Comparison of the performance of Implantable Cardiac Monitors and Cardiac Implantable Electronic Devices in detecting Atrial Fibrillation (ID-AF)

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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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2. LAY SUMMARY

Atrial fibrillation (AF) is the most common abnormal heart rhythm disturbance, affecting 1-2 million people in the UK. The irregular heartbeat caused by AF can make the heart pump blood less efficiently. This may lead to small blood clots forming inside the heart that, if they were to breakaway, can lead to blockage of small blood vessels. As a result, AF significantly increases the risk of having a stroke, heart failure and dementia. Despite having AF, a significant proportion of people have no symptoms, and they may be only found to be in AF after having a stroke. Therefore, diagnosis largely relies on accurate ECG monitoring.

AF episodes can be unpredictable, of very short duration and easily missed unless continuous ECG monitoring is undertaken. Pacemakers can continuously record the heart's electrical activity and detect AF with a high degree of confidence. However, they are invasive and rely on electrical wires implanted inside the heart, and hence less suited to be used as primary monitoring devices. To overcome these difficulties, implantable cardiac monitors (ICM) have been designed to be placed under the skin.

The new generation of ICMs has been miniaturised and are can now be injected under the skin. Moreover, they connect with the patient's smartphone and which can used to annotate symptoms and send ECG recording to their doctor when experiencing symptoms. Previous generation of ICMs could only transmit once a day (at night) and require close proximity to a home-based stationary monitor. This resulted in frequent failed transmission and delays from arrhythmic episodes detected by ICM and transmission to their physician.

Despite these significant improvements, their ability to reliably capture AF has never been tested against pacemakers.

The aim of this project is to study the performance of the two commonly used ICMs in detecting AF episodes and explore how the new connectivity can empower patients and improve patient care. We plan to inject an ICM in 30 patients with AF and pre-existing pacemaker. After a period of 6 months, we will compare how many episodes were detected in each device. With the information collected we will try to understand the pitfalls in the current technology and develop strategies to improve it.

Accurate, minimally-invasive long-term ECG monitoring can have far reaching benefits for patients, both in routine clinical practice and research. It can help identify AF in patients that have had an unexplained stroke, it can aid doctors' decisions in patients with infrequent but severe symptoms and monitor response to treatment. Furthermore, it is an important research tool that may provide more insight into the natural history of the disease and reliably test the efficacy of new drugs and procedures.

3. SYNOPSIS

Trial Title	Comparison of the performance of **I**mplantable Cardiac Monitors and Cardiac Implantable Electronic **D**evices in detecting **Atrial Fibrillation**		
Internal ref. no. (or short title)	**ID-AF**		
Trial registration	Intended register – Clinicaltrials.gov		
Sponsor	Oxford University Hospitals NHS Foundation Trust		
Funder	Cardiac Rhythm Research Hub (Oxford University Hospitals) Abbott Medical Medtronic		
Clinical Phase	Pilot study		
Trial Design	Prospective, single centre, randomised observational study.		
Trial Participants	Male and female adults with a dual-chamber CIED with a functioning atrial lead and Paroxysmal or Persistent Atrial Fibrillation		
Sample Size	30 subjects (15 on each investigation arm)		
Planned Trial Period	~~15 months~~Extension of study end date until 30th June 2024		
Planned Recruitment period	~~3 – 6 months~~Extension of recruitment period until 31st December 2023		
	Objectives	Outcome Measures	Timepoint(s)
Primary	**Primary Objective** 1. To compare the performance of the Confirm Rx™ ICM and Reveal LINQ™ ICM in detecting clinically significant AF episodes (episodes longer than 6 minutes) to CIED (gold standard).	1. Confirm Rx and Reveal LINQ™ ICM sensitivity, specificity, positive predictive value and negative predictive value will be calculated for AF episodes longer than 6 minutes	During follow-up (6 months)
Secondary	**Secondary Objectives** 1. To compare the changes in R-wave amplitude following implantation in both ICMs. 2. To compare the transmission success rate	1. Compared the percentage of changes in R-wave amplitude between both ICMs 2. The percentage of successful transmission in both ICMs will be calculated.	1. During the follow-up period (6 month) 2. During the follow-up period (6 month)

