ring.



**Figure 1.** SkyLabs CART-I ring and Apple Watch Series 6

## 6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
<b>Primary Objective</b>  Compare the accuracy of physician rhythm interpretation of 1-lead ECG generated by SkyLabs CART-I ring and Apple Watch versus 12-lead ECG (gold-standard)	Sensitivity, specificity, positive and negative predictive value of the SkyLabs CART-I ring and Apple Watch 1-lead ECGs interpretation for different cardiac arrhythmias compared with a 12-lead ECG (gold-standard)	At the time of ECG acquisition
<b>Secondary Objective</b>  1. Compare the accuracy of automatic AF detection of the SkyLabs CART-I Ring and Apple Watch versus a cardiologist interpretation of a 12-lead ECG (gold-standard)  2. Compare the accuracy of ECG interval measurement for the SkyLabs CART-I Ring and Apple Watch to a 12-lead ECG (gold-standard)  3. Compare the accuracy of heart rate detection of the SkyLabs CART-I ring and Apple Watch 1-lead ECG to a 30-second 12-lead ECG  4. Compare the accuracy of rhythm interpretation of SkyLabs CART-I ring 1-lead ECG to combined (plethosmography) PPG signal and 1-lead ECG.	1. Sensitivity, specificity, positive and negative predictive value of the AF detection algorithm of the Skylab CART-I ring and Apple Watch compared to a 12-lead ECG (gold-standard)  2. Level of agreement of measured interval duration between the SkyLabs CART-I ring, Apple Watch 1-lead ECG and a 12-lead ECG.  3. Correlation coefficient between the mean heart rate from simultaneous single lead and 12 lead ECG acquisitions  4. Compare sensitivity, specificity, positive and negative predictive value of the Skylab CART-I ring if a PPG signal is added	At the time of ECG acquisition

## 7. STUDY DESIGN

This study is a prospective, multicentre, observational study comparing rhythm and heart rate detection of two novel wearable devices — the Skylab CART-I ring and Apple Watch Series 6 — to a 12-lead ECG (gold-standard) for different cardiac rhythm disorders. We will recruit 500 participants attending Cardiology outpatient appointments, procedures or investigations (including the catheterisation laboratory) and inpatients in the cardiology and cardiothoracic wards in three hospitals across the UK. All patients will be due a 12-lead ECG as part of their standard of care.

If participants agree to take part in this study, the research team will provide them with instructions and will demonstrate how to use the wearable devices. Participants will then be asked to perform a simultaneous 30-seconds 12-lead ECG and 1-lead ECG for each wearable device (Skylab CART-I ring or Apple Watch). The order of recordings will be randomly assigned. If the first recording is uninterpretable due to artefact, a second recording will be allowed.

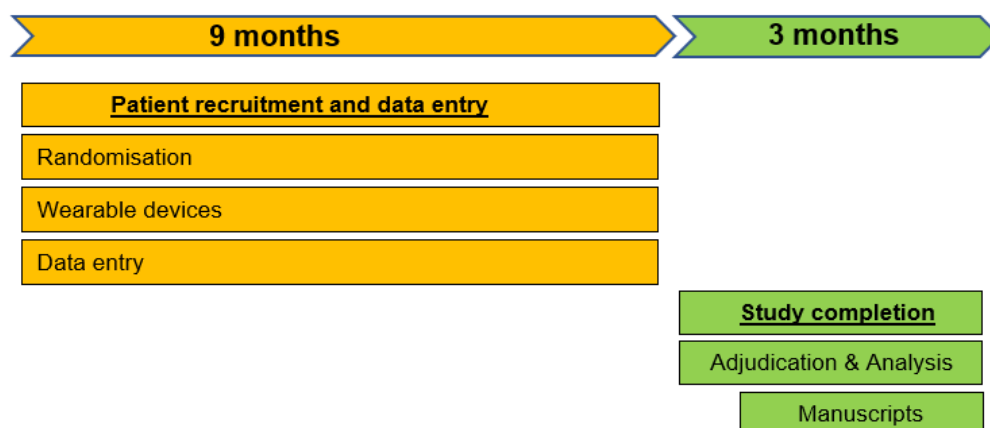
The SkyLabs CART-I Ring generates a 30-second 1-lead ECG by placing the participants finger on the rings' metal casing. Similarly, the Apple Watch 1-lead ECG requires the participant to place his/her finger on the metal crown. The 1-lead ECGs will be displayed and saved in the CART-I ring app and Apple Health app of a research iPhone SE, respectively. The smartphone apps will not contain any identifiable data and participants will only be identified by the time stamp of their recordings. The clocks of the Apple Watch, SkyLabs CART-I ring and ECG machine will be synchronised. The 12-lead ECG will also contain a time stamp and the study ID number (site code and participant number), it will then be recorded by using the iPhone SE camera and exported in PDF format for subsequent analysis. The 12-lead ECGs time stamp will also be documented in the CRF. The 12-lead ECGs will be added to the participants medical notes and available to the clinical team. The 1-lead ECGs from the wearable devices will only be available to the research team.

