Chelsea and Westminster Hospital NHS
NHS Foundation Trust

AMLA- AF

Application of machine learning algorithm to identify patients at highest risk of atrial fibrillation for targeted screening

Version 1.1
25/10/2021

MAIN SPONSOR: Chelsea and Westminster Hospital NHS Foundation Trust
FUNDERS: Bristol Myers-Squibb Pharmaceuticals Ltd, CW+ Charity (Chelsea and Westminster Hospital NHS Foundation Trust)
STUDY COORDINATION CENTRE: West Middlesex University Hospital

IRAS Project ID: 293493
REC reference: 21/LO/0709

Protocol authorised by:

Name & Role	Date	Signature

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and breaches of GCP from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:
Signature: Date:
..../...../.....
Name (please print):
.....
Position:
.....
Chief Investigator:
Signature: Date:
..../...../.....
Name: (please print):
.....

Study Management Group

Chief Investigator: Dr Sadia Khan

Co-investigators: Dr Pavidra Sivanandarajah, Dr Fu Siong Ng

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dr Pavidra Sivanandarajah
Address: West Middlesex Hospital, Twickenham Road, Isleworth, TW7 6AF
Registration:
Tel:
E-mail: pavidra.sivanandarajah1@nhs.net
Fax:
Web address:

Clinical Queries

Clinical queries should be directed to Dr Sadia Khan who will direct the query to the appropriate person.

Sponsor

Chelsea and Westminster Hospital NHS Foundation Trust is the main research Sponsor for this study.

For further information regarding the sponsorship conditions, please contact:

Chelsea and Westminster Hospital NHS Foundation Trust
Research & Development Office
Unit G2, Harbour Yard
Chelsea Harbour
London
SW10 0XD
Telephone number: 020 3315 6825
Email: research.development@chelwest.nhs.uk

Funder

CW+ Charity (Chelsea and Westminster Hospital NHS Foundation Trust) and Bristol Myers Squibb Pharmaceuticals Ltd are funding this study.

This protocol describes the ALMA-AF trial and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Principal Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research It will be conducted in compliance with the protocol, Data Protection Act 2018 and General Data Protection Regulations (Europe) and other regulatory requirements as appropriate.

Keywords
Atrial fibrillation, Screening, Machine learning

LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	**Adverse Event**
AF	**Atrial fibrillation**
AR	**Adverse Reaction**
CI	**Chief Investigator**
ECG	**Electrocardiogram**
GCP	**Good Clinical Practice**
ICF	**Informed Consent Form**
ISRCTN	**International Standard Randomised Controlled Trials Number**
ML	**Machine learning**
MLA	**Machine learning algorithm**
NHS R&D	**National Health Service Research & Development**
PI	**Principal Investigator**
PIC	**Participant Identification Centre**
PIS	**Participant Information Sheet**
PPG	**Photoplethysmography**
QA	**Quality Assurance**
QC	**Quality Control**
QP	**Qualified Person**
REC	**Research Ethics Committee**
SAE	**Serious Adverse Event**
SAR	**Serious Adverse Reaction**
SDV	**Source Data Verification**
SOP	**Standard Operating Procedure**
SSI	**Site Specific Information**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**

STUDY SUMMARY

TITLE	Application of machine learning algorithm to identify patients at highest risk of atrial fibrillation (AF) for targeted screening
DESIGN	Prospective cohort study
AIMS	To evaluate the potential benefit of using our machine learning algorithm to aid AF screening. To compare the use of different health technologies for AF screening To evaluate the optimal duration and frequency of rhythm monitoring for AF screening
OUTCOME MEASURES	Detection of atrial fibrillation Diagnostic yield of machine learning algorithm for detection of AF
POPULATION	Primary care patients in Hounslow community
SAMPLE SIZE	~ 9 000 high risk AF patients identified from machine learning algorithm ~ 1 800 patients for further AF screening
ELIGIBILITY	**Inclusion criteria** Aged 18 years old or above Identified as high-risk for AF by our machine learning algorithm Access to smartphone depending on allocated screening group **Exclusion criteria** Have already a diagnosis of atrial fibrillation prior to study enrolment Below the age of 18 years old Presence of cardiac electronic implantable device
DURATION	1.5 years