	of both devices. 3. To compare between both devices the number of patient- activated recordings that contains symptoms attributed to those episodes.	3. The percentage of activated recordings with symptoms will be calculated.	3. During follow-up period (6 months)
Intervention(s) • Medical Device	Implantable cardiac monitors (ICM): Confirm Rx™ (Abbott) and Reveal LINQ™(Medtronic)		
Comparator	Cardiac Implantable Electronic Devices (Pacemakers, Cardiac resynchronisation therapy, Implantable cardioverter-defibrillator) with a functioning atrial lead		

4. ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
AR	Adverse Reaction
AT	Atrial Tachycardia
CI	Chief Investigator
CIED	Cardiac Implantable Electronic Device
CRF	Case Report Form
CRT	Cardiac Resynchronisation therapy
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IB	Investigators Brochure
ICD	Implanted Cardioverter-Defibrillator
ICM	Implanted Cardiac Monitor
ICF	Informed Consent Form
IRB	Independent Review Board
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Clinical significance: Atrial fibrillation (AF) is the most common sustained arrhythmia affecting millions of people worldwide, leading to significant morbidity and mortality. [1] It is associated with a 5-fold increase risk of ischaemic stroke[2], accounting for 20-25% of all strokes which are generally more severe and disabling than non-AF related strokes.[3] In addition, patients with AF have a 3-fold increase in heart failure and 2- fold increase in dementia.[4]

Although the exact duration of AF required to cause a thromboembolic stroke is not known, episodes longer than 6 minutes detected by a CIED have been shown to increase the risk of stroke[5]. Significant morbidity is associated with the duration and total burden of AF.[6, 7] Nonetheless, a large proportion of patients remains asymptomatic despite being in AF. [8] In pacemaker patients, only 21% reported symptoms during AF episodes that were recorded by their device. [9] In addition, the perception of AF related symptoms may change following an AF ablation with a 2-5 fold increase in the number of asymptomatic AF episodes. [10, 11] Thus, symptoms alone are unreliable in identifying the presence or absence of AF. Consequently, ECG monitoring tools play a critical role in the documentation of AF.

ECG monitoring: There is a correlation between the duration and intensity of ECG monitoring and the detection of AF, with continuous long-term ECG monitoring being superior to intermittent monitoring.[11] Continuous long-term ECG monitoring can be performed either intracardiac, with cardiac implantable electronic devices (CIED), or subcutaneously, with implantable cardiac monitors (ICM).

Dual-chamber cardiac implantable electronic devices (CIED): Pacemakers, ICDs, CRTs have excellent AF diagnostic capability with high sensitivity and specificity.[12-14] The atrial lead is in direct contact with the atrial myocardium and generates high quality intracardiac electrograms (EGM) that are interpreted by advanced AF algorithms. However, the invasive nature of the procedure, potentially serious long-term complications, and high cost make them an inadequate primary arrhythmia monitoring device. Yet, in patients with pre-existing CIEDs, they can be used as a 'gold-standard' AF detection monitor to validate other devices.[14]

First generation implantable cardiac monitors (ICM) were implanted subcutaneously, using blunt dissection, in the catherisation laboratory. Their AF detection algorithm was rudimentary, relying solely on irregular R-R intervals measurements. As a result, they were prone to false positive results caused by artefact and other irregular rhythms such as ventricular ectopy. The SMJ Confirm™ ICM had a sensitivity of 94% but a positive predictive value of only 64% for detection of clinically significant AF episodes (longer than 6 minutes).[15] Furthermore, all ICMs transmissions to the Clinician's Web Portal required the subject to be within 2 metres of the home transmitter which resulted in suboptimal transmission success.