This study does not involve any follow-up visits. All the 1-lead ECGs stored in the CART-I Ring app and Apple Health app will be exported in PDF format. All ECGs (12-lead ECGs and 1-lead ECGs from the wearable devices) will be analysed by two Cardiologists (based at Oxford University Hospital NHS Foundation Trust/OUHFT) blinded to patient's data. Any disagreement will be resolved by a third Cardiologist (CI of the study).

### 7.1 Study Timeline

This 12-month multicentre, prospective, observational study is to be conducted in 2 phases:

1. Patient recruitment, single-lead and 12-lead ECG recordings and data entry (9 months): Period recruitment will take place and ECG recording with wearable devices
2. Completion of data entry and analysis (3 months): to finalise the data entry, adjudicate all ECGs and perform the statistical analysis. A final wrap up meeting will be convened at the end of the study with all key investigative staff contributing to the final report and manuscript.



## 7.2 Study Risks

This study only involves performing a 12-lead ECG, which is standard of care, and two additional 30-second 1-lead ECG recordings with a SkyLabs CART-I ring and an Apple Watch.

There are no known contraindications for the SkyLabs CART-I ring or Apple Watch and potential adverse events only include skin reactions to the metal or silicone wrist band. The devices are only in place long enough to obtain two 30-second recordings, so this risk is negligible.

A 12-lead ECG is safe and painless. Removing the sensors from your skin may cause some slight discomfort and some people may develop a mild rash which usually resolves quickly.

To reduce the risk of infection, doctors and research nurses will wear appropriate personal protective equipment according to local infection control guidelines. Both wearable devices will be thoroughly cleaned with a Clinell® wipes before and after each use. A minimum of 10 minutes will elapse before the device is used in a different participant.

## 7.3 Study Benefits

The main benefit from this study will be for future patients. However, participants may get direct benefit from the study if the second (extra) 12-lead ECG records any heart rhythm abnormality that was not seen during the first 12-lead ECG. Both 12-lead ECGs (usual care and extra) will be added to the medical notes and available to the clinical team.

We anticipate that with widespread use of wearable devices with optical sensors and electrodes capable of recording and analysing PPG signals and 1-lead ECGs, will significantly increase the number of patients seeking expert medical opinion due to 'abnormal findings' by their device. It is therefore important to validate and understand the limitations of arrhythmia detection from commonly used wearable devices. Moreover, the new ESC guidelines on Management of Atrial Fibrillation recommended 1-lead ECG validation studies prior to widespread adoption.<sup>(1)</sup>

## 8. PARTICIPANT IDENTIFICATION

### 8.1. Trial Participants

This trial is designed to include male and female adults attending cardiology outpatient clinics, outpatient investigations, catheterisation lab day unit or inpatients at a Heart Centre, having a routine 12-lead ECG.

## **8.2. Inclusion Criteria**

The participant must satisfy the following conditions:

- Participant is willing and able to give informed consent for participation in the trial.
- Male or female's aged 18 years or above.
- Indication for 12-lead ECG.

## **8.3. Exclusion Criteria**

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

- Unable to comply with instructions.
- Tattoos in the wrists or fingers where the device will be placed.
- Severe skin allergy to silicone (Apple Watch wrist band) or nickel allergies.

