Pill-in-Pocket Oral Anticoagulation Responding to Atrial Fibrillation Episodes Guided by Continuous Rhythm Monitoring and Automated Smartphone Alerts

Internal Reference Number / Short title: RESPOND-AF

Date and Version No: 10th January 2025 version 3.0

Chief Investigator:

Prof Tim R. Betts MD MBChB FRCP
Consultant Cardiologist & Electrophysiologist
Oxford University Hospitals NHS Foundation Trust
Associate Professor, Department of Cardiovascular Medicine, Oxford University
Tel: +44 1865 220256
Email: tim.betts@ouh.nhs.uk

Investigators:

Dr Richard Varini MBChB MRCPI
Clinical Research Fellow,
Oxford University Hospitals NHS Foundation Trust
Tel: +441865220255
Email: richard.varini@ouh.nhs.uk

Dr Abhirup Banerjee PhD
Royal Society University Research Fellow
Institute of Biomedical Engineering
Department of Engineering Science
University of Oxford, UK
Tel: +44 1865 617667
Email: abhirup.banerjee@eng.ox.ac.uk

Sponsor:

Oxford University Hospitals NHS Foundation Trust

Headley Way, Headington, Oxford (OX3 9DU)

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1. KEY TRIAL CONTACTS

Chief Investigator	Prof Tim R. Betts MD MBChB FRCP. Consultant Cardiologist & Electrophysiologist, Oxford University Hospitals NHS Foundation Trust Associate Professor, Department of Cardiovascular Medicine, Oxford University Tel: +44 1865 220256 Email: tim.betts@ouh.nhs.uk
Sponsor	Oxford University Hospitals NHS Foundation Trust Headley Way, Headington, Oxford OX3 9NU Email: ouh.sponsorship@ouh.nhs.uk
Funder(s)	Medtronic Limited
Clinical Trials Unit	N/A
Committees	N/A

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1. SYNOPSIS

Trial Title	**Pill-in-Pocket Oral Anticoagulation: Responding to Atrial Fibrillation Episodes Guided by Continuous Rhythm Monitoring and Smartphone Alerts**		
Internal ref. no. (or short title)	**RESPOND-AF**		
Trial registration	Clinicaltrials.gov		
Sponsor	Oxford University Hospitals NHS Foundation Trust		
Funder	Medtronic Limited		
Clinical Phase	Feasibility study		
Study Design	Investigator-initiated single centre feasibility study		
Study Participants	Participants will be recruited from Cardiology outpatient clinics and outpatient lists for DC Cardioversion, as well as those presenting for the first time with recent onset AF to Emergency Department or Acute Medical Unit. Those recruited will be aged 18 years or above with non-valvular paroxysmal atrial fibrillation or persistent AF with a rhythm control strategy. They will have to own a smartphone with operating system compatible with the My Carelink Heart application by Medtronic and be willing and able to use the application. They must fulfill the inclusion criteria listed later in this protocol and on the consent form.		
Sample Size	50 subjects		
Planned Study Period	24 months		
	Objectives	Outcome Measures	Timepoint(s)
Primary	**Primary Objective** To investigate the reduction in oral anticoagulation (OAC) utilization during follow-up.	**Primary Outcome Measures** Calculate the proportion of time off anticoagulation	During follow-up (minimum 13 months)
Secondary	**Secondary Objectives** 1. Thromboembolic events (ischaemic stroke, transient ischaemic	**Secondary Outcome Measures** 1. Calculate the rate of ischaemic stroke, TIA and systemic embolism in	1. During follow-up (minimum 13 months)

	attacks (TIA) and systemic embolism)	patients on as-required OAC	
	2. Major bleeding	2. Calculate the rate of major bleeding in patients on as-required OAC	2. During follow-up (minimum 13 months)
	3. Minor bleeding	3. Calculate the rate of minor bleeding in patients on as-required OAC	3. During follow-up (minimum 13 months)
	4. Any stroke (ischaemic, haemorrhagic or undermined)	4. Calculate the stroke rate (ischaemic, haemorrhagic or undetermined)	4. During follow-up (minimum 13 months)
	5. All-cause mortality	5. Calculate the rate of all-cause mortality in patients on as-required OAC	5. During follow-up (minimum 13 months)
	6. Protocol adherence	6. Calculate the percentage of daily automatic transmissions and percentage of patients that restart OAC within 24 hours of the smartphone-alert.	6. During follow-up (minimum 13 months)
	7. To assess response time from AF episode onset to patient starting as-required OAC	7. Time from AF episode onset to detection, time to alerts being sent and acknowledged and OAC being taken by the participant. Proportion of missed AF episodes, transmissions or alerts.	7. During follow-up (minimum 13 months)

Intervention(s)	As-required oral anticoagulation (OAC):
	• Initiate OAC if continuous AF episodes longer than 1 hour or total AF burden of more than 60 minutes (>4.2%) over a 24-hour period.
	  ○ Dabigatran
	  ○ Rivaroxaban
	  ○ Apixaban		

	○ Edoxaban • Discontinue OAC if freedom over a consecutive 30-day period from: (1) AF episodes longer than 1 hour, and (2) AF burden more than 60 minutes in any 24-hour period.

2. ABBREVIATIONS

AE	Adverse event
AF	Atrial fibrillation
AR	Adverse Reaction
AE	Adverse event
CI	Chief Investigator
CRF	Case Report Form
CRT	Cardiac Resynchronisation therapy
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DOAC	Direct oral anticoagulant
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICD	Implanted Cardioverter-Defibrillator
ICM	Implanted Cardiac Monitor
ICF	Informed Consent Form
IRB	Independent Review Board
NHS	National Health Service
OAC	Oral anticoagulation
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PPG	Photoplethysmography
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RSI	Reference Safety Information
TIA	Transient ischaemic attack
SAE	Serious Adverse Event
TMF	Trial Master File

3. BACKGROUND AND RATIONALE

Disease burden: 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 increased 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] OAC remains the cornerstone of AF management: it reduces by two-thirds the risk of stroke, but at the expense of major bleeding (1 in 25 patients per year).[1, 4]

Clinical Challenge: Risk scores that inform anticoagulation decisions, such as the CHA_2DS_2-VASc score, do not incorporate AF temporal patterns or burden and are based solely on co-morbidities.[1] If the predicted yearly stroke rate is above 1%, there is a net clinical benefit of OAC.[5] Once OAC is initiated, patients are committed to lifelong anticoagulation regardless of the number or duration of AF episodes.