New generation Implantable cardiac monitors (ICM): They offer a minimally invasive approach for continuous ECG monitoring. ICMs outperform the external ambulatory ECG in the diagnosis of clinically significant arrhythmias in patients presenting with palpitations, syncope, cryptogenic stroke and post-AF ablation. [16, 17]. AF detection relies on a two-step approach. Firstly, they identify irregular R-R intervals and either a Markov chain model or Lorenzo plot to assign an AF probability score. Secondly, they review

the electrograms for any evidence of P waves. If no P waves are detected it is logged as AF. The two ICM to be studied are:

Reveal LINQ™ ICM (Medtronic™): Commonly used ICM with reported high sensitivity and positive predicted value. However, its AF algorithm has never been validated against CIED. Transmissions are performed through a home-monitor, 20% of which are unsuccessful [4]. The most current version can use a smartphone app (Medtronic™) and Bluetooth® connection to transmit the recording, however the transmission success rate has not been studied.

Confirm Rx™ ICM X (Abbott™): Was the first ICM equipped with Bluetooth® wireless technology that connects directly with the patient's smartphone via the myMerlin™ app (Abbott™). The myMerlin™ app features include activation of ECG recordings when experiencing symptoms, viewing of transmission history to confirm successful data transfer and receiving notifications for scheduled transmission and device checks. Neither the AF algorithm nor the myMerlin App have been independently validated.

Only CE-marked devices and respective smartphone apps will be used in this trial .

Future direction:

Injectable technologies have a large potential to improve the management of patients with AF, both as a diagnostic tool but also to guide therapies. However, its utility is dependent on having very sensitive, reasonably specific detection of clinically relevant AF episodes and high transmission success. This pilot study will investigate the accuracy of the new generation ICM and lay the foundation for future trials using different management strategies will be guided by ICM recordings and alerts from smartphone apps.

5. 1 Hypothesis

Injectable and wearable technologies have huge potential to improve the management of patients with AF, both as a diagnostic tool but also to guide therapies. "As-needed" use of oral anticoagulants has been proposed as a cost-effective way to prevent thromboembolic stroke as well as increasing patient compliance and satisfaction. However, its utility is dependent on having very sensitive, reasonably specific detection of clinically relevant AF episodes and high transmission success. It is therefore important to determine how accurate the latest devices and their detection algorithms are when compared to the gold standard of CIEDs (pacemakers, implantable cardiac defibrillators (ICD) and cardiac resynchronisation therapy (CRT) devices) that have atrial leads and constant monitoring

We hypothesize that the new generation ICMs (Confirm Rx™ and Reveal LINQ™) can identify the majority (sensitivity above 95%, positive predictive value above 85%) of clinically significant AF episodes (longer than 6 minutes). We also estimate that with Bluetooth® technology connecting to patients' smartphone will improve the transmission success rate above 80%.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective 1. To compare the performance of the Confirm Rx™ ICM and Reveal LINQ™ ICM in detecting clinically significant AF episodes (episodes longer than 6 minutes) to cardiac implantable electronic devices (CIED).	1. Confirm Rx and Reveal LINQ™ ICM sensitivity, specificity, positive predictive value and negative predictive value will be calculated for AF episodes longer than 6 minutes	During follow-up (6 months)
Secondary Objectives 1. To compare changes in the recording of electrograms (heart's electrical activity) R- wave amplitude from time of implant to end of follow-up (6 months) 2. To compare the transmission success rate of episodes recorded by the implantable cardiac monitors to the Clinician's Web Portal. 3. To compare between both devices the number of patient-activated recordings that contains symptoms \\cts attributed to those episodes	1. Compared the percentage of changes in R-wave amplitude between both ICMs 2. The percentage of successful transmission in both ICMs will be calculated. 3. The percentage of activated recordings with symptoms will be calculated.	1. During the follow-up period (6 month) 2. During the follow-up period (6 month) 3. During follow-up period (6 months)
Exploratory Objectives 1. To study the changes in P-wave amplitude between different positions in the chest.	1. Percentage of change in P and R-wave amplitudes between V1 and V2 position. Percentage of change in P and R-wave amplitudes between surface	1. During implant

	and subcutaneous electrograms.	

