Proposal

Increasing medication adherence among adults with atrial fibrillation: an mHealth digital intervention feasibility RCT study.

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INTRODUCTION

1.1 BACKGROUND

Atrial Fibrillation (AF) affects over 1.4 million people in the UK. A major public health issue, AF requires frequent hospital admissions and increases risk of ischaemic stroke five-fold. Of greatest concern, AF-related stroke are more likely to be fatal or severely disabling compared to other types of stroke.

Oral anticoagulation medication reduces stroke risk in AF by two-thirds. Despite demonstrated effectiveness of anticoagulation, adherence among AF patients is sub-optimal. Missing just 1-2 anticoagulant doses increases stroke risk and worryingly in Scotland only 35% of people with AF still take anticoagulants after 18 months (1), significantly lower than for other cardiovascular medications. People living with AF are frequently managing multiple medications and interventions to improve medication adherence need to encourage self-management.

There is growing evidence that mobile health (mHealth) interventions are effective at improving both intentional and non-intentional adherence to medications (2). Mobile applications (apps) offer the opportunity to support hard to reach populations and can deliver personalised self-management techniques such as educational content, tracking functions and medication reminders. Recent systematic review by the research team failed to identify currently available AF self-management apps of sufficient standard to help support individuals with AF. In response, we have developed a new mHealth app, which has been co-designed with patients.

This study will undertake a pilot feasibility randomised controlled trial of the newly developed AF app among people living with AF in the community. We will identify whether it is possible to recruit patients from general practice and cardiology outpatient clinics, check that participants can complete outcome and identify challenges to be addressed in the implementation of a full trial. It will also provide an opportunity to ensure the app is intuitive and requires little instruction to operate. Data and ideas developed from the feasibility study will inform a larger randomised controlled trial.

1.2 RATIONALE FOR STUDY

The financial and social burden of AF related stroke has been estimated to cost the NHS £770 million over a five-year period. This is set to increase as prevalence of AF continues to rise. To mitigate health costs and improve clinical outcomes the National Institute for Health and Care Excellence (2014) recommends that AF treatment should emphasise the prevention of thromboembolic complications through increased stroke awareness and oral anticoagulation (OAC), concurrent with heart rate control. To address this, national and international guidelines increasingly advocate implementing interventions that empower patients to self-manage their own condition.

Adherence to oral anticoagulant medication remains a challenge for stroke prevention in AF. Adherence to anticoagulation medication is an essential part of AF management for those deemed at risk of stroke. Some patient non-adherence is unintentional. This is largely due to forgetfulness and lack of routine and evidence-based strategies to address this can be incorporated into any intervention. Unintentional non-adherers may benefit from memory aids such as regular medication reminders and establishing routines/habits. Poor understanding of the risks that AF pose is contributing to intentional non-adherence to prescribed treatments (3). A screening study demonstrated that 44% (n=23/52) of people with AF, were unaware of the diagnosis and did not know why they were taking oral anticoagulation (4). In the recent Scottish national AF public inquiry, only 17% of people with AF remembered being given any information at all about AF (5), and they commented that this was a primary area of concern. In a large systematic review (25,072 patients), higher adherence was associated with stronger perceptions of necessity of treatment, OR=1.742, 95% CI [1.569, 1.934], $p<0.0001$, and fewer concerns about treatment, OR=0.504, 95% CI: [0.450, 0.564], $p<0.0001$ (6). Our team has demonstrated that high concerns predicted poor adherence in stroke patients and that brief interventions can address these concerns, thus increasing adherence (3).

It is necessary to take anticoagulation every day at the same time and just 1-2 missed doses increases stroke risk. A recent cohort analysis of 64,661 AF patients prescribed OACs demonstrated that at 1-year only 40% of those taking warfarin had a proportion of days effectively covered >80% of the time. This increased slightly to 47.5% of effective cover for those prescribed NOACs. To improve clinical outcomes,

interventions need to specifically target medication adherence through patient educational content and behaviour change techniques.