STUDY FLOW CHART

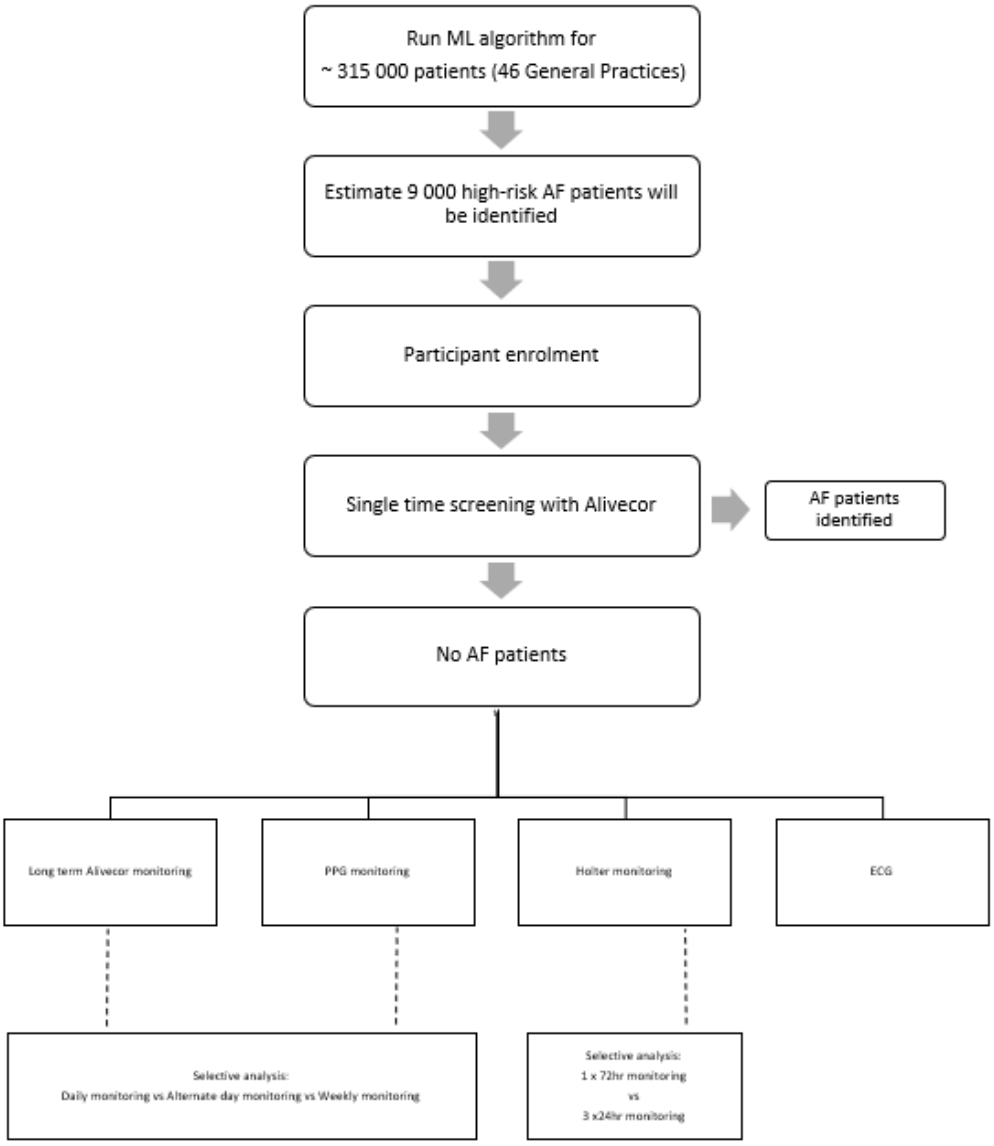

Figure 1 Study Design

1. INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disturbance (arrhythmia). Individuals with atrial fibrillation have a five-fold increased risk of developing strokes. AF can be persistent or paroxysmal (intermittent). People with AF can be unaware that they have the condition as they may not display any symptoms. This results in many people presenting with AF at the time they present to hospital with a stroke. Strokes are debilitating, cause significant permanent disability and are a burden to the healthcare system.