## **8.4. Recruitment**

The vast majority of patients attending the hospital for an outpatient cardiology clinic or procedure will have a routine 12-lead ECG performed as part of their standard care. Patients on the cardiology ward have routine daily 12-lead ECGs.

A participant information sheet will be given by the research team to patients attending a Heart Centre for outpatient appointments, investigation, catheterisation lab day unit, and to inpatient in a cardiology ward. Members to the research team are also members of the clinical care team. If the participants meet the inclusion criteria, they will be invited to participate in this study. An invitation letter may be sent in advance to patients attending the hospital for cardiac procedures.

## **8.5. Informed Consent**

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

A written version of the Participant Information Sheet and Informed Consent form 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.

Participants will be allowed until the end of their appointment and/or clinic to consider the information provided and the opportunity to question the investigator or other independent parties if they so wish. Patients admitted in the Cardiology/Cardiothoracic Wards will have until the end of their admission to decide if they want to participate. 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 and a copy will be filed in the patients' medical note. The original signed form will be retained at the trial site. Screening, Eligibility and Baseline Assessment

After agreeing to participate and signing the consent form the baseline assessment will include demographics information and medical history.

## **8.6 Randomisation**

The order in which the wearable devices being investigated will be randomly assigned in a 1:1 fashion. There are two investigation arms:

- Group 1: SkyLabs CART-I ring and then Apple Watch
- Group 2: Apple Watch and then SkyLabs CART-I ring

A simple randomisation will be performed by using the Robust Randomisation app (RRapp, developed by Icahn School of Medicine Mount Sinai) which will assign each participant to either Group 1 or Group 2.

## **8.7 Blinding**

Investigators and subjects will not be blinded to investigation arms during data collection. At the end of the follow-up, all the anonymised ECGs (12-lead and 1-lead from wearables), from all sites, will be adjudicated by two cardiologists blinded to patients' data.

## **8.9. Wearable Devices**

The Apple Watch Series 6 will be worn snugly on the left or right wrist according to patient's preference. The participants will rest their arm comfortably on their lap. The investigator will open the ECG app on the Apple Watch. With the hand opposite to the watch the participant will be asked to hold their finger on the digital crown to generate a 30-second 1-lead ECG. During the same 30 seconds a simultaneous 12-lead ECG recording will be performed. The Apple Watch recording will be stored in the research iPhone SE Health app (with no identifiable data), uploaded to the iCloud and will be exported in PDF format for analysis.

The SkyLabs CART-I ring will be worn on the same hand as the Apple Watch, preferably in the ring finger. Similarly, a simultaneous 30-seconds recording with a 12-lead ECG will be performed with the participant resting his/her hand comfortably. A 30-second 1-lead ECG can be generated by placing a finger from the opposite hand on the metal casing and selecting the 'measure' tab in the CART-I ring app. The SkyLabs recording will be stored in the CART-I Ring app and uploaded to the SkyLabs CRM account (with no identifiable participant's data) and will be exported at a later date in PDF format for analysis.

If the first recording of any of the wearable devices has artefacts a second recording will be allowed, and the first recording discarded. The order of the devices will be randomly selected at the time of the baseline visit.

By enrolling in the study, participants will likely extend their hospital visit by 20-30 minutes to complete all study procedures. A minimum of 10 minutes will elapse before the device is used by a different participant.

## **8.8 Subsequent Visits**

This study does not include any planned subsequent visits or collection of follow-up data. Both 12-lead ECGs will be added to the clinical notes and available to the clinical team at the time of their appointment. However, if we pick-up any abnormal rhythms which were not previously known and not detected by the clinical team at the time of their appointment, we will inform the participants' clinical team and their GP. They will then decide if any action and/or follow-up is needed.

## **8.10 Early Discontinuation/Withdrawal of Participants**

This study only involves recording a 1-lead ECG from two wearable devices and does not include any follow-up visits. During the course of the study, which is anticipated to be only 20 minutes, a participant may choose to withdraw early from the study 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 (severe skin reaction to the silicone band of the Apple Watch or metal casing of the SkyLabs CART-I ring.
- Inability to comply with trial procedures
- Participant decision

Participants may withdraw their consent, meaning that they wish to withdraw from the study completely. Their data will not be analysed, and another participant will be recruited.