There is growing evidence that mobile health (mHealth) interventions are an effective and acceptable means of improving both intentional and non-intentional adherence. More than 95% of UK households own at least one smart device allowing extensive reach, utilisation and potential effectiveness of mHealth solutions (7). In addition, internet use via internet-enabled mobile devices has increased rapidly among older people in the UK. Mobile apps can provide updated, clinically relevant and targeted information to individuals. They have the potential to be successful in a range of settings and offer far-reaching support for individuals. Their capability for delivering evidence-based, targeted educational content alongside tracking functions makes them a pragmatic intervention to support self-management and target intentional and non-intentional non-adherence (8). Multimedia content delivered via an app platform unlike SMS interventions can help overcome low health literacy and low digital health literacy levels in patients.

We have also shown that there is no age barrier to the use of apps in people with cardiovascular disease. In our recent study of 282 patients with a range of cardiovascular conditions, the majority (91.1%, 257/282) used at least one type of technology device, 70.9% (200/282) used mobile technology (mobile phone/tablet), and 31.9% (90/282) used all types (9). Technology was used by 54.6% (154/282) for health purposes, most often to access information on health conditions (41.4%, 117/282) and medications (34.8%, 98/282) (9). With support, older adults can, and do, use technology to manage their cardiovascular health.

In our recent systematic review of ten studies of varying designs, 607 patients from five countries were included (8). Interventions targeted hypertension, heart failure, stroke and cardiac rehabilitation populations. Factors that improved among app users were rehospitalisation rates, disease-specific knowledge, quality of life, psychosocial well-being, blood pressure, body mass index, waist circumference, cholesterol and exercise capacity. Improved physical activity, medication adherence and smoking cessation were also characteristic of app users.

There has been a surge of health apps making their way to commercial markets. Many lack the underpinning evidence to provide meaningful behaviour change in patients (9). Of more concern, content analysis of apps available to support hypertension, pain,

diabetes, smoking cessation and other conditions consistently report the absence of clinical trial to test app effectiveness as an intervention (2, 10-12).

We conducted a systematic scoping review of existing apps to identify the existence of any suitable app already available to patients. From 555 apps initially identified, five potential apps were analysed for their characteristics, functions, privacy/security, incorporated behaviour change techniques, and quality and usability. We did not identify any app of sufficient standard to use in healthcare settings and importantly no app had undergone clinical trial to evaluate their effectiveness. We therefore designed a new app to encourage medication adherence for people living with AF.
We have co-designed the new app with 20 people who are living with AF. We recruited co-design participants through advertisement via AF third sector organisations. Participants took part in three developmental workshops. Workshop 1 discussed ideas about what might be included in an AF app. Workshop 2 allowed participants to interact with the apps identified through systematic review and feedback on what features, if any would be helpful. Workshop 3 used the prototype app developed by the research team, allowing for the identification of any issues before the app implementation of the feasibility study. This process was overseen by a steering group, which included four patient representatives, and an expert panel.

The scientific justification for this study is to develop an evidence base for an AF app intervention. Designed in conjunction with patients and clinician experts, it is hoped the feasibility study will inform a randomised controlled trial that will substantiate the use of an mHealth app underpinned by behaviour change theory to improve medication adherence in patients with AF. The feasibility study will help address a) recruiting clinicians/centres to take part b) retention of participants c) valid, reliable and practical measures of adherence in an AF population d) What estimates of effect size/variability should be used in the design of the full trial e) What are patients' and providers' experiences of the complete intervention.

The primary benefit for taking part in this study is potentially improved clinical outcomes from increased adherence to oral anticoagulation and its effects on reduced stroke risk and associated morbidity and mortality. Secondary benefits may include improved quality of life from implementing lifestyle changes, increased knowledge of condition and the feeling of support that an app can provide.

Healthcare professionals interviewed as part of the study to understand recruitment and healthcare professional experiences will have to give up an hour of time to complete a telephone interview. The interview will be arranged at a convenient time for the healthcare professional so as to lessen the burden.