7. STUDY DESIGN

The ID-AF study is a prospective, single centre, randomised observational study aimed at comparing the performance of the Confirm Rx™ and Reveal LINQ™ ICMs in the detection of clinically relevant atrial fibrillation (AF) episodes to cardiac implantable electronic devices (CIED)

Subjects with pre-existing cardiac implanted electronic devices (Pacemakers, CRT and ICD devices) who have remote monitoring ability and are able to record electrograms will be identified by interrogation of the John Radcliffe Hospital Pacemaker Database. Subjects with a functioning atrial lead, on remote monitoring, non-permanent AF with an AF burden of more >2% in the last year will be invited to participate. Those who have expressed an interest in participating will be invited for an initial interview (eligibility assessment, baseline assessment and informed consent).

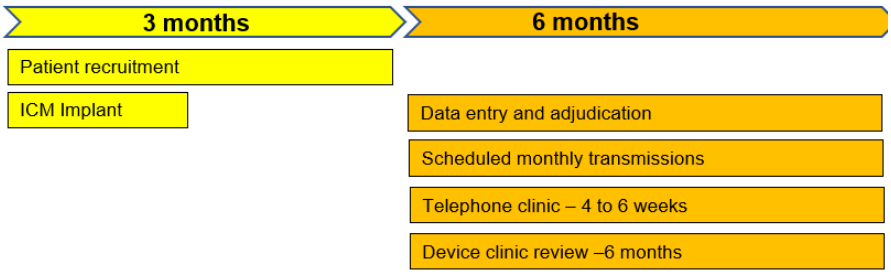
This study will randomise 30 subjects to receive either a Confirm Rx™ ICM or a Reveal LINQ™ ICM. The ICM will be implanted in the Outpatient setting as a Day Case Procedure according to manufacturer instructions. Prior to the implant, 2 minutes of recording in V1 and V2 position with the surface ICM mapping will be performed. The R-wave amplitude will be recorded at the end of the procedure. Subjects will be taught how to use the home-based transmitter and mobile app.

As it is standard of care, the research team will book a telephone follow-up appointment at 4-6 weeks to address any questions the subjects may have regarding the ICM, review ICM battery and wound. The ICMs are programmed for automatic daily transmissions of the recorded episodes to the Clinician's Web Portal. Scheduled remote transmissions for CIED will be performed at least monthly. At 6 months, subjects will be invited to attend a Device Clinic appointment for the final download from both devices. At this time, they may choose to have the ICM removed or left in-situ but turned off. During this last visit, ICM transmissions log will be interrogated. The end of the study for each patient will be the date of the 6 months follow-up appointment.

7.1 Study Timeline

This 15-month single centre, randomised observational study is to be conducted in 3 phases:

1. Start-up period (3 months): to finalise and submit the REC form, to screen the CIED database for potential participants with high burden and/or episodes of AF.
2. Patient recruitment, ICM implant and data entry (9 months): during this period recruitment will take place and the confirm Rx will be implanted. Data entry to be completed within 6 weeks of enrolment and will be monitored every 2 months.
3. Completion of data entry and analysis (3 months): to finalise the data entry, adjudicate all electrograms 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

The Confirm Rx™ ICM and the Reveal LINQ™ ICM implant procedure is safe and minimally invasive. They are both have CE marking and having been used in routine clinical practice for several years. The procedure will be performed under sterile conditions and local anaesthetic using the insertion tools supplied by the manufacturer. They have very similar implant techniques and they are both injected subcutaneously in the anterior chest wall.

There are no known contraindications. Potential adverse events include:

- bruising,
- haematoma (<1%),
- superficial infection (<1%),
- keloid formation,
- migration
- extrusion.

7.3 Study Benefits

Patient could get direct benefit from the study if the ICM is able to record arrhythmias that were not capture by the CIED. However, the main benefits from this study will be for future patients. It is important to understand how well the AF detection algorithms of these new generation ICM perform in comparison to the gold standard CIED. Furthermore, it will provide an opportunity to understand the pitfalls of the AF the current AF diagnostic algorithms and inform future optimisations.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

This trial is designed to include male and female adults with a dual-chamber CIED with a functioning atrial lead and Paroxysmal or Persistent Atrial Fibrillation.