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:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements

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.

## 8.12 Definition of end of study

The end of the study will be 3 months following the date of the last 12-lead ECG and 1-lead ECG. During this period, the investigators will finish adjudication and data analysis.

## 9 SAFETY REPORTING

### 9.1 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.

### 9.2 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.

## 10 STATISTICS AND ANALYSIS

Descriptive statistics are reported as count and percentage for categorical variables and mean and standard deviation for continuous variables.

Adjudication of all anonymised ECGs (12-lead ECGs, 1-lead ECGs from Apple Watch and SkyLabs CART-I ring) will be performed by two Cardiologists blinded to participants' data. Any disagreements will be decided by a third Cardiologist (CI of the study). Following adjudication, the sensitivity, specificity, positive negative predictive values will be calculated for different cardiac rhythm disorders. The level agreement between adjudicators will be calculated using the Cohen's kappa.

ECG waveform analysis and intervals (PR, QRS, QT and RR) will be measured by using callipers to the nearest 0.25 mm. The first three consecutive waveforms will be analysed in each ECG and the intervals averaged. In the 12-lead ECG, it will be to the physician's discretion which lead is chosen to measure the

intervals. To investigate the level of agreement, correlation coefficient and Band-Altman plots will be generated.

## **11 DATA MANAGEMENT**

### **11.1 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 study-specific documents, other than the signed consent, the participant will be referred to by the study ID number, not by name.

### **11.2 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.

### **11.3 Data Recording and Record Keeping**

The participants will be identified by a unique study specific ID number (includes the site ID code and participant number) which will be assigned following consent. The study ID number (will be used in both hard-copies and electronic documents (PDF of 12-lead ECGs, excel spreadsheets for analysis and adjudication). The hard copies (CRF and consent forms) of data will be securely kept in the Research Fellows' Office at each site. The key to the study ID number for each site will be maintained on a single document will be kept in a separate folder in the PI's office.

The participants name and any other identifying detail will NOT be included in any trial data electronic file (PDF of 12-lead ECGs, 1-lead ECGs, excel spreadsheets for adjudication and analysis).

Each individual site will have an Apple Watch and SkyLabs CART-I rings (five different sizes) which will be paired with a research iPhone SE. No identifiable data will be recorded in the iPhone SE. Apple Watch 1-lead ECGs are transmitted to the research iPhone health app with no patient identifiable information. The time stamp on each ECG will be documented on the CRF and used to identify study participants. All the data pertaining to the Apple Watch will be stored in the research iPhone SE and uploaded to the iCloud so that it can be assessed remotely for adjudication. All 3 research iPhones (one per site) will be registered to a research account ([crm.tb@gmail.com](mailto:crm.tb@gmail.com)) and thus all uploads to the iCloud can be accessed centrally by the investigators in OUHFT. Individual upload can be identified by the serial number for the CART-I rings and by the name of the Apple Watch (different for each site) and thus if there are two recordings with the same time stamp we can easily identify the site and match it to the matching 12-lead ECG.

The SkyLabs CART-I ring data is recorded to its app (CART-I smpl) in the iPhone SE and to a password protected Oxford CRM Skylab online account (<https://www.CART-Icardiotracker.com>; see Appendix C) created for the purpose of this study ([crm.tb@gmail.com](mailto:crm.tb@gmail.com)). Only the investigators will have access to the

Oxford CRM SkyLabs account). The CART-I smpl app will not have any identifiable patient information, only a time stamp. The 1-lead ECGs and PPGs recordings will be exported in PDF format for further analysis and stored in OUHFT computers. The study ID number will be added to the 12-lead ECG and a high-resolution photo will be taken with the research iPhone and uploaded to the iCloud. Adjudication of the 12-lead ECG will be performed in OUHFT computers.

The CRF contain will demographic data and past medical history which will be collected directly from the participants and their medical notes.

Data collected during this study may be used in anonymous form to support other research in the future.

Identifiable data will not be kept more than 5 years following the end of the study, unless participants would like to receive a summary of the study results in which case it will be kept for longer than 5 years.

Study data will be kept for a minimum of five years.