2 STUDY AIM and OBJECTIVES

2.1 Aim/Primary Objective

1) Can we recruit clinicians/centres to take part in the study?
2) Can we recruit and retain participants to the study and is access equitable?
3) Can participants complete the outcome assessments?
4) What is the most valid, reliable and practical measure of adherence in this population?
5) What estimates of effect size/variability should be used in the design of the full trial?
6) What are patients' and providers' experiences of the complete intervention?

2.1.1 Secondary Objectives

1) What are patient barriers and facilitators to engaging with an app based intervention?
2) What, if any, improvements are seen in patient quality of life following use of the intervention?

2.2 Primary Endpoint/Outcome Measure

Our aim for this phase of the study is to identify a scalable measure of adherence. Reliably quantifying adherence presents several challenges and no measure is perfect. Therefore, multiple measures are preferred. Accordingly, we propose using the Medication Adherence Rating Scale, Beliefs about Medications Questionnaire (BMQ) and blood assays (Anti-Xa or International Normalised Ratio) to assess anticoagulation blood plasma concentration. We will also link into patient pharmacy data from baseline to 12 weeks and 24 weeks via eDRIS.

2.2.1 Secondary Endpoints/Outcome Measures

Quality of life: Quality of life has been shown to be a predictor of medication adherence and we will evaluate health-related quality of life using the SF-12 questionnaire (Appendix 9 – part 2).

Measures of Uptake: Retention and data completion rates at baseline, post intervention (12 weeks) and at 24-week follow-up. Data will be gathered on demographic and morbidity variables (e.g. hospitalisation for AF (acute and elective), stroke incidence and cardiovascular events). Web analytics will be used during the pilot to determine actual app use, and in the 12 weeks after completion of the intervention to determine attrition. Web analytics will also be used to inform which functions participants used most often and when.

Qualitative Data Collection: A purposive sample of 20 max study participants who were randomised into the app use group will be interviewed using semi-structured telephone interviews (Appendix 8). Topics considered will be acceptability and experience of the process of recruitment and delivery of the intervention, use of the intervention, and suggestions for delivery improvement. Healthcare professionals will also be invited to a semi-structured telephone interview. We will seek to involve at least 60% of healthcare professionals involved in the study. The topic guide (Appendix 7) will focus on service providers' experience and perceptions of feasibility for delivery in real world settings. Suggestions for improvements to design and delivery of the mHealth intervention will inform the future clinical trial protocol.

3 STUDY DESIGN

OVERVIEW

We will engage clinicians from GP practise and cardiology clinics to recruit for a pilot randomised controlled feasibility trial. The study will compromise two work packages:

Work package 1 will recruit patients, who will be randomised into two groups. One group will receive normal care and one group will test the app for a 12-week period. Following participation, some participants (N=20) will be invited to take part in a semi-structured telephone interview to discuss their experiences of using the app (Appendix 8).

Work package 2 will recruit healthcare professionals who have been involved in the study (60% of those involved) and use qualitative methodology to explore barriers and facilitators to implementation of the pilot randomised controlled feasibility trial. We will ask participants to take part in a telephone interview to discuss their experiences.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

	Work package 1	**Work package 2**
Setting	People living with AF in the community will be invited to participate. We will seek to recruit patients from general practice and cardiology outpatient departments. Participants will be randomised to either receive normal care, or to test the app on their personal mobile device over a 12-week period. Similar studies conducted by the study team have found most individuals have access to a personal smart device (whether their own or close family).	Healthcare professionals working in NHS Lothian primary care settings and cardiology outpatient clinics who have taken part in the feasibility study will be invited post study intervention delivery.
Participants	Adults (>18 years) with diagnosed AF, who are able to give informed consent in English, will be recruited to test the intervention.	All healthcare professionals who are involved in the study will be formally invited to take part in a semi-structured telephone interviews post intervention delivery. This will include cardiologists, GPs, practice nurses and nurse practitioners running chronic disease management clinics. Participations is voluntary, healthcare professionals will be aware that they may take part in recruiting potential participants to the feasibility study but decline to take part in the follow up interview process.