If AF is identified earlier, strokes can be prevented with treatment in the form of a blood thinner (known as anticoagulation). In order to make a diagnosis, a heart tracing called an electrocardiogram (ECG) will be required. Currently, over 100 individuals will need to be screened in order to pick one individual with AF. However, a new machine learning algorithm has been developed (using previous AF risk score models and primary care data) and it has been predicted to increase our yield in identifying patients at risk of developing atrial fibrillation. Early data has suggested that it reduces the number needed to screen to 9 to pick one patient with atrial fibrillation.

We will run this machine learning algorithm on the databases of general practices in the Hounslow area. Once the high-risk AF individuals have been identified, they were cluster randomised to four groups according to their general practice. Individuals from four groups will be invited to be screened for AF. Individuals from each group without a diagnosis of AF will be invited to receive a health technology to aid AF detection.

There has been a recent surge in the number of technologies available for ECG monitoring. As more people have smartphones, this provides us with more opportunities to monitor patients for longer and more frequently and ultimately, diagnose AF earlier. There have been no comparative trials of mobile health technologies. This study will allow them to be compared for the first time.

The ability of the machine learning algorithm and different health technologies to detect AF will be analysed. Due to the paroxysmal nature of AF, we will also use health technologies to determine the optimal duration and frequency of rhythm monitoring for AF screening as this is currently unknown.

2. STUDY OBJECTIVES

AIMS

1. To evaluate the potential benefit of using our machine learning algorithm to aid AF screening

2. To compare the use of different health technologies for AF screening

3. To evaluate the optimal duration and frequency of rhythm monitoring for AF screening

3. STUDY DESIGN

This will be a 1.5-year study in which participants will be recruited prospectively from databases of 46 general practices (GPs) in the Hounslow area. Our machine learning algorithm will be used on these databases to identify our participants. Our participants will be identified as those at risk of developing atrial fibrillation. The practices will be cluster randomised into 4 groups. The high- risk AF individuals will be invited for screening for

AF. The four groups are as follows: (1) ECG group (2) Holter monitoring group, (3) a Photoplethysmography (PPG) monitoring group and (4) a long term AliveCor monitoring group.

All individuals who have agreed to participate in the study will be screened initially once with a single lead ECG recording using an AliveCor device. This will be done either at their general practice or a research clinic at West Middlesex University Hospital. Any individual found to have AF will be followed up by their general practice to receive appropriate treatment. They will also not be required to have any further screening.

After this initial screening, if an individual has not been found to have AF and belongs to groups 2-4, they will undergo further screening for a period of 3 months. This will be based on their allocated group. They will be able to take their screening technology home. Again, if any individual is found to have AF, they will be followed up by their general practice to receive appropriate treatment.

Participation in this study will be entirely voluntary and will not affect participants' current or future care. Participants will be free to withdraw from the study at any time without having to provide a reason. Participants will be recruited prospectively from general practices, on a first-come first-serve basis, to minimise bias. Recruitment will continue throughout the study.

Data collected from participants prior to drop out or loss to follow-up will be included in the data analysis. We are not aware of any ongoing studies that are competing for the same group of participants or whose results may affect recruitment. Similarly, our study will not jeopardise other studies either.

3.1 STUDY OUTCOME MEASURES

The primary endpoint will be the detection of atrial fibrillation with a one-off ECG. The diagnostic yield of the machine learning algorithm will be analysed.

The diagnostic yield for AF detection of each health technology will be analysed. The time to first detection of AF will also be measured for each health technology.

Selective analysis will be performed looking at diagnostic yield for AF detection for different rhythm monitoring strategies which vary in frequency and duration.

4. PARTICIPANT ELIGIBILITY CRITERIA

Prospective participants will only be recruited from the high-risk AF population identified by the machine learning algorithm. They will need to fulfil the inclusion criteria in order to enrol into the study.