Current risk scores may overestimate the stroke risk in patients with paroxysmal atrial fibrillation (PAF), low AF burden and short episodes. A meta-analysis of almost 100,000 patients with AF suggests that both the adjusted and unadjusted stroke and mortality risks are higher in non-Paroxysmal AF than in Paroxysmal AF.[6] Moreover, in a study of 21,768 non-anticoagulated patients with AF detected by cardiac implantable electronic devices, longer AF episode duration was associated with increased thromboembolic risk. Patients with intermediate CHA_2DS_2-VASc score (1-3) and AF episodes lasting less than 23.5 hours had a yearly stroke rate below 1%.[7] Therefore, indefinite OAC may expose patients with shorter, infrequent AF episodes to a high bleeding risk with limited benefit in stroke risk reduction, in particular those with low-to-moderate risk.

Biological plausibility: Interrogation of more than 9,000 patients with cardiac implantable electronic devices (CIEDs) showed a seventeen-fold increase in the odds of having a stroke in the first 5 days after an AF episode which returns to baseline at 30 days.[8] This may be explained by both atrial stunning —transient disruption of atrial and atrial appendage contractility — following restoration of sinus rhythm, and an increase in thrombogenesis, from platelet activation and thrombin generation during AF episodes.. Atrial stunning occurs irrespective of mode of cardioversion (spontaneous, pharmacological or electric),[9-12] and gradually improves over time if sinus rhythm is restored.[13, 14] In patients undergoing direct current cardioversion, recovery of atrial mechanical function is strongly influenced by the duration of AF episodes.[14] Recovery within 24 hours was observed in patients with AF episode duration of less than two weeks; recovery increased to one month in those with documented AF lasting for more than 6 weeks.[15]

Evidence gap: "As-required" OAC, guided by continuous rhythm monitoring, may be an alternative management strategy in patients with paroxysmal AF and persistent AF on a rhythm-control strategy who have short, infrequent episodes. OAC is started at the onset of an AF episode and continued for the duration of the episode and for a period afterwards. This may offer the same thromboembolic protection as continuous OAC, whilst at the same time reducing cost and bleeding complications.

As-required OAC: Four small feasibility studies have used an implantable cardiac monitor (ICM, e.g. Medtronic LINQ and Reveal XT) to guide "as required" OAC in low-to-moderate risk patients.[16-19] Although the authors concluded that this strategy appears safe, reducing both OAC utilisation and

bleeding, none of these studies were adequately powered to assess for rate of thromboembolic events. Our research group therefore conducted a systematic review and meta-analysis[32] of studies using rhythm monitoring (intermittent and continuous) to guide OAC. Across 8 studies and a total of 711 patients on an intermittent anticoagulation regime, the annualised mortality and ischaemic stroke rates per patient-year of follow-up were very low, 0.024 (95% CI [0.018–0.051]) and 0.005 (95% CI [0.002–0.012]), respectively.

A significant limitation seen in studies using continuous rhythm monitoring (ICMs or cardiac implantable electronic devices) was the large volume of data that required adjudication and potential delays between episode detection and restarting OAC — patients had to be contacted by telephone.[16-19] In REACT.COM, during a mean follow-up of 1.2 years, 59 patients generated 24,000 manual transmissions. These limitations in technology and methodology hindered any attempts at a large RCT or incorporation into routine clinical practice.

Innovations in digital health technology may lead to a paradigm shift: personalised treatment for patients with AF. The LINQ II ICM™ (Medtronic, MN, USA) with True-rhythm now incorporates P-wave evidence which significantly reduces the number of false positives whilst still maintaining a very high positive predictive value for AF episodes.[20, 21] It is also now equipped with low-energy Bluetooth wireless technology that connects directly with users' smartphones, allowing transmission of data to the physicians' web portal (CareLink™) without needing a home monitor. This opens the possibility of real-time, automated notifications to patients informing them of the onset of an AF episode.

Our research group at Oxford University Hospitals, UK have developed a patient messaging software to facilitate sending alerts to patients, which patients can respond to. We confirmed the feasibility of this closed-loop alert system in the recent SMART-ALERT study (discussed below).

In the RESPOND-AF study, patients will have a LINQ II ICM implant. If the ICM picks up an episode of AF, this transmission will trigger our software to send an SMS alert to the patient. This alert will inform them of the AF episode, therefore prompting them to restart their oral anticoagulation. This closed-loop alert system will allow for reduced time from AF episode detection to initiation of OAC and facilitates remote monitoring workflow.

Figure 1. LINQ II implantable cardiac monitor (ICM) connectivity

The duration of AF episodes that start to increase thromboembolic risk (and thus merit OAC) remains unclear. The arbitrary diagnostic cut-off of 30 seconds of AF on an electrocardiogram was introduced as an inclusion criterion in clinical trials and it is still used to diagnose AF. Continuous rhythm monitoring with cardiac implantable electronic devices allows detection of atrial high-rate episodes (AHRE)/subclinical AF and assessment of episode duration and stroke risk. In published trials, stroke risk began to increase after subclinical AF episodes longer than 5 minutes in the MOST trial, after 1 hour in SOS, 5.5 hours in TRENDS, and 24 hours in the Veteran Affairs study and ASSERT (post-hoc analysis).[22-26] The data therefore suggest that longer episodes (hours) rather than shorter episodes (minutes) increase the risk of thromboembolism.

The 2020 ESC AF guideline acknowledges the uncertainty between the duration of subclinical AF episode and the thromboembolic risk but highlights that longer episodes (>24hours) have a higher risk of thromboembolic complications and progression to clinical AF.[27] Furthermore, it states that OAC may be considered in patients with high stroke risk and subclinical AF episodes longer than 24h, pending data from ongoing RCTs.[28, 29]

These RCTs (ARTESIA[28] study and NOAH-AFNET 6[29]) have since reported. They were designed to assess the treatment of AHRE/subclinical AF episodes of >6 minutes (and <24 hours in ARTESIA) with a direct-acting oral anticoagulant. In ARTESIA, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin, but a higher risk of major bleeding. In NOAH-AFNET 6, edoxaban did not lead to a significant reduction in the composite endpoint of stroke, systemic embolism, or cardiovascular death compared with placebo, and led to a higher incidence of a composite of death or major bleeding. A meta-analysis of these two studies[33] has demonstrated an overall significant reduction in ischaemic stroke in anticoagulated patients, with no reduction in cardiovascular death or all-cause mortality, and a significant increase in major bleeding. These results would appear to support the ESC guideline to consider OAC in this subclinical AF patient group.