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 aged 18 years or above.
- History of paroxysmal and persistent AF
- Dual-chamber pacemaker, ICD or CRT device with a functioning atrial lead, able to record electrograms and remote monitoring.

8.3. Exclusion Criteria

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

- Diagnosis of permanent AF.
- Contra-indications for implantable cardiac monitor.
- Unable to comply with the follow-up schedule.

8.4. Recruitment

Potential participants with a Cardiac Implanted Electronic Devices (Pacemakers, CRT and ICD) with a functioning atrial lead will be selected in Outpatient Pacemaker Clinics, Remote Pacemaker Clinics and hospital pacemaker database by the OUH NHS Trust Cardiac Rhythm Management Team. All members of the research team are part of the Cardiac Rhythm Management Care Team. Patients will be invited to participate in the study if there is presence of high AF burden or frequent AF episodes in a device download within the last year.

A letter of invitation, a patient information brochure and a consent form will be given to potential participants at the time of the Outpatient Clinic. In the Remote Pacemaker Clinic, as potential participants are not physically present, a letter of invitation and patient information brochure will be sent by post if they have non-permanent AF in their most recent transmission. Upon receiving and considering the information participants can use the contact the Arrhythmia Research Team by email or telephone to request more information or to express their interest in being enrolled.

If they wish to participate a baseline visit will be organised which will include informed consent, screening, and eligibility assessment.

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.

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. 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 another copy will be filed in the notes The original signed form will be retained at the trial site.

8.6 Screening and Eligibility Assessment

If a subject meets the inclusion criteria they will be invited to participate in the study. The inclusion criteria are based on the pacemaker interrogation performed in clinic.

After agreeing to participate and signing the consent form, the following data will be collected:

1. Demographics (age, gender, ethnicity)
2. Detailed collection of medical history which should include atrial fibrillation history, previous cardiac procedure (cardiac surgery, atrial fibrillation ablation, direct current cardioversion), significant co-morbidities
3. Imaging data recorded previously as part of standard clinical practice: left ventricular systolic function, diastolic function, evidence of valvular heart disease, cardiac chamber size.
4. Current medications
5. Height, weight and BMI
6. Current CIED name, model, implant indication

8.7 Randomisation

A block randomisation with block size of 2 will be used to assign each study subject with an ICM. There are two investigation arms in this study:

- Group A: Confirm Rx™
- Group B: Reveal LINQ™

As this study will enrol a total of 30 patients there will be 3 blocks of 10 patients each. In each block, subjects will be randomised to either Group A or Group B; therefore, at the end of each block there will be 5 subjects in each investigation arm. Randomisation will be performed during the baseline visit. A telephone call will be made to the research office and an envelope from the current block of 10 with the investigation of arm letter will be opened.

8.8 Blinding

Investigators and subjects will not be blinded to investigation arm.

At the end of follow-up, the CIED and ICM electrograms catalogued by the devices as AF will be adjudicated by two electrophysiologists blinded to patient data.

8.9 Baseline Assessments

Baseline assessment will include:

1. Detailed collection of medical history which should include atrial fibrillation history, previous cardiac procedure (cardiac surgery, atrial fibrillation ablation, direct current cardioversion), significant co-morbidities
2. Imaging data recorded previously as part of standard clinical practice: left ventricular systolic function, diastolic function, evidence of valvular heart disease, cardiac chamber size.
3. Current medications
4. Height, weight and BMI

8.9.1 Intervention – ICM implant (Confirm Rx™ or Reveal LINQ™)

The Confirm Rx™ ICM or Reveal LINQ™ ICM will be implanted as a Day Case. Prior to implant, recording of surface electrograms will be performed in V1 and V2 position to assess P and R-wave amplitudes. The procedure will be performed under sterile conditions and local anaesthetic (lidocaine 1%) using the insertion tools supplied by the manufacturer. They have very similar implant techniques and they are both injected subcutaneously in the anterior chest wall. If there is suboptimal R wave amplitude the operator can reposition the device. The subject will be premedicated with intravenous antibiotics as per Trust Policy to reduce the risk of infection. The operator may choose to close the wound with steri-strips, glue or a suture.