## **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.

### **12.1 Risk assessment**

Not applicable

### **12.2 Study monitoring**

Not applicable:

### **12.3 Study Committees**

This is a small, multicentre study using commonly available devices with minimal patient risk, no oversight committees are required.

## **13 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.

## **14 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.

## **15 ETHICAL AND REGULATORY CONSIDERATIONS**

### **15.1 Declaration of Helsinki**

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

### **15.2 Guidelines for Good Clinical Practice**

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

### **15.3 Approvals**

Following Sponsor approval, the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions 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.

### **15.4 Reporting**

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

### **15.5 Other ethical issues**

In the event of a clinically relevant arrhythmia being detected by the ICM but not by the pacemaker, the research team will take steps to quickly inform the subject's clinical team so that if required, it can be promptly acted upon.

### **15.6 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 documents, with the exception of the CRF. 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.

No identifiable details will be published.

## **15.7 Expenses and Benefits**

N/A

## **15.8 Funding**

This trial will be partially supported by the Cardiac Rhythm Management Research Hub and SkyLabs grant for consumables and an Abbott Educational Grant.

## **15.9 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 Sponsor, Oxford University Hospitals NHS Foundation Trust, therefore cannot agree in advance to pay compensation in these circumstances.

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

## **15.10 Contractual arrangements**

Appropriate contractual arrangements will be put in place with all third parties.

## **16 PUBLICATION POLICY**

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study.

Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. An email with a report of the main findings of the study will be sent to the participants upon completion of the WEAR-TECH ECG study.

## **17 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY**

N/A.

## **18 ARCHIVING**

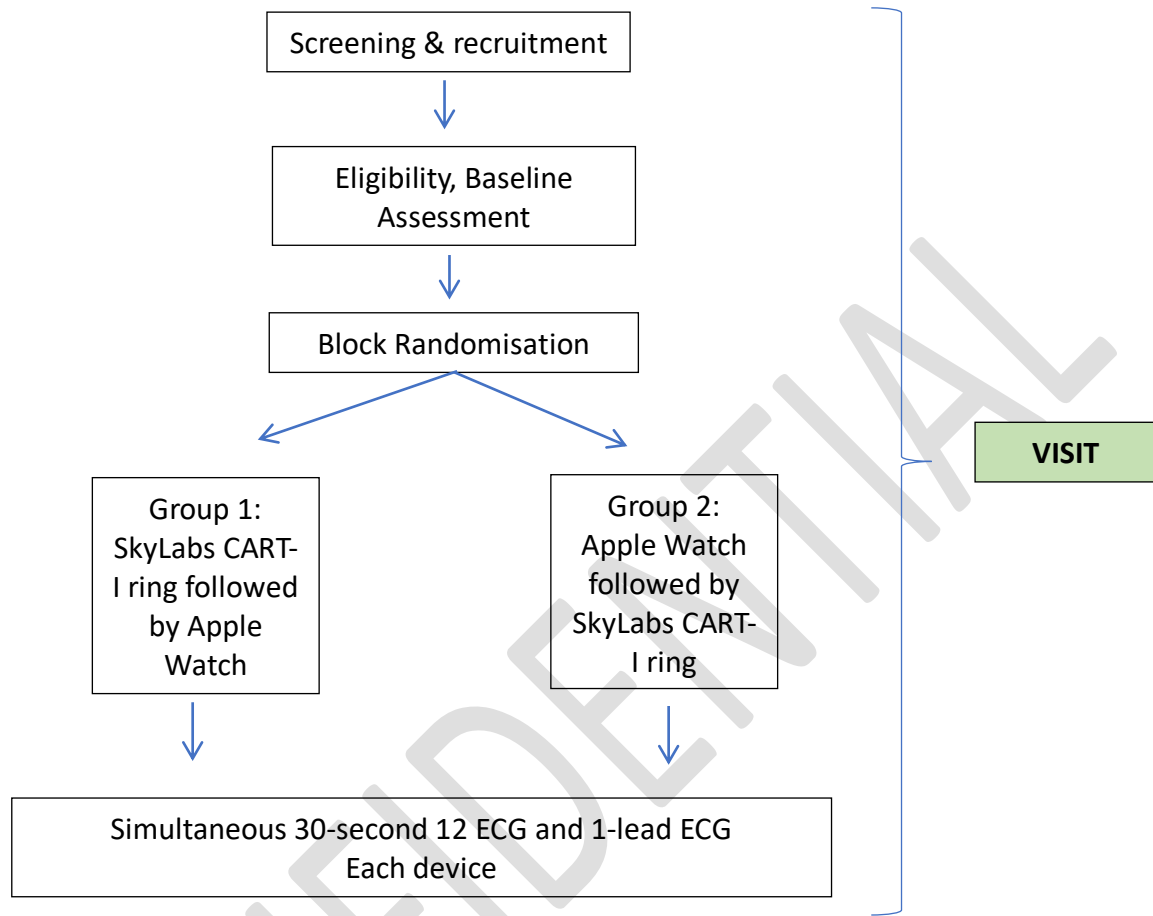
All documents will be stored securely in Clinical Fellows Research Office in each individual centre which requires a code to gain entrance to the office. The documents will only be accessible by study staff and