In the RESPOND-AF study, we have chosen a pragmatic cut-off of a continuous AF episode longer than one hour and/or a daily AF burden of more than 1 hour during a 24-hour period (>4.2%) to initiate OAC. Built into our protocol is a target for participants to commence OAC within 24 hours of AF onset, and no later than 48 hours.

Preliminary data: Our research group conducted a review of patients with AF and complex cardiac devices treated at Oxford University Hospitals, to assess potential reduction in OAC usage if they were treated with an "as-required" OAC approach. Retrospective analysis of 331 patients identified 106 with AF, corresponding to a total follow-up period of 393 patient-years. An "as-required" strategy of OAC for 1 month following an AF episode longer than 1 hour (as per RESPOND-AF protocol) would lead to a significant reduction of time on OAC: 86.5% reduction for paroxysmal AF patients, and 46.3% reduction in recurrent persistent AF patients.[30]

3.1 SMART-ALERT study

SMART-ALERT study: (*study complete, analysis and preparation of manuscript ongoing*) In this study our research group aimed to assess the feasibility and robustness of: (1) the closed-loop system

using LINQ II™ ICM remote monitoring to detect AF, (2) our custom software platform (discussed in section below) to alert patients of the AF episode, (3) of patients acknowledging receipt of the alert.

We also assessed the accuracy of wearable devices during the follow-up period: the Apple Watch and the SkyLabs CART-I Smart Ring. We used the LINQ II as the gold standard comparator of their accuracy.

Preliminary results: We recruited 50 patients with known frequent episodes of AF. Early results indicate this approach is reliable and accurate. On interim analysis, the median time from AF episode detection to SMS alert was 183 minutes (3.1 hours). The median time from SMS alert to patient reply was 5.1 minutes. Only 1 episode took longer than 24 hours for the patient to reply. On 3 occasions there was no patient reply. The median total time from AF episode detection to patient reply was 296.5 minutes (4.9 hours) and 94% of replies occurred within 24 hours.

In the context of the RESPOND-AF study, a median time of 4.9 hours from AF episode detection to commencing oral anticoagulation would be deemed safe and appropriate. In fact, most of the patient responses in SMART-ALERT occurred within 1 - 3 hours.

These timings represent the combined results from versions 1.0, 2.0 and 3.0 of our custom software programme. The earlier versions had intermittent technical issues, with periods of the software programme crashing and not automatically restarting. On these occasions manual restart of the software programme was required. This resulted in occasions with delays to SMS alerts being sent to patients while versions 1.0 and 2.0 of the software programme were running. Version 3.0 did not require any manual restart while operational, correcting the previous technical issues.

We are undertaking further analysis of the performance of each version of the software programme. We expect that the detection and response times will be much improved for version 3.0 of the software programme.

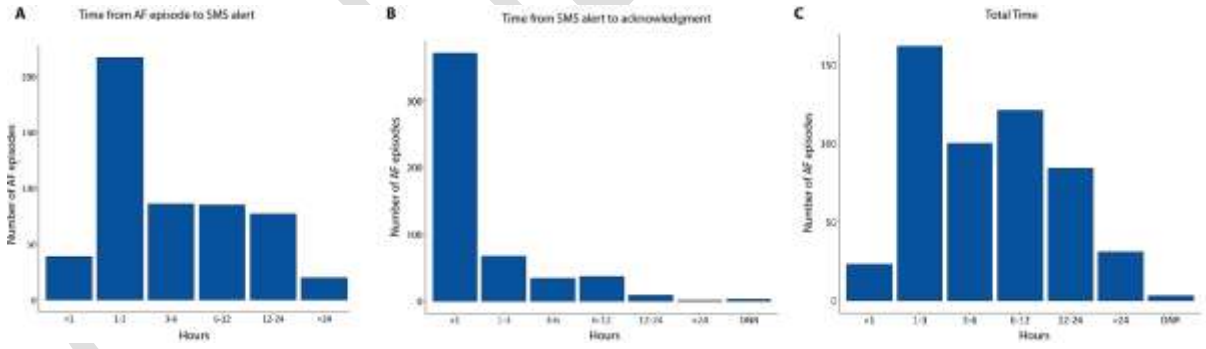

Figure 2. Preliminary results of interim analysis A) Time to AF episodes to SMS alert, B) time from SMS alert to acknowledgment, total time

Wearable device performance: Our preliminary analysis has also shown episodes of AF detected by the LINQ II™ that were missed by the wearable devices. As an example, in one patient, over the course of a 6-month period with 11 AF episodes detected by the LINQ II ICM, a total of 6/11 episodes were missed by the wearable device (on 3 of these occasions because the device was not being worn).

This raises the issues of accuracy of and patient compliance with wearable devices and gives us confidence in our approach for RESPOND-AF in using remote-monitoring with the LINQ II™ ICM.

3.2 Custom patient notification programme

Custom Software: Our patient messaging software was developed in-house at Oxford University Hospitals in collaboration with BrainLogic Ltd software development company. The programme is designed to monitor the Medtronic Carelink™ records of our patient cohort every 5 minutes continuously, and alert them via SMS message when AF episodes are detected by the LINQ II™ ICM. The patient is prompted to acknowledge the alert with a reply SMS, and this response is logged by our software programme.

During the SMART-ALERT study the custom software had two major updates to its code. These were in response to issues with delays to SMS alerts being sent to patients and minor ad-hoc updates due to CareLink™ and Google Chrome™ browser updates and/or changes. Version 3.0 ran seamlessly from January 2023 until study closure in June 2023 without any human intervention or manual restarting required. We continue to observe and analyse participant transmissions in a post-study clinic for patients who have completed follow-up and agreed to ongoing remote monitoring with the implanted cardiac monitor.