At the end of the procedure the R-wave amplitude will be recorded. Subjects will be taught how to use the mobile apps or the home-based monitor, depending on the device. They will be able to initiate recordings, send transmission and record their symptoms The CIED will be programmed to record any AT/AF and save the electrogram for future adjudication. The CIED and ILR date and time clocks will be synchronized.

The Confirm Rx™ ICM and the Reveal LINQ™ ICM implant procedure is safe and minimally invasive. There are no known contraindications. Potential adverse events include bruising, haematoma, superficial infection, keloid formation, migration or extrusion.

The LINQ™ and the Confirm Rx™ only transmit recordings to their company's servers (Carelink™, for Medronic; Merlin.net™, for Abbott) via their respective smartphone app or homebased monitor. ICM recordings can only be accessed on these servers by using the clinician web portal. The assigned trial specific ID number will be used to register the device in the Carelink (for Medtronic devices) and Merlin.net (for Abbott devices); thus, no identifiable patient information will be in the servers. Access to these servers is via the clinician web portal is password protected. Transmission reports will be downloaded from the Medtronic™ and Abbott™ servers and stored in password protect excel spreadsheet that will only be used in OUH trust computers.

8.10 Subsequent Visits

8.10.1 Scheduled Remote ICM and CIED Transmissions

Scheduled monthly remote ICM and CIED transmissions will be performed. Electrograms catalogued as AF episodes by the both devices will be downloaded for analysis from the clinicians web portal where the data is safely stored in Medtronic™ and Abbott™ server as it standard practice. All transmissions will be anonymous and only identified by the trial ID number.

If due to technical difficulties remote download is not possible subjects will be invited to attend Pacemaker Clinic for a download.

8.10.2 Visits

Visit 1: As is standard of care, Telephone Clinic review at 4-6 weeks after the ICM implant to review the wound, check performance and battery of ICM.

Visit 2: At 6 months, subjects will attend Device Clinic for a final download of both devices and at this time, they may choose to have the ICM removed. An updated drug history will be recorded.

8.11 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
- Loss to follow-up

Participants may choose to withdraw from 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.

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
- 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
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

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

In case of withdrawal from the study in an early stage (before intervention), the patient data will be excluded from the analysis and a new participant will be enrolled.

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

If the participant withdraws, he may choose to:

- Continue to have the routine ICM (Confirm Rx™ or LINQ™) downloads as per clinical need
- To have the ICM (Confirm Rx™ or LINQ™)) turned off.
- Have the ICM (Confirm Rx™ or LINQ™)) removed. The investigators will organise an outpatient procedure.

8.12 Definition of end of study

The end of the study will be the date of the last 6 month Confirm Rx™ ICM or LINQ™ ICM and CIED report download.

9 TRIAL INTERVENTIONS

9.1 Other Interventions

No other interventions will be performed except for the ICM implant and, at the end of the trial, if the subject wishes, ICM explant (see 8.9.1)

10 SAFETY REPORTING

10.1 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.

10.2 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.

11 STATISTICS AND ANALYSIS

11.1 Sample size calculation

The largest study to date using ICMs was performed in 1049 patients with known AF which were followed for 3 months. AF episodes longer than 6 minutes were seen in 53% of patients who had, on average, 7 AF episodes per month. We will recruit patients with known high frequency of AF episodes therefore we can assume AF episodes in least 40% of patients during the 6 months study period. Using the Buderer's formula, 327 episodes of AF are required if the expected AF detection algorithm sensitivity is 95% and the specificity is 85% with a 95% confidence interval. Therefore, with a rate of 7 episodes per month a minimum of 8 subjects for each ICM is needed. We will aim to recruit 30 patients so that a broad spectrum of patient characteristics can be accounted for.

11.2 Analysis of Outcome measures

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

The ICM performance will be investigated by calculating the sensitivity, specificity, positive predictive value and negative predictive value of AF episodes longer than 6 minutes will be calculated

12 DATA MANAGEMENT

12.1 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, ICM and CIED reports 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 participant ID number, not by name.