authorised personnel. All electronic documents (PDF of 12-lead ECGs, excel spreadsheets used for adjudication and analysis) will be stored in OUHFT computers.

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## 20 APPENDIX A: STUDY FLOW CHART



## 22 APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Visit 1
Eligibility assessment	x
Informed consent	x
Randomisation	x
Demographics	x
Medical history	x
12-lead ECG	x
1-lead ECG Apple Watch	x
1-lead ECG SkyLabs CART-I ring	x

## 22 APPENDIX C: SkyLabs CART-I Ring

### A) CRM Research Hub CART-I Ring Dashboard (www.CART-Icardiotracker.com)

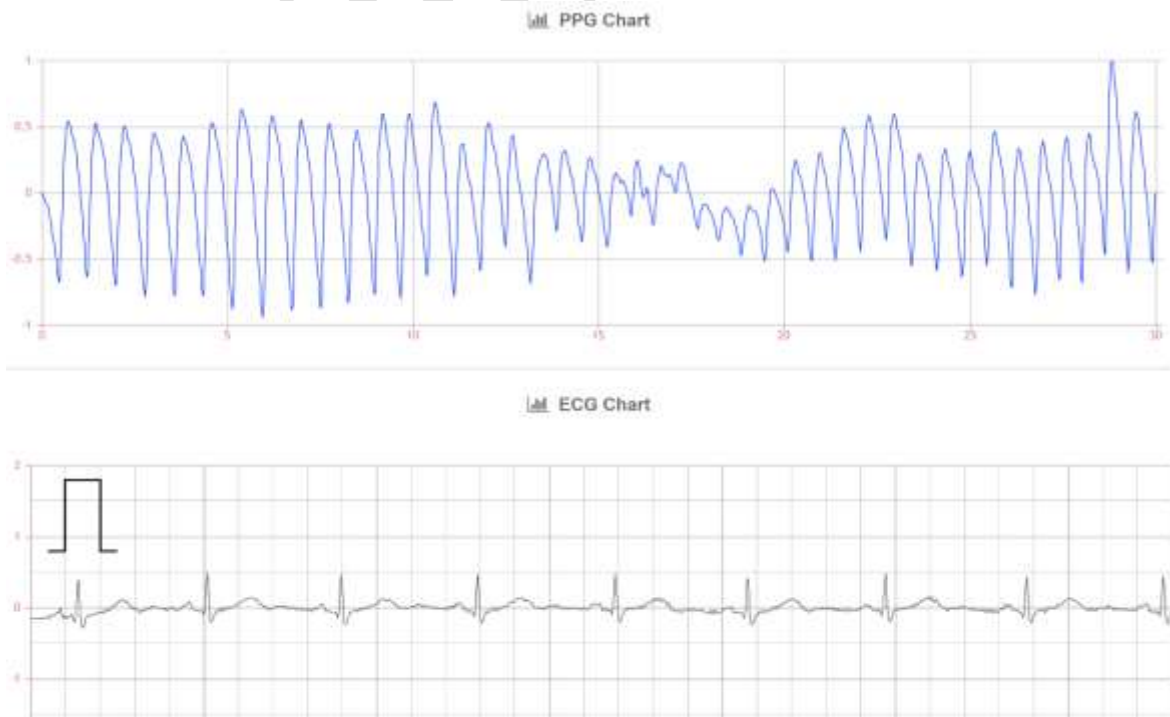
- The CART-I rings are registered to Andre Gala, co-investigator, (left side of the dashboard; red arrow) and all the recording are identified by a time stamp with no participants identifiable information (right side of the dashboard, green arrow).