BrainLogic will continue to host and manage the running of the software. We also maintain communication with the Medtronic engineering team regarding how our software interacts with the Carelink™ system.

The overall objective of the RESPOND-AF study is to assess the feasibility of an automated approach to “as-required” anticoagulation. We are not assessing the performance of the LINQ II device or of our messaging software, which was assessed extensively during the previous SMART-ALERT study.

RESPOND-AF is not being carried out for the purposes of seeking CE-marking for our patient messaging software, and we do not intend to commercialise it. The software was developed in-house to be used solely as a research tool for patients recruited at our single-site research institution and will not be used outside of the remit of this study.

3.3 Public and patient involvement

Patient-public involvement: We conducted a survey in 320 patients with a diagnosis of AF in collaboration with the AF association. In this survey, a quarter of patients forget to take their OAC at least once a week, one third has experienced side effects from taking OAC and 70% worry about bleeding complications. Importantly, it highlights that patients would welcome alternative stroke prevention strategies, and more than half (55%) would choose an as-required OAC guided by an ICM if this strategy was deemed safe.

An ICM implant does not appear to be a barrier to recruitment in trials using as-required OAC. In a short survey of patients with a Reveal LINQ at the John Radcliffe Hospital, 92% were very satisfied and would have a Reveal LINQ purely as a research device.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To investigate the reduction in oral anticoagulation (OAC) utilisation during follow-up.	**Primary Outcome Measures** Calculate the proportion of time off anticoagulation OAC	During follow-up (minimum 13 months)
Secondary Objectives 1. Thromboembolic events (Ischaemic stroke, transient ischaemic attack (TIA) and systemic embolism)	**Secondary Outcome Measures** 1. Calculate the rate of ischaemic stroke, TIA and systemic embolism in patients on as-required OAC	1. During follow-up (minimum 13 months)
2. Major bleeding	2. Calculate the rate of major bleeding in patients on as-required OAC	2. During follow-up (minimum 13 months)
3. Minor bleeding	3. Calculate the rate of minor bleeding in patients on as-required OAC	3. During follow-up (minimum 13 months)
4. Any stroke (ischaemic, haemorrhagic or undetermined).	4. Calculate the stroke rate (ischaemic, haemorrhagic or undetermined)	4. During follow-up (minimum 13 months)
5. All-cause mortality	5. Calculate the rate of all-cause mortality in patients on as-required OAC	5. During follow-up (minimum 13 months)
6. Protocol adherence	6. Calculate the number of daily transmissions and percentage of patients that restarts OAC within 24 hours of the smartphone-alert.	6. During follow-up (minimum 13 months)
7. To assess response time from AF episode onset to patient starting as-required OAC	7. Time from AF episode onset to detection, time to alerts being sent and acknowledged and OAC	7. During follow-up (minimum 13 months)

	being taken by the participant. Proportion of missed AF episodes, transmissions or alerts.	

5. STUDY DESIGN

The objective of the RESPOND-AF study is to evaluate the feasibility of delivering "as-required" oral anticoagulation (OAC) guided by continuous rhythm monitoring with an implantable cardiac monitor (LINQ II™ ICM) and automated patient smartphone alerts, and to assess if this approach reduces OAC utilisation.

This study will recruit 50 participants with current paroxysmal or persistent AF being treated with a rhythm control strategy and infrequent AF episodes. The study consists of two main phases: (1) the active run-in period, which lasts one month, and (2) the treatment period which will last a minimum of 12 months.

All potentially eligible participants will undergo an enrolment visit (Visit 1) and, if they fulfil all the eligibility requirements, they will enter the active run-in period and will have a LINQ II™ ICM implant as a Day Case Procedure. A 3-month supply of their previously prescribed oral anticoagulant will be issued.

During the run-in period, participants will continue to take OAC for 30 days. Day 30 will be the start of the treatment period and the participant will be contacted by the research team. If participants meet the discontinuation criteria, they will be asked to stop OAC, otherwise they will remain on OAC until discontinuation criteria (freedom from AF episodes longer than 1 hour and/or daily burden of more than 1 hour for 30 consecutive days) are met. The purpose of the run-in period is to ensure that patients do not discontinue their pre-study OAC prematurely, i.e., less than 30 days after their last significant AF episode.

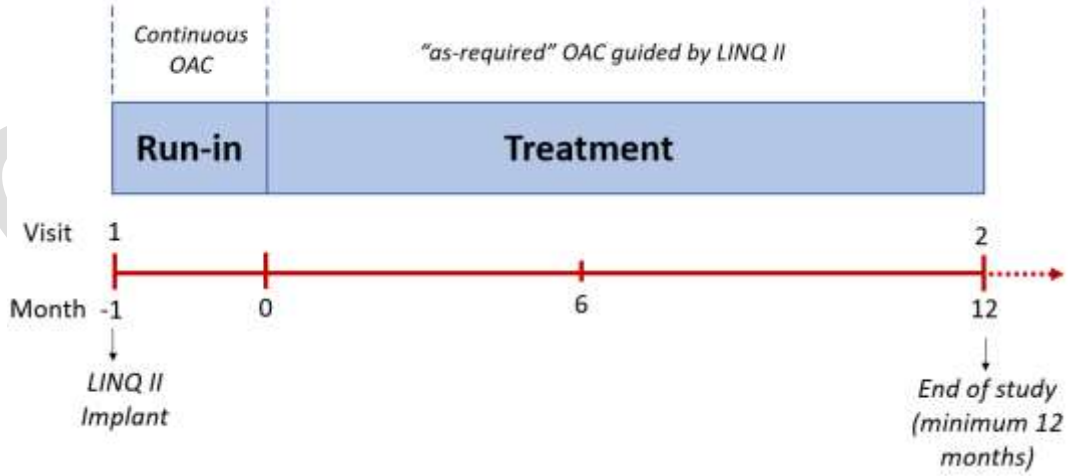

Figure 3. Study flow chart

In the treatment period patients will only be taking daily OAC if there has been an AF episode in the previous 30 days. If the LINQ II™ ICM detects an episode of AF meeting the initiation of OAC criteria,

it will send an alert to the CareLink™ Network. Our software programme actively screens Carelink every 5 minutes and will generate a patient SMS text message in response to an AF episode. The SMS is sent to the participant advising of the episode, prompting them to restart OAC. They must respond to the notification to acknowledge receipt and confirm they have commenced their OAC. The software will also send an email notification to the research team that the threshold for OAC initiation has been met. If there is no response from the patient within 24 hours, they will receive a second notification. If they do not respond to this second notification, a member of the research team will make direct contact with the patient (within 48 hours of AF episode onset) to ensure they have commenced their OAC and troubleshoot any issues they may be having.