12.2 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.

12.3 Data Recording and Record Keeping

The participants will be identified by a unique trial specific ID number which will be assigned following consent. The trial ID number will be used in both hard-copies and electronic documents. The hard copies (CRF and consent forms) of data will be securely kept in the Research Fellows' Office located in the John Radcliffe Hospital, Level 2 Blue Outpatients.

The key to the trial specific ID number will be maintained on a single document will be kept on a separate folder in the PI's office (Dr Tim Betts). This office only be accessed by authorised personnel via a door-code and it is also located in the John Radcliffe Hospital, Level 2 Blue Outpatients.

The name and any other identifying detail will NOT be included in any trial data electronic file.

The LINQ™ and the Confirm Rx™ only transmit recordings to their company's servers (Carelink™, for Medtronic; Merlin.net™, for Abbott) via their respective smartphone app. ICM recordings can only be accessed on these servers by using the clinician web portal. This is the routine clinical practice in OUH for devices which are one remote monitoring (patients don't have to physically attend hospital for a device interrogation). Smartphone apps from Medtronic and Abbott are already used OUH to transmit information from the devices rather than using home-based monitors. The assigned trial specific ID number will be used to register the device in the Carelink (for Medtronic devices) and Merlin.net (for Abbott devices); thus, no identifiable patient information will be in the servers. Access to these servers is via the clinician web portal is password protected.

Transmission reports will be downloaded from the Medtronic™ and Abbott™ servers and stored in password protect excel spreadsheet that will only be used in OUH trust computers.

Personal data will not be kept more than 3 months following the end of the study. Study data will be kept for a minimum of five years.

13 QUALITY ASSURANCE PROCEDURES

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

13.1 Risk assessment

Not applicable

13.2 Study monitoring

The study will be monitored via the study amendments and progress reports. If any issues arise the study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulation and standard operating procedures.

Not applicable:

13.3 Study Committees

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

14 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.

15 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.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

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

16.3 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.

16.4 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.

16.5 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'

16.6 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 database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

No identifiable details will be published.

16.7 Expenses and Benefits

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

17 FINANCE AND INSURANCE

17.1 Funding

This trial will be partially supported by a grant from Abbott Medical Grant, Medtronic Grant or consumables and Rhythm Management Research Hub.

17.2 Insurance

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

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University 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.

17.3 Contractual arrangements

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

18 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.

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

Ownership of IP generated by employees of the OUH vests in OUH. The protection and exploitation of any new IP is managed by the IP and Research Contracts Team at OUH unless it is generated in collaboration with Oxford University in which case this is led by the University's technology transfer office, Oxford University Innovations.

20 ARCHIVING

All documents will be stored securely in Clinical Fellows Research Office in the John Radcliffe Hospitals which requires a code to gain entrance to the office. The documents will only be accessible by study staff and authorised personnel.

The study staff will safeguard the privacy of participants' personal data.