The dashboard is titled "Dr. Andre Gala (GB20c1001)". It features a navigation bar with icons for Dashboard, Patients, Notice, PAG, G&A, and My Page. The main content area is divided into three sections:

- Patients:** A table with columns: Name, Age, Sex, Request Date, Status. It shows one entry: Andre gala, 34, Male, 15-Oct-2020, Active. A red arrow points to this entry.
- Notice:** A section with a search bar and a table with columns: No., Title, View, Date. It states "No data available in table".
- Status:** A table with columns: Date, Analyzable, AF, Confidence(%), HR. It shows five entries for recordings from 15-Oct-2020. A green arrow points to the first entry.

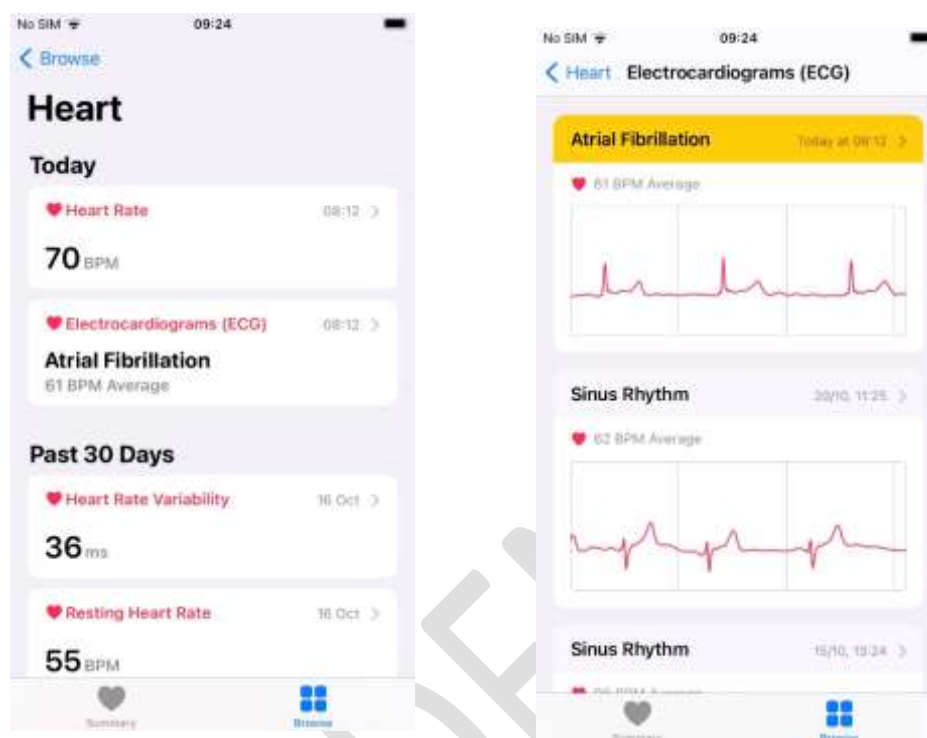
Date	Analyzable	AF	Confidence(%)	HR
15-Oct-2020 13:25:34	Yes	No	100.0	83
15-Oct-2020 09:41:47	Yes	No	100.0	70
15-Oct-2020 09:40:48	No	No	88.3	44
15-Oct-2020 09:20:30	Yes	No	78.3	71
15-Oct-2020 09:18:48	No	No	63.6	81

### B) Example of anonymised PPG and 1-lead ECG signal from the CART-I Ring



## 23 APPENDIX D: Apple Watch Series 6

A) Example of ECG stored in the Health app without any identifiable data, only time stamps.



B) Example of an exported Apple Watch 1-lead ECG (note DOB from co-investigator [red arrow]; no other identifiable data)



## 24 APPENDIX C: 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. This is not necessary prior to initial REC / HRA submission.

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

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