A member of the research team will adjudicate all alerts and contact participants within 48 hours. If the alert was appropriate, participants will be advised to continue OAC for at least 30 days. If, after reviewing the episode, the alert is deemed inappropriate (false positive alert i.e., did not meet criteria for OAC initiation) participants will be instructed to stop OAC and this false positive alert will be logged.

Once OAC is initiated, participants may discontinue OAC if they have 30-day freedom from: 1) any continuous AF episode longer than 60 minutes, and 2) any AF burden of more than 1 hour in a 24-hour period. A member of the research team will contact them by telephone to do so.

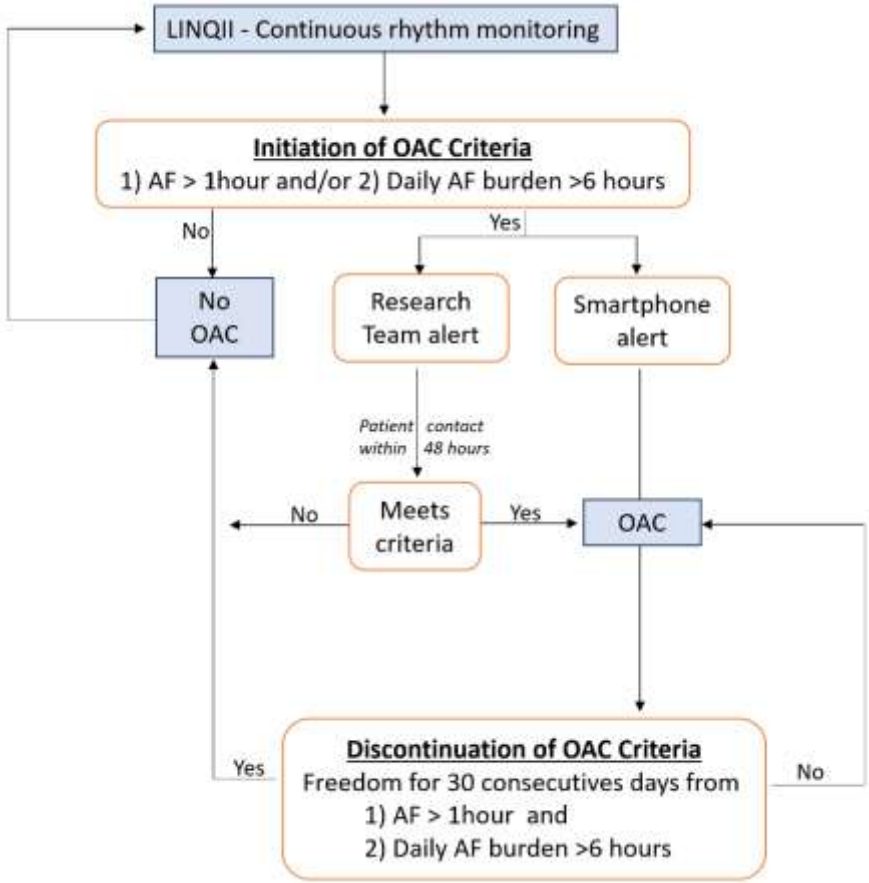

Figure 4. Study algorithm for the initiation and discontinuation of oral anticoagulation (OAC)

As a safety measure, the LINQ II™ ICMs perform automatic transmissions every 24 hours to CareLink™. The research team will conduct a daily review of all transmissions. If an AF episode/AF burden is identified that meets initiation criteria but failed to trigger an appropriate smartphone alert, participants will be contacted within 24 hours and instructed to restart OAC. Any failure of the system to generate an alert will be reviewed and logged.

During the study (run-in and treatment period), participants will keep a diary of any new drugs started, stopped or dose changes.

At the end of the study, participants will be invited to attend the Device Clinic for a final manual device interrogation and full clinical review of their medical care over the previous 12 months (Visit 2). They may choose to have the LINQ II™ ICM explanted during the final visit or leave it in-situ. It can be deactivated or else continue to monitor the patient's heart rhythm. The primary endpoint is total OAC utilisation which will be calculated by dividing the number of days on OAC by the total number of days during the treatment period.

5.1 Study Timeline

This 24-month prospective single centre feasibility study is to be conducted in 2 phases:

1. Patient recruitment, ICM implant and data entry (20 months): during this period recruitment will take place and the LINQ II™ ICM will be implanted at the start of the active run-in period for 1 month. They will then enter the treatment period for a minimum of 12 months. Data entry to be completed within 6 weeks of enrolment and will be monitored every 2 months.
2.
3. Completion of data entry and analysis (4 months): to finalise the data entry, adjudicate all AF episodes 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.