4.1 INCLUSION CRITERIA

To take part in the study, participants must meet all the following requirements:

a) Aged 18 years old and above
b) Identified as high-risk for AF by our machine learning algorithm

c) Access to smartphone if part of Photoplethysmography or long term AliveCor monitoring groups

4.2 EXCLUSION CRITERIA

Participants with any of the following will not be able to take part in the study:

a) Have already a diagnosis of atrial fibrillation prior to study enrolment
b) Below the age of 18 years old
c) Presence of cardiac electronic implantable device

4.3 WITHDRAWAL CRITERIA

Participants will be withdrawn from the study if they fulfil one of the following:

a) Unable to use their screening health technology
b) Withdrawal of consent
c) Presence of cardiac electronic implantable device

5. STUDY PROCEDURES AND RANDOMISATION

Prior to patient recruitment, the machine learning algorithm will be run centrally at NHS Hounslow Clinical Commissioning Group, Hounslow House. It will be run across 46 general practice databases in the Hounslow area, which includes an estimated population of 315 000 people.
The algorithm will generate an anonymised list of high- risk AF individuals with their associated general practice. It is expected that this will be approximately 9 000 people.

Each general practice will be clustered into three different sets depending on the size of the population of high- risk AF patients found at that practice. The sets are classed into large (>200 patients identified screen), medium (100-200 patients) and small (< 100 patients). This will allow the GP practices to be later cluster randomised into four groups corresponding to the different screening strategies, with roughly equal number of large/medium/small GP practices in each group. These four groups that we will compare are: (1) ECG group, (2) holter monitoring group, (3) a PPG monitoring group and (4) a long term AliveCor monitoring group.

5.1 RECRUITMENT

Following this, each general practice will be visited separately and the algorithm will be run at each individual practice to identify individual high-risk AF patients. A member of each general practice will be shown how to run the algorithm and will run it on the database of the general practice. High-risk AF participants will be invited to be recruited into the study by a member of the general practice team. Every effort will be made to recruit vulnerable adults who lack capacity so they can be recruited if they wish to be involved. All high -risk participants recruited will be registered and flagged up on a depersonalised health data set covering the North West London (NWL) population, known as the Discover dataset, which is the NWL health research cohort register. This will allow the retrieval of health care data of these participants while keeping their anonymity. Each participant will have an anonymous identifier number. Approval for this has been sought from NWL Data Access Committee.

6. ADVERSE EVENTS

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject 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*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

6.2 REPORTING PROCEDURES

All serious & non serious adverse effects, whether expected or not, will be recorded. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the Chief Investigator in the first instance.

Non serious AEs

All such events, whether expected or not, will be recorded.

Serious AEs

An SAE form will be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to any pre-existing medical or surgical conditions and hospitalisations for elective treatment of a pre-existing conditions will not be reported as SAEs.

All SAEs will be reported to the London- Bloomsbury REC where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

The Chief Investigator will inform the sponsor of the study of all SAEs. Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event.

Local investigators will report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs
CI email (Dr Sadia Khan; sadiakhan1@nhs.net)

7. SCREENING AND FOLLOWUP

Participants' care will continue under their normal clinical or healthcare teams. Therefore, their followup will be arranged by and conducted by these team(s).

Following recruitment into the study, each participant will be invited for screening for AF at their practice or a research clinic at West Middlesex University Hospital.

At the baseline assessment, each participant will be required to have a single lead ECG recording for a minimum of 30 seconds using an AliveCor device (two metal pads on a plastic strip, Figure 2) and smartphone which will be provided by the research team. Figure 3 demonstrates the use of the device with a smartphone. For a recording, at least 1 finger is required to rest on each of the metal pad (electrodes). If AF is identified from this recording, the patient will be referred back to their practice for appropriate treatment.

Figure 2: AliveCor device

Figure 3: AliveCor recording

Participants without a diagnosis of AF in the holter monitoring group, photoplethysmography (PPG) monitoring group and the long term AliveCor monitoring group will be given a health technology to take away. They will have monitored with this technology for 3 months. The technology that they receive will be based on the monitoring group they belong to. The ECG group will not have any further monitoring.

For the holter monitoring group, the participants will receive a 72-hr holter monitor/ECG patch initially, and two further 24-hr holter monitors/ ECG patches at 6 and 12 weeks. These will be returned to the research team following completion of each monitoring period.