21 REFERENCES

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7. Sarkar, S., et al., *Burden of atrial fibrillation and poor rate control detected by continuous monitoring and the risk for heart failure hospitalization.* Am Heart J, 2012. **164**(4): p. 616-24.
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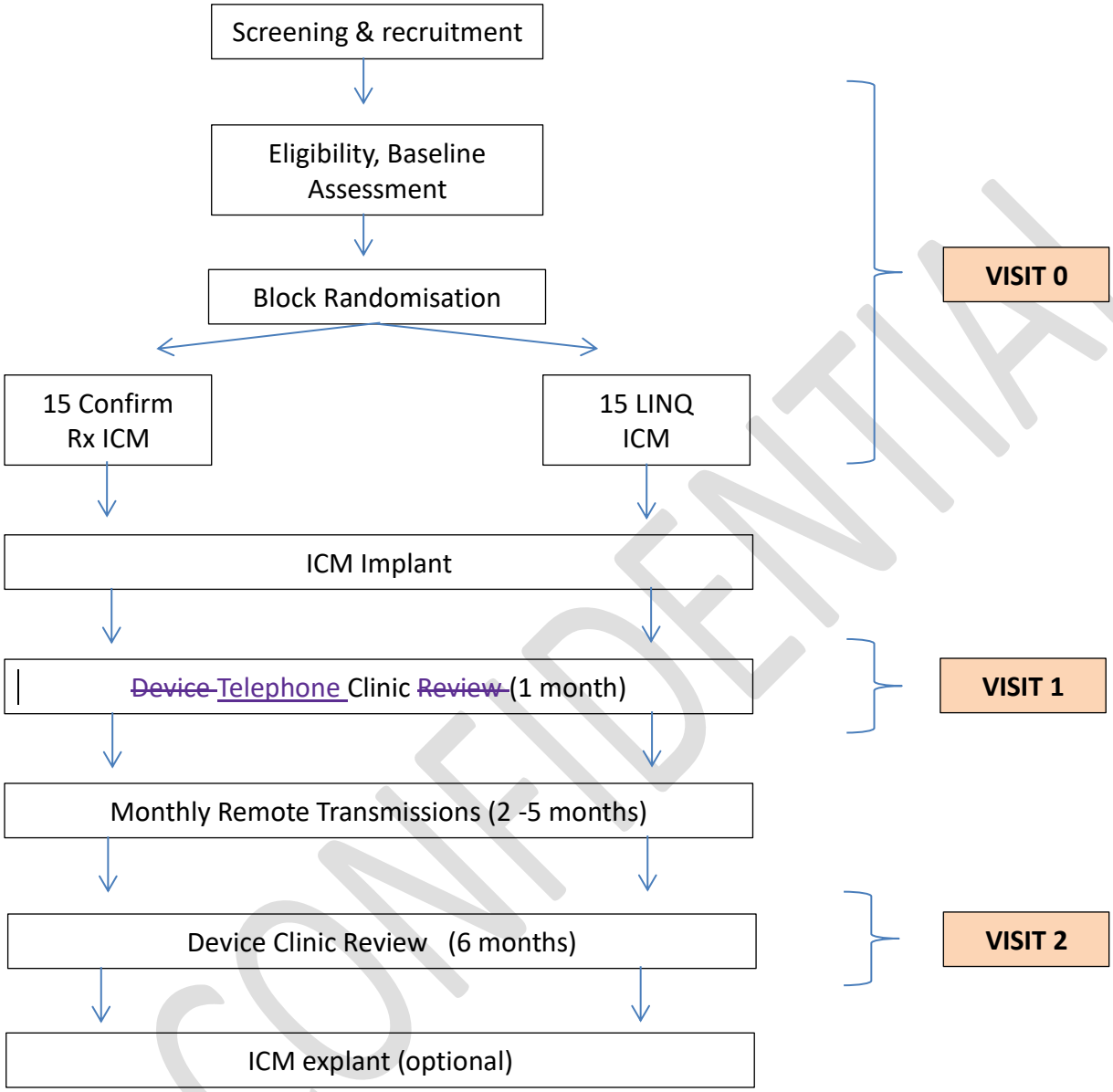
12. Healey, J.S., et al., *Subclinical atrial fibrillation and the risk of stroke.* N Engl J Med, 2012. **366**(2): p. 120-9.
13. de Voogt, W.G., et al., *Verification of pacemaker automatic mode switching for the detection of atrial fibrillation and atrial tachycardia with Holter recording.* Europace, 2006. **8**(11): p. 950-61.

22 APPENDIX A: STUDY FLOW CHART



23 APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Number of visits: 3**					
	Assessment			**Visit 1 (Telephone Clinic)**		**Final visit**
	Day 0	**Day 0**	**Day 0**	**4-6 weeks**	**2-5 months**	**6 Months**
	Screening	**Baseline**	**Implant**		**Monthly Remote Downloads**	**Device interrogation ICM explant**
Informed consent	x					
Demographics	x					
Medical history	x			x		
Physical examination	x					
Medications		x		x		
Eligibility assessment	x					
Implant indication		x				
Randomisation		x				
ICM Implant			x			
Device interrogation and programming				x	x	x
ICM Explant						x
Adverse event assessments						x

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).