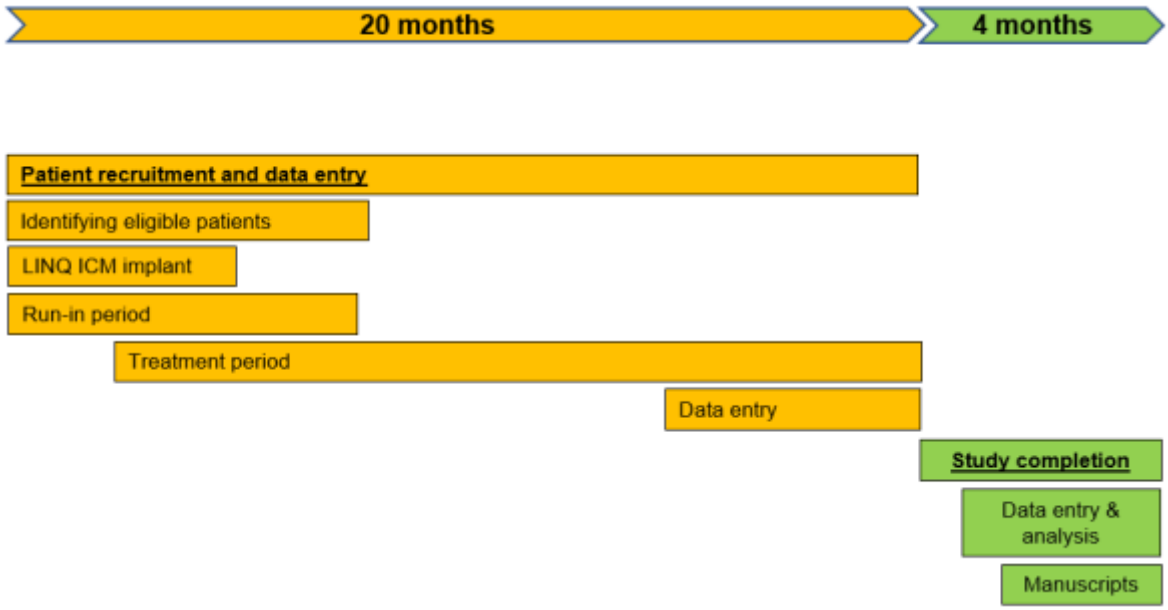

Figure 5. Study timeline.

5.2 Study Risks

The LINQ II™ ICM has CE marking and is used in routine clinical practice; the implant procedure is safe and minimally invasive. The procedure will be performed under sterile conditions and local anaesthetic using the insertion tools supplied by the manufacturer to inject the ICM under the skin in the anterior chest wall.

There are no known contraindications. Potential adverse events include:

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

By taking part in this study, participants understand that the stroke prevention strategy proposed is not the standard of care in current guidelines. Although the thromboembolic and bleeding events were low in the small studies that tested the hypothesis of as-required OAC with DOACs, they were not designed to provide a definitive answer regarding safety or efficacy of this novel management strategy. The initial data is nonetheless encouraging, and we believe that in a carefully selected population with low-risk of stroke and with low AF burden an as-required approach is safe and effective at preventing AF-related strokes.

5.3 Study Benefits

The main benefit from this study will before for future patients. It is important to understand if this novel approach to OAC in AF patients is a feasible, effective, and safe. It is important to develop a robust platform that can accurately monitor and notify patients during AF episodes, paving the way for a randomised trial testing the hypothesis of “as required” oral anticoagulation.

A reliable as-required OAC strategy will offer the same thromboembolic protection as continuous OAC, whilst at the same time reducing bleeding complications, reduce oral anticoagulation requirement, and may reduce overall healthcare associated costs. Participants may experience these benefits directly while taking part in the study, as well as future patients experiencing these benefits.

Patients may benefit directly from continuous heart rhythm monitoring during the study, which may help guide better clinical management decisions of their Atrial Fibrillation (ie. it may help their clinical team make decisions on medications, cardioversion, need for permanent pacemaker implant, need for AF ablation procedure). This would not be available if they were not part of this trial. The LINQ II™ ICM may also pick up other clinically relevant arrhythmia, which would not otherwise have been known about.

6. PARTICIPANT IDENTIFICATION

6.1 Inclusion Criteria

Study participants must satisfy the following conditions:

- Participant is willing and able to give informed consent for participation in the trial.
- Understand the risk and willing to discontinue oral anticoagulation (OAC).
- Any gender aged 18 years or above.
- Non-valvular paroxysmal atrial or persistent atrial fibrillation (AF) with a current rhythm control strategy. Paroxysmal patients must have < 3 documented or symptomatic episodes of >1 hour duration in the previous 3 months. Persistent patients must have been in continuous sinus rhythm for at least 4 weeks prior to enrolment.
- CHA_2DS_2-VASc score between 1 and 3 in men and between 2 and 4 in women.
- Able to take DOAC in guideline recommended doses.
- Left atrial diameter on echocardiogram less than 5 cm (AP dimensions) or LA volume less than 48 ml/m^2.

6.2 Exclusion Criteria

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

- Any contraindication to OAC therapy with a DOAC in guideline recommended doses.
- Mechanical heart valve prosthesis or moderate-to-severe mitral valve stenosis.
- Permanent atrial fibrillation.
- Hypertrophic cardiomyopathy.
- Documented previous thromboembolic event (stroke, TIA or systemic embolism).
- Spontaneous echo contrast observed in any imaging modality.
- History of intracardiac thrombi.
- History of congenital heart disease.
- Severe chronic renal disease (eGFR <15 ml/m) or on renal replacement therapy.
- Pregnant or planning pregnancy.
- Indication for OAC other than atrial fibrillation.
- Inability to comply with protocol.
- Smartphone with OS not compatible with MyCareLink Heart™ app.
- Contraindication for implantable cardiac monitor.
- Visual or physical impairment that prevents ability to read and acknowledge smartphone/watch notifications.
- As far as is practicable, language barriers between the investigators and study participants will be circumvented using NHS interpreters. If necessary, we will arrange for smartphone alerts to be sent to participants in their native language.

6.3 Recruitment

The research team will screen the Arrhythmia Outpatient Clinics, Remote Device Clinics, AF Ablation lists and Cardioversion Lists at Oxford University Hospitals for potential participants. All members of the research team are part of the Cardiac Rhythm Management Care Team, and as such, all screened participants will be under their direct care.

A letter of invitation, a patient information sheet (PIS) and a consent form will be given to potential participants at the time of the Outpatient Clinic or posted to them later.

Patients will have the opportunity to contact the Research team if they wish to take part. A member of the Research team will also make a follow-up contact with potential participants after they have received their PIS.

Once the potential participants have considered the information and had the opportunity to have their questions addressed and speak with their family members and /or GP, if they agree to take part in the study, they will be invited for Visit 1.

During Visit 1, if participants are found to be eligible and wish to participate, they will have a Baseline Assessment performed and Informed Consent taken to enter the study. The aim is to recruit 50 patients in total.

Members of the clinical team (who are not members of the Research team) may also identify patients through their clinical practice and provide information (including a patient information leaflet) regarding the trial and put them in contact with the research team. If the participants meet the inclusion criteria, they will be invited to participate in this study and, if they agree to participate, they will undergo screening and eligibility assessment.