Inclusion Criteria	Adults living with AF; prescribed oral anticoagulant therapy; able to provide written informed consent in English. Participants must have access to a personal device (e.g. mobile or tablet)	Healthcare professionals (Cardiologists, GPs, practise nurses and nurse practitioners) involved in the care of patients with atrial fibrillation. The healthcare professional must be a care provider of the patients and part of the study recruitment process. Due to COVID-19 this patient contact will be both in person and during telephone consultations.
Exclusion Criteria	Unstable AF or newly initiated on warfarin.	There is no exclusion criteria within this group
Sample Size	A sample size of 60 people will be sufficient to identify any potential problems in feasibility that have a 5% probability of occurrence, with 95% confidence. In a previous study conducted by the PI, similar in design, retention was 91%, therefore we aim to recruit a total of 76 (38 at each setting) to allow for 20% drop-out at 24 week follow up.	The ability to engage health care professionals in recruitment will be evaluated using in-depth interviews with staff involved in both recruitment and delivery of the intervention. We will seek to involve at least 60% of healthcare professionals involved in the study. The topic guide (Appendix 7) will focus on service providers' experience and perceptions of feasibility for delivery in real world settings. Suggestions for improvements to design and delivery of the mHealth intervention will inform the future clinical trial protocol.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING AND RECRUITMENT OF PARTICIPANTS

Work package 1: We will recruit 30% from primary care and 70% from cardiology. Patients attending surgeries for normal AF care will be informed about the intervention by the practice nurse or general practitioner in general practice, or by the cardiology clinic staff in the out-patient department. Patients with AF attending a routine appointment will be informed about the study. The healthcare professional will provide a study participant invitation, information sheet and consent form. Within primary care and the permission of recruitment centres, opportunistic recruitment using posters in waiting rooms will ask patients to contact Edinburgh Napier university researcher directly who will then be able to provide detailed study information. Participants will

return the consent form to researchers at Edinburgh Napier University to register for the study. Due to the potential demographic of participants the option of leaving the consent forms with their clinical provider will also be provided. The information sheet will contain contact details for the research team so that participants will have the opportunity to ask further questions about the study. Written informed consent will be obtained for all participants. We will request permission to contact all participants for an in depth telephone interview to discuss their experience of using the intervention, barriers to uptake and suggestions for future delivery improvement.

Participants will be made aware they will be able to withdraw at any point throughout the duration of the study. As this is a feasibility study, we will however, request a reason for drop-out with no pressure to continue with the study and ask permission to carry out a withdrawal interview (Appendix 8- Part B). This will be voluntary and we will make it clear that participants are not under any obligation to take part in a withdrawal interview.

Work package 2: Potential recruitment sites will be assessed and identified by the research team. The team will approach the clinical healthcare settings (Primary care and cardiology outpatients) with full study information and expectations for the recruitment site. As a feasibility study the ability to recruit potential clinicians/centres is a primary objective that we wish to test. Therefore healthcare professionals directly involved in recruitment will be invited for an interview to explore the acceptability of the app based intervention.

5.2 CONSENTING PARTICIPANTS

Work package 1: Clinical staff who would normally be involved in the patient's routine care will inform patients identified as having an AF diagnosis of the proposed study. This will involve an informal impartial conversation from the healthcare professional. The healthcare professional will provide full written study information to patients to be taken away, (participant invitation sheet- Appendix 1, participant information sheet- Appendix 2, consent form- Appendix 3 and Privacy notice- Appendix 14a). This information will include what will be involved, the potential study benefits, risks, time commitments, withdrawal information and data privacy information. It will also make clear that randomisation will mean that they may not receive use of the intervention throughout the study. Researchers who are contacted by potential participants will objectively discuss the study with the participants. Any questions or concerns will be

answered without persuasion. With the permission of recruitment centres we will also advertise he study via recruitment posters in waiting rooms (Appendix 11). Anyone contacting the research team in response to a poster advert deemed to fit the inclusion/exclusion criteria will be sent full study information (participant invitation sheet- Appendix 1, participant information sheet- Appendix 2, consent form- Appendix 3 and Privacy notice- Appendix 14a) via post or email.