For the Photoplethysmography (PPG) monitoring group, the participants will be given access to a smartphone application called Fibricheck to use on their own smartphone. The participant will be provided with a QR code to scan for the prescription of 3- month

monitoring period. The participant will need to download the Fibricheck App on their own smartphone from the App store. They will then need to scan the QR code with the Fibricheck App. The participant will then be able to start making recordings by placing their finger on the camera for 1 minute. Figure 4 demonstrates how to set the Fibricheck App on a smartphone and Figure 5 shows how to take a recording with the App.

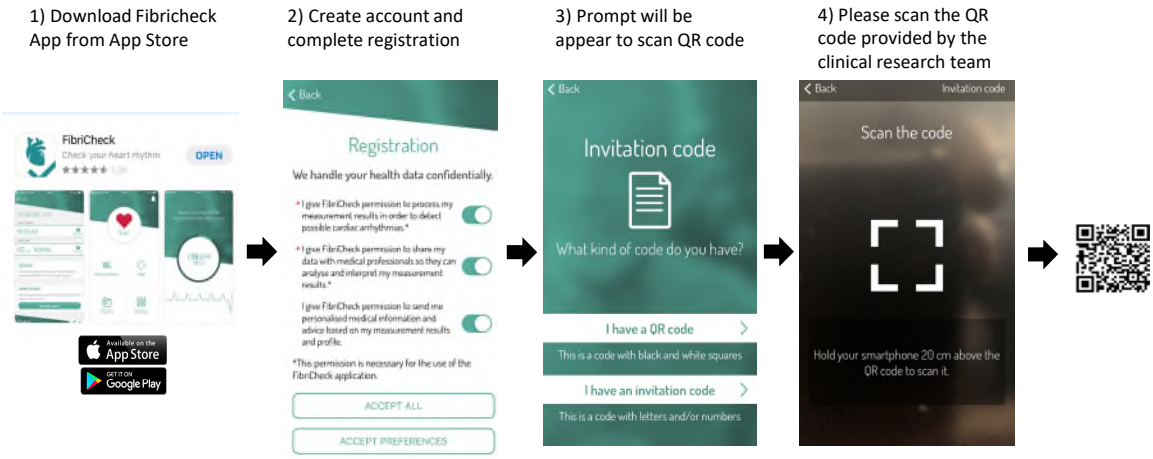

Figure 4: How to set up Fibricheck App on smartphone

Entering their pincode | *Clicking on the heart to start measurement* | *Placing their finger on the camera, measurement starts automatically* | *Annotating their symptoms* | *Real-time (limited) results*

Figure 5: How to take a recording using the Fibricheck App

The participants will be asked to perform twice daily recordings lasting 1 minute each using the camera light of their smartphone. If they have symptoms, they can also make further recordings. They will also be able to annotate the recording afterwards with their symptoms. The recordings will be performed over a period of 3 months. Following each recording, feedback will be given. The recordings will be sent to Fibricheck's secure cloud. Irregular results will be reviewed by Fibricheck's monitoring center under the supervision of cardiologists. The clinical research team will have access to all participant's data via the physician dashboard. They will regularly review the data on a weekly basis and will inform the participant if irregular results are seen which warrant further management. The clinical research team will also receive daily emails including notifications of any participants with new heart rhythm disturbances.

If a recording alerts an irregular pulse notification, the participant will be invited to their practice or a research clinic at the West Middlesex University Hospital to have a single lead ECG with AliveCor device or 12-lead ECG or a Holter monitor to detect AF.

For the long term AliveCor monitoring group, the participants will be given access to a smartphone application called Kardia to use on their own smartphone. They will also be a metal pad AliveCor device. The procedure for taking a recording will be explained when given access to the application and device. They will be asked to make twice daily recordings using the application and submit it to the research team for 3 months.

If AF is identified at any point during the 3- month monitoring period, the patient will be referred back to their practice for appropriate treatment.

8. STATISTICS AND DATA ANALYSIS

It is estimated that 9 000 participants will be identified to be high risk for AF. Taking into account the dropout from previous screening exercises, we estimate that 1 800 (20%) participants will belong to the four groups.

The diagnostic yield for AF detection will be analysed for the machine learning algorithm and each health technology.

There will be selective analysis of the data collected from the monitoring groups to determine the optimal frequency and duration.