6.4 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 versions of the Participant Information Sheet 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/Cardiologist 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. The original signed form will be retained at

the trial site, kept in a marked lever arch folder, in the Cardiology Clinical Research Fellows' office, Level 2, John Radcliffe Hospital. This office is on a staff-only corridor, and the door is combination locked. Only members of the Cardiology Research team have access to this office.

6.5 Screening and Eligibility Assessment

If a participant meets the inclusion criteria they will be invited to participate in the study. 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 (including previous thromboembolic events)
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

6.6 Randomisation

Not applicable. Single-arm feasibility study.

6.7 Blinding

Not applicable. Single-arm feasibility study.

6.8 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

6.9 Intervention – LINQ II ICM implant

The LINQ II™ ICM will be implanted as a Day Case. The procedure will be performed under sterile conditions, will require local anaesthetic (lidocaine 1%), and insertion tools supplied by the manufacturer will be used. If there is suboptimal R-wave amplitude the operator can reposition the device. The operator may choose to close the wound with steri-strips, surgical glue or a suture. LINQ II™ ICM implant procedure is safe and minimally invasive and takes <15 minutes to do. There are no

known contraindications. Potential adverse events occur in less than 1% of procedures and include bruising, haematoma, superficial infection, keloid scar formation, migration or extrusion.

The LINQ II™ ICM is in constant communication with the smartphone app through low-energy Bluetooth and transmits stored episodes to Medtronic servers via its smartphone app. Participants will be instructed to always keep the Bluetooth "on" and to permit a pop-up notification to appear on their smartphone if the LINQ II™ ICM loses connection with the smartphone app. ICM recordings can only be accessed on Medtronic servers through the clinician web portal (Medtronic CareLink™ Network). The assigned study ID number will be used to register the device in the CareLink™ Network; thus, no identifiable patient information will be in the servers. Access to these servers is via the clinician web portal and it is password-protected. Transmission reports will be downloaded from the Medtronic™ servers and stored in a password protected folder that will only be used in OUH trust computers for adjudication at the end of study. This system is part of routine clinical practice around the UK in according with GDPR guidelines.

For this trial, if the LINQ II™ ICM detects an AF episode or AF burden that meet criteria for OAC initiation it will transmit in real-time to CareLink™. Our messaging software will then generate an email to the research team and a text message to the participant's smartphone. The sender info of the text message will include the RESPOND-AF research team telephone number and prompts patients to initiate OAC. Participants will be instructed to acknowledge receipt of the notification by replying to the text message once they have taken their OAC, and thus record a time stamp (figure 4). Adjudication of all alerts as either appropriate or inappropriate by members of the research team and participants contact will take place within 48 hours.

Figure 6. Summary of study procedures during treatment period.

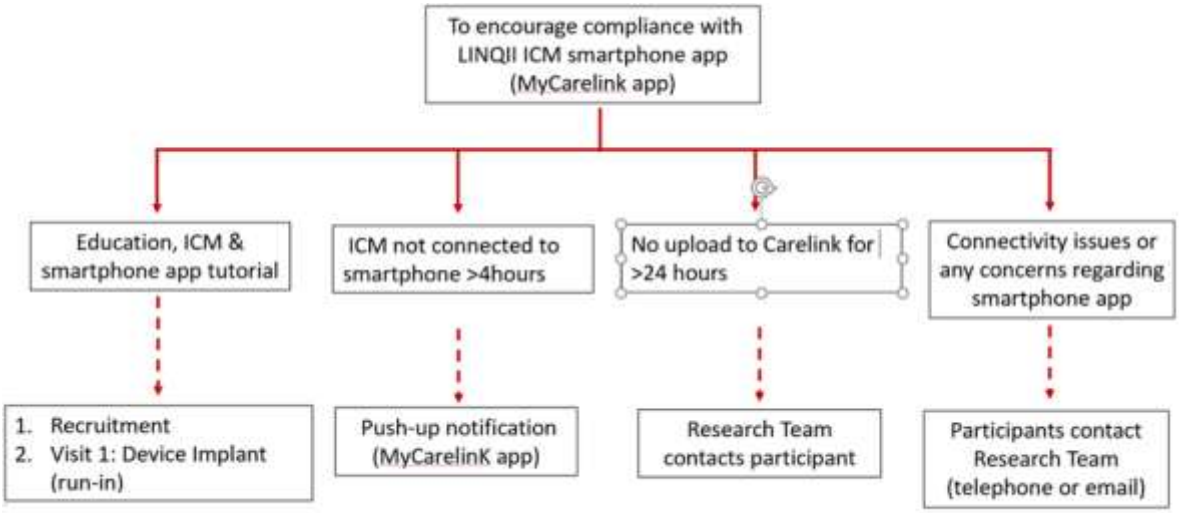

Figure 7. Algorithm to improve compliance with LINQ II ICM and ensure daily transmission of monitoring data.

6.10 Subsequent Visits

Visit 1 (Eligibility assessment, LINQII ICM Implant and Run-in period): If a participant agrees to take part, he/she will be evaluated against the entry criteria and exclusion criteria. Other tests, such as echocardiography, may be organised. If eligible, the participant will be asked to sign an informed consent.

Participants will have a LINQ II ICM implant. They will be taught how to pair the LINQ II ICM to their smartphone and how to use the smartphone app (MyCareLink) to record and send manual transmissions. Participants will be given a 3-month supply of a DOAC and instructed to continue OAC for 30 days (run-in period). At the end of the run-in period, they will enter the treatment period and will be contacted by the research team to either continue on OAC (if they have not met the discontinuation criteria) or to discontinue their OAC and commence the "as-required" regimen guided by smartphone alerts.

The investigator may consider the initiation or optimisation of anti-arrhythmic drugs at this time.

Visit 2 (End of study): At the end of study, patients will attend Device Clinic for a final clinical review. At this time, they may choose to have the ICM removed. An updated medical and drug history will be recorded. At this point, patients will be instructed to revert to standard clinical care.

Unscheduled visits: In addition to the protocol-specified visits, patients may be seen at any time throughout the study at the discretion of the investigator. This may include and it is not limited to visits to review medication, LINQII ICM troubleshooting, review adverse events, perform direct current cardioversion or other procedures such as catheter ablations. Periprocedural OAC will follow current ESC guidelines recommendation.