Study inclusion criteria consists of being able to provide informed written consent in English. Consent forms will be provided at the same time as written study information from the initial interaction with the healthcare professional. The consent form is included within this application (Appendix 3). Participants will be able to post their consent back or return via email. Due to the potential demographic of participants a third option of leaving the consent forms with their clinical provider will also be an option with permission from the recruitment site. However, this will not be encouraged due to COVID-19 restrictions.

To ensure that time is given to allow potential participants to decide whether or not to take part participants will be advised that the researcher will contact them again in 24-48 hours as an initial timeframe. If potential participants require longer, more time will be given. As this is not a medical device or invasive intervention it is believed 7-10 days would be the maximum amount of time a participant would require to decide whether or not to take part.

It will be the role of the recruitment site to document within the patients notes that they have consented to be part of this proposed study. Written consent forms received will be stored on Edinburgh Napier University secure data centres. These datacentres are resilient and feature access controls, environmental monitoring, backup power supplies and redundant hardware. Information on these servers is backed up regularly. The University has various data protection and information security policies and procedures to ensure that appropriate organisational and technical measures are in place to protect the privacy or your personal data. Paper documents will be scanned to create an electronic record and then shredded as confidential waste within one month of completion. At the end of the research, electronic data will be kept securely for 10 years and then will be destroyed as per Edinburgh Napier University guidance on the safe disposal of confidential waste.

Work Package 2: The healthcare professionals involved in recruitment will be asked to consent to the semi-structured interviews by Edinburgh Napier University researchers. We will provide full written study information to staff to be taken away, (participant invitation sheet- Appendix 5a, participant information sheet- Appendix 5b, consent form- Appendix 5c and Privacy notice- Appendix 14a). This information will include what will be involved, the potential study benefits, risks, time commitments, withdrawal information and data privacy information. Healthcare professionals will be made away that their healthcare setting will still be involved with the study regardless of whether or not they chose to take part in the semi-structured interviews exploring the feasibility and acceptability of the intervention.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point, without giving any reason. A participant can be withdrawn by the Investigator as well. This information will be made clear in the PIS (Appendix 2 for work package 1 and Appendix 5b for work package 2) and the consent forms (Appendix 3 for work package 1 and Appendix 5c for work package 2).

It will be made clear participants can

(i) withdraw from all aspects of the study but continued use of data collected up to that point

(ii) withdraw from all aspects of the study with removal of all previously collected data (and any stored participant samples, where appropriate).

The intervention period is only 3 months and the intervention does not constitute a medical device. We do not anticipate the requirement for any discontinuation criteria from the research team perspective.

6 STUDY PROCEDURE AND DATA COLLECTION (Questionnaires and interview guides available in Appendices 7-9c)

Method	Collection Method	Participants	Why method was selected	How the data will be analysed
Baseline Survey Questionnaires: 1- Demographic questionnaire (including age, sex, ethnicity, education level, employment status, Scottish Index of Multiple Deprivation (SIMD) calculated from postcode, and relevant medical history and medication regimen) 2- Medication Adherence Report Scale (MARS) 3- Beliefs about Medicines (BMQ) 4- SF-12 questionnaire.	Via telephone in light of COVID-19	**Work package 1:** Participants in both the intervention and routine care group	Reliably quantifying adherence presents several challenges and no measure is perfect. Therefore, multiple measures are preferred.	Data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined. Additional statistical support will be provided by Associate Professor Nadine Dougall.
12 week Survey Questionnaires: 1- Medication Adherence Report Scale (MARS) 2- Beliefs about Medicines (BMQ) 3- SF-12 questionnaire 4- Healthcare Questionnaire 5- Satisfaction with care Likert Scale rating	Via telephone in light of COVID-19	**Work package 1:** Participants in both the intervention and routine care group	Reliably quantifying adherence presents several challenges and no measure is perfect. Therefore, multiple measures are preferred. An additional healthcare questionnaire has been included to gather data on AF related morbidity during the intervention period. A satisfaction with care rating will be used as a quick and simple method to quantitatively compare experiences of care across the two groups.	Data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined. Additional statistical support will be provided by Associate Professor Nadine Dougall.