For each participant for the holter monitoring group, two rhythm histories will be created. The first rhythm history will just include the results of 72hr monitor. The second rhythm history will include the results of first 24hrs of the 72hr monitor, the results of the second 24hr monitor and the third 24hr monitor. This will allow the screening strategies of 3 x24hr monitoring and 1 x 72hr monitoring to be compared. The diagnostic yield of AF detection for the two strategies will be compared.

The data from the PPG and long term AliveCor monitoring groups will then be selectively analysed with some recordings blanked from analysis to compare the diagnostic yield of different durations (1-month vs 3 months) and different frequencies (Daily vs alternate days vs weekly).

Data analysis will be performed at West Middlesex University Hospital.

All high-risk AF patients will be followed up for the detection of AF. This will be at least 1 year from the last recruited patient.

The end of the study will be defined as last followup required for the purposes of the study.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from London-Bloomsbury Research Ethics Committee (REC) and Health Research Authority (HRA).

The study has obtained confirmation of capacity and capability from Chelsea and Westminster Hospital NHS Foundation Trust to accept participants into the study for the purposes of research.

This study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.2 CONSENT

A member of the general practice care team will approach prospective participants to offer participation in the study in the first instance.

Members of the research team will only make contact with prospective participants after a member of the clinical care team has introduced the option of partaking in this study to them.

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet (patient information sheet) offered and time allowed for consideration. Signed written and verbal informed consent will be obtained from every participant/ witness/ relative at the beginning of the study at the point of enrolment. For vulnerable participants, every effort will be made to help their understanding of the study. We will also involve witnesses and/or relatives as necessary. Participants' suitability to partake will be checked prior to screening occurring after enrolment, according to inclusion and exclusion criteria. The right of the participant to refuse to participate or withdraw from the study at any point without giving reasons will be respected at all times.

After the participant has entered the study, their general practice clinician(s) remain free to give an alternative treatment or monitoring to that specified at the start of the research study, at any stage if they feel it is in the participant's best interest. The reasons for doing so will be recorded. In these cases, the participants can remain within the study for the purposes of data collection, follow-up and data analysis if they wish.

All participants are free to withdraw at any time from the study without giving reasons and without prejudicing current, further or future treatment.

9.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

All participants will have an anonymous identifier that will be generated by the research team during the recruitment process. Participants will be entered into a study database which will contain all research records. This database can be accessed at the West Middlesex University Hospital. It will be password protected and will have restricted access to specific members of the research team only. Anonymised data will be available to researchers. Similarly, during the course of the study, all medical history, ECG recordings, PPG recordings, holter monitor recordings and any other clinical data for the study will be stored in an anonymised format and securely on a password protected study database at West Middlesex University Hospital. This will also only be accessible by the research team.

Chelsea and Westminster Hospital NHS Foundation Trust retention schedule states that all study data should be retained for 10 years after completion of the study. This will include some identifiable data such as consent forms and will be stored in a secure Chelsea and Westminster Hospital NHS Foundation Trust archiving facility, in-line with institutional policy. All other personal data, such as contact details that will be kept securely during the study, will be irretrievably deleted and disposed at the end of the study.

Fully anonymised data from the database may be shared with approved research collaborators, if required during the course of the study.

In the event that the research participant loses capacity to consent during the study, their identifiable samples and data will be withdrawn from the study. Any samples or data that is not identifiable may be retained and used for the purpose of which they consented to.

9.4 INDEMNITY

Chelsea and Westminster Hospital NHS Foundation Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

9.5 SPONSOR

Chelsea and Westminster Hospital NHS Foundation Trust will act as the main Sponsor for this study.

9.6 FUNDING

Bristol Myers Squibb Pharmaceuticals Ltd and CW+ Charity **(**Chelsea and Westminster NHS Foundation Trust) are funding this study.

9.7 AUDITS AND INSPECTION

The study may be subject to inspection and audit by Chelsea and Westminster NHS Foundation Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

10 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the research team and clinical research fellow (Dr Pavidra Sivanandarajah) with overview from the chief investigator (Dr Sadia Khan).

11 PUBLICATION POLICY

All publications and data-sharing will be in accordance with the current guidance provided by Chelsea and Westminster Hospital NHS Foundation Trust.