6.11 Early Discontinuation/Withdrawal of Participants

During the trial a participant may choose to withdraw early from the trial treatment at any time. This may happen for several 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 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/she may choose to:

- Continue to have the routine LINQ II ICM downloads as per clinical need.
- To have the LINQ II ICM turned off.
- To have the LINQ II ICM removed. The investigators will organise an outpatient procedure.

6.12 Definition of end of study

The end of the follow-up period will be when all participants have had a minimum of 12 months in the treatment period. The end of the study period will be 4 months after the end of follow-up. During this time investigator will conduct the analysis and draft a report of the findings.

9 TRIAL INTERVENTIONS

9.1 Other Interventions

The decision to organise a direct current cardioversion and/or optimisation of any antiarrhythmic medications is common in the management of AF and will be left to the Investigators discretion. Investigator may also decide to offer participants a catheter ablation if deemed appropriate. Periprocedural OAC will follow current ESC guidelines recommendation.

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.

10.3 Adverse Events

Adverse events (AE) will be collected upon enrolment to the study until and including the final visit. All adverse events will be recorded in the CRF and should include the following:

- AE.
- Date of AE.

- Date when investigator become aware of AE.
- Date of hospitalisation.
- Date of discharge.
- Outcome.
- Whether this event constitutes a serious adverse event (SAE).
- Whether this event is a clinical endpoint.
- Action taken.

All potential neurological symptoms or events will be formally assessed by stroke physicians or neurologists.

Clinical endpoint definitions are according to the outcome measures in AF endorsed by the Heart Rhythm Society.[31]

- Stroke: defined as acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction. Symptoms or signs must persist for more than 24 hours, or if documented by CT, MRI or autopsy, the duration of symptoms/signs may be less than 24 hours. Stroke may be classified as ischemic (including haemorrhagic transformation of ischemic stroke), haemorrhagic, or undetermined.
- Systemic embolism: defined as an acute arterial insufficiency or occlusion of the extremities or any non-central nervous system (CNS) organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism.
- Major bleeding: Fatal bleeding AND/OR symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome AND/OR bleeding causing a fall in haemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of blood.
- Minor bleeding: All nonmajor bleeds. Minor bleeds are further divided into clinically relevant and not.

11 STATISTICS AND ANALYSIS

11.1 Analysis of Outcome measures

Descriptive statistics will be reported as count (percentage) for the categorical variables and mean (± standard deviation) for the continuous variables. The primary endpoint will be total OAC utilisation, which will be calculated by dividing the total number of days on OAC with the total follow-up duration. Adjudication of all LINQ II™ ICM electrograms will be performed by the research team to determine if notification was appropriate or inappropriate. The percentage of appropriate notifications and the mean time (± standard deviation) from notification to taking OAC will be measured. The associations of the measurements with the patient demography, medical history, imaging biomarkers, medications, etc. will be investigated.

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 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 study ID number which will be assigned following consent. The study ID number will be used in both hard-copies and electronic documents (Excel spreadsheets for analysis, PDF of device downloads). The hard copies (paper Consent forms and external hard-drive data backup) 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 study ID number will be maintained on a single document and will be kept on a separate folder in the PI's office (Prof Tim Betts). This office can only be accessed by authorised personnel via a door-code and it is also located in the John Radcliffe Hospital, Level 2 Blue Outpatients.

For electronic records, all records will be stored securely on OUH servers (CTS01 drive >> CRM >> Research folder) in a separate, password-protected folder for the RESPOND-AF study. Only Research staff directly working on RESPOND-AF study will have access to this folder. This folder will have sub-folders for each individual participant, named using their study ID.

Our study will use Microsoft Excel as an electronic Case Report Form. At every new time-point of patient contact (patients visits or electronic transmissions) a blank eCRF template will be opened on Microsoft Excel and used for data input. Once data has been entered for that time-point, the file will be saved in the format "mm.dd.yyyy.hh.mm.studyID". For example, for participant AF001 transmission data entered on the 24th December 2024 at 13:45, the file would be saved as "12.24.2024.13.45.AF001". The file will be saved in that participant's individual folder on the RESPOND-AF research folder on OUH drive (as detailed above).

All files will also be saved on an external password protected hard-drive for data backup, which will be kept securely in the Research Fellows' Office (see above) with other physical study documents.

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

Individual Excel files for each timepoint data entry for each patient will eventually be merged to create a master database. This master database will be used for subsequent statistical analysis.

The LINQ II™ ICM only transmits recordings to their company's servers which can be accessed through the clinician's web portal (CareLink™). This is the routine clinical practice in OUH for devices which are on remote monitoring (patients don't have to physically attend hospital for a device interrogation). The assigned study ID number will be used to register the device in CareLink™; thus, no identifiable patient information will be held on Carelink servers. Moreover, all participants will be assigned to the RESPOND-AF research clinic in CareLink™ and all transmissions will be routinely monitored by the research team. AF alerts generated by CareLink™ will be sent to the research team email (respond-af@ouh.nhs.uk) and to participants' smartphones. Participants will acknowledge AF alerts by replying to a text message generated by CareLink which will include the research team telephone number in the sender details. Participants will be identified by their trial ID and the date and time will be recorded in the participant's CRF.

Our patient messaging software will be hosted and run 24 hours per day on Brain Logic servers. The only participant data held on the Medtronic Carelink system will be the anonymous study ID and mobile number. Therefore, the software programme and BrainLogic will only be able to "see" the study ID and mobile numbers for our participants. If there is a new AF transmission, our software programme will use the mobile number stored on Carelink to send an SMS alert to the participant. BrainLogic will not at any point have access to other participant details such as name, gender, DOB, address, hospital ID, etc.

Access to CareLink™ is password protected. Transmission reports will be downloaded from CareLink™ and stored in a password-protected file that will only be used in OUH trust computers.

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

Not applicable

13.3 Study Committees

Not applicable.

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 their 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

Funding provided by Medtronic Limited. Medtronic will provide the 50 LINQ II implantable cardiac monitors at no cost. They have also supplied financial funding for the setup and running of the study.

17.2 Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a 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 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 rests 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, Level 2 Blue Outpatients, 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.

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