24 weeks Survey Questionnaires: 1- Medication Adherence Report Scale (MARS) 2- Beliefs about Medicines (BMQ) 3- SF-12 questionnaire 4- Healthcare Questionnaire	Via telephone in light of COVID-19	**Work package 1:** Participants in both the intervention and routine care group	Reliably quantifying adherence presents several challenges and no measure is perfect. Therefore, multiple measures are preferred. An additional healthcare questionnaire has been included to gather data on AF related morbidity following the intervention period.	Data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined. Additional statistical support will be provided by Associate Professor Nadine Dougall.
12 week Semi-structured qualitative interviews	Via telephone in light of COVID-19	**Work package 1:** Participants randomised into the intervention group will be randomly invited to take part (n=20). Participants from the intervention group that withdraw from the study will also be invited. **Work package 2:** Healthcare professionals from the recruitment centres will be invited. We aim for 60% of healthcare professionals	Qualitative data from intervention participants will provide contextual information on the usability and acceptability of an app based intervention. Qualitative data from the healthcare professionals will provide service providers' experience and perceptions of feasibility for delivery in real world settings. Suggestions for improvements to design and delivery of the app intervention will inform the future clinical trial protocol.	Qualitative data: Data will be transcribed and imported into NVivo12® (QSR International, Melbourne, Australia) for analysis. After familiarisation with the data, the transcripts will be thematically analysed against qualitative framework for assessing research evidence by researchers with expertise in qualitative analysis.
Blood Assay (Anti-Xa blood Assay or International Normalised Ratio)	Via healthcare professionals from recruitment sites	**Work package 1:** at baseline, 12 weeks and 24 weeks	This will work as a clinical indicator for medication adherence.	Data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined. Additional statistical support will be provided by Associate Professor Nadine Dougall.

App Analytics	Using google analytics (No personally identifiable data is collected using this method)	**Work package 1:** App users only throughout the course of the intervention and at 24 weeks	Web analytics will be used during the pilot to determine actual app use, and after completion of the intervention to determine attrition. Web analytics will also be used to inform which functions participants used most often and when.	Data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined. Additional statistical support will be provided by Associate Professor Nadine Dougall.

7 STUDY PROCEDURE

7.1 STORAGE AND ANALYSIS OF SAMPLES

Within their role as recruitment sites, centres will need to agree to collect blood assays from participants. Blood tests will be taken by suitably trained healthcare professionals and analysed as per standard procedures. Results will be shared with the research team subject to a suitable data sharing agreement. Consent for the blood assays to be taken will be obtained within the original study consent forms (Appendix 3) as will the permission from participants for their blood test data to be shared with the research team.

8 DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION (if appropriate)

This is a feasibility study and no formal power calculations have been performed

8.2 PROPOSED ANALYSES

Quantitative Data: In consultation with an expert in statistical analysis data will be coded and imported into statistical software package SPSS and appropriate statistical tests carried out. As this is a feasibility study these have yet to be defined.

Qualitative Data: Data will be transcribed and imported into NVivo12® (QSR International, Melbourne, Australia) for analysis. After familiarisation with the data, the transcripts will be thematically analysed (13) against qualitative framework for assessing research evidence by researchers with expertise in qualitative analysis (14).

9 ADVERSE EVENTS

The intervention does not involve the testing of any drugs and is of short duration (12 weeks). Patients are being assessed at exit of the intervention and again at 24 weeks. Participants will be provided with the appropriate contact details of the researchers conducting the study and can get immediate support if they feel it is required. It is not anticipated that there will be any adverse affects.

Researchers will only be working from their usual working environments and all data collection will take place via the telephone due to COVID-19 safety precautions. Therefore no additional risk assessments will be required.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS (where appropriate)

Investigators and institutions involved in studies (classed as 'clinical trials') will permit study monitoring and audits on behalf of the sponsor, NHS REC review, and regulatory inspection(s) where relevant. In the event of audit or monitoring, the Investigator shall agree to allow representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator shall agree to allow inspectors direct access to all study records and source documentation.

10.2 RISK ASSESSMENT

A study specific risk assessment may be performed by representatives of the sponsor/s, in accordance with RIO governance and sponsorship arrangements. Input will be sought from the Chief/Principal Investigator. The risk assessment outcomes will form the basis of the monitoring and audit plans.

10.3 STUDY MONITORING AND AUDIT

The Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the designated Health Research Governance Manager to determine if an audit should be performed before/during/after the study and, if so, at what frequency. Should audit be required, details will be captured in an audit plan.

11 ETHICAL CONSIDERATIONS and GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

Where relevant, studies will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for **Good Clinical Practice** (ICH GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

Where relevant, the participant will be informed and agree to their health/social care records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy should be filed in the Study File (SF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded at each Investigator Site.

11.2.4 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.2.5 Confidentiality

At the point where participants consent to being part of the study researchers will not have access to the medical records. After informed written consent has been obtained participants will be anonymised. They will be allocated a unique study identification number. Data collected under this unique identification number will be stored separately from the identifiable participation list. No personal identifiable information will be collected within the app itself.

All data will be collected and stored in line with The Edinburgh Napier University Code of Practice on Research Integrity. These datacentres are resilient and feature access controls, environmental monitoring, backup power supplies and redundant hardware. Information on these servers is backed up regularly. The University has various data protection and information security policies and procedures to ensure that appropriate organisational and technical measures are in place to protect the privacy of personal data. No data will be shared. If this changes, a suitable data sharing agreement will implemented.

Participants must provide written permission for the release of, or access to, any confidential or clinical information. The Investigator and study site staff involved with the study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed for the purpose of the study (unless specifically stated otherwise – for example, for the

purposes of child and/or adult protection). Prior written agreement from the sponsor must be obtained for the disclosure of any said confidential information to other parties.

11.2.6 Data Protection

A suitable Data Management Plan will be in place (Appendix 15) which details the collection, transfer, storage, processing and disclosure of personal information related to the study.

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team, representatives of the sponsor(s) and representatives of regulatory authorities. Computers used to collate data will have encryption or limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, which involve a change in the study protocol (except those required to manage an urgent safety issue), must be reviewed and approved by the Chief Investigator. All study amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 SERIOUS BREACH OF PROTOCOL REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental wellbeing of the participants in the study; or

(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsor must be notified within 24 hours. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the study, to

determine whether the incident constitutes a serious breach and report to the relevant research ethics committee/s as necessary.

12.3 STUDY RECORD RETENTION

All study documentation (excluding audio and media files) will be kept for a minimum of 3 years from the protocol defined end of study point. For studies classed as 'clinical trials', study documentation can be destroyed with permission from the sponsor after the minimum retention period has elapsed.

12.4 END OF STUDY

The end of study is defined as the last participant's last visit. The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

For studies involving NHS REC and R&D Office(s), the end of the study must be reported to NHS REC and R&D Office(s) and any co-sponsors within 90 days, or 15 days if the study is terminated prematurely. A summary report of the study must be provided to the NHS REC within 1 year of the end of the study.

12.5 CONTINUATION OF TREATMENT/CARE FOLLOWING THE END OF STUDY

For participants included in the intervention arm who have found personal benefit from using the app and wish to continue using the app, they will be allowed to do so freely. It is not a medical device or treatment. Ongoing use would not require any overseeing.

If clinical benefit were to be evidenced from the proposed study, it is the aim of the research team to make the mobile app publically available via commercial app platforms (GooglePlay and Apple Store). It is unclear at this stage whether a charge for downloading the app would be necessary.

12.6 INSURANCE AND INDEMNITY

The following arrangements are in place to fulfil the Sponsors' insurance and indemnity responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor/s require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites outwith the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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