Observational Study Protocol

EVALUATING QUALITY OF LIFE OF AF PATIENTS FOLLOWING A BLEED (EQUAL-AF)

V2.0

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol (v1.0)	21-Jul-2020	Not Applicable
V2.0	15-Jan-2021	Update to study design to specify JCRF role in study – no ward visits will be conducted, in line with COVID-19 regulations.

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RESEARCH REFERENCE NUMBERS

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Signature Page

I, the undersigned, confirm that the following protocol has been read and understood agree to perform and conduct the study as described in the following protocol. The PI will adhere to the principles outlined in the Declaration of Helsinki, and other appropriate regulatory requirements.

I agree to ensure that the document will be kept confidential and not be used for any other purpose other than the evaluation or conduct of the study 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 from the study as planned in this protocol will be explained.

Funder representative:

Date: | dd | mmm | yy |

Signature:_____

Name (print):_____

Position:_____

Principal Investigator (PI):

Date: | dd | mmm | yy |

Signature:_____

Name (print):_____

Position:_____

COVID-19 IMPACT STATEMENT

The proposed study design outlined in the following protocol will be appropriately implemented in line with current guidelines set out by the UK and Welsh Government for Coronavirus management. Up to date Government guidance will be followed throughout the study, which will potentially impact certain aspects of study conduct, as described in this protocol. Study visits will be conducted remotely while necessary, until such time where face-to-face visits are permitted to recommence. Key members of the study team will monitor relevant guidance for GP surgeries and hospitals closely and adjust study conduct accordingly, consistent with any new information and/or restrictions as it is released. Where study tasks are conducted remotely, recent HRA advice released for conducting clinical trials during COVID-19 outbreak will be adhered to, where applicable. Any study visits conducted in person will take place with all required precautions in place to prevent the spread of the virus. Due to the restrictions and guidance in place from the government, recruitment efforts designated to JCRF nurses in Swansea will be limited to screening of A&E databases at Morriston hospital and sending recruitment letters via secondary care where applicable/appropriate.

Additionally, the study acknowledges that the current pandemic of COVID-19 and resulting restrictions and dramatic changes to patient lifestyle has the potential to cause additional adverse impact on quality of life issues for the study population being investigated. Quality of life issues directly caused due to the global pandemic of Coronavirus will not be investigated as part of this study. However, anecdotal information will be collected about how patients manage their diagnosis of AF during relevant clinic closures, lockdown environment and social distancing restrictions.

SYNOPSIS

Protocol Title: Evaluating QUAlity of Life of AF patients following a bleed (EQUAL-AF)

Study Design:

A cross-sectional, observational feasibility study which will provide a descriptive evaluation of the quality of life (QoL) of atrial fibrillation (AF) patients experiencing a bleed, both in primary care and hospital settings (wards and emergency department (ED)). No control patients (i.e. no-bleed patients) will be enrolled as part of this feasibility phase.

Objective(s):

Primary objective

- To test the feasibility of identifying patients with both minor and major bleeds as a result of anticoagulant treatment for AF and evaluating their QoL through both primary and secondary care settings.

Secondary Objectives

- To describe and interpret the observed differences in QoL by type of bleed.
- To describe the treatment received and the nature of the bleed experienced by the patient.
- To undertake structured qualitative interviews to gain detailed insight into issues from a patient perspective, for those who live with AF and have experienced a recent bleed while taking anticoagulants.
- To observe appropriateness of three chosen PROMs (EQ5D, AFEQT and PACT-Q, part 2) in capturing QoL data, specifically post a bleeding event for AF patients who are taking anticoagulants.

Outcome measure(s):

Primary outcome measures

- The study will be considered feasible if recruitment efforts prove successful:
    - A sample size of 50-80 patients will be required for the study in line with the guidance outlined in the Lancaster et al (2004) publication regarding feasibility studies[1]. A minimum of 50 patients recruited will deem the study as successful.

- Patient reported outcome measures (PROMs) will be used in the study using a survey design to collect QoL data from patients directly in both primary and secondary care settings. Three validated questionnaires will be used in this study: EQ5D, AFEQT and PACT-Q. All questionnaires have previously been used in atrial fibrillation studies to collect QoL data.

Secondary outcome measures

- Patients will be asked to provide their anticoagulant medication information along with full details of the bleed they have experienced, which will be used to later categorise the bleeds as minor or major by a medical professional, during the data cleaning and analysis. Medication and bleed details will be recorded before each patient completes the selected study PROMs.
- A sub-set of 10 patients will be asked to take part in a qualitative semi-structured interview, which will aim to further describe patient QoL after a bleed, while anticoagulated. Patients completing the interview will also be asked to provide any comments and opinions regarding the suitability of the chosen study PROMs for properly capturing all QoL issues after a diagnosis of AF.

Study Population:

Primary and secondary care patients with AF (aged ≥18) who are actively prescribed oral anticoagulant therapies (OATs) and have recently experienced bleeds, up to a maximum of 4 weeks prior to enrolment. No upper age limit will apply but potential study participants must match all inclusion/exclusion criteria, detailed fully in section 3.2.1 & 3.2.2.

Data Collection Methods:

Data sources: Electronic and/or paper records kept at primary and secondary care will be regularly searched for identification of suitable patients. Patients routinely attending anticoagulation clinics will be asked if they have experienced a recent bleed, and those who present as eligible will be asked to take part in the study. Posters placed in appropriate locations in GP clinics will encourage patients who have AF and are anti-coagulated to discuss minor bleeds with GPs. Lastly, e-cards will be sent out to patients with AF groups on forums, social media pages, web site and newsletters run by online AF support networks.

Exposure: Anticoagulated to prevent stroke following diagnosis of AF.

Data collection: Data will be obtained using questionnaires supplied on paper case report forms or via an electronic device, depending on participants' preference and up to date restrictions due to coronavirus outbreak in regards to using touchscreen devices. Data captured via an electronic device will be submitted directly to a REDCap database which has been designed for the study. Completed paper versions of the survey will later be transcribed into the database by a member of the study team. A random subset of enrolled AF patients will also undergo recorded interviews with research nurses in order to capture valuable free-form, emotive data regarding effect on quality of life after a bleed and to document patient opinion on current available PROMs used in the study.

Data Analyses:

Descriptive analysis of QoL reported by AF patients following a minor or major bleed while anticoagulated. Comparison to age-adjusted population norms may be insightful but no comparisons with controls are planned for this feasibility assessment, as no control patients will be enrolled.

Sample Size/Power:

Between 50 and 80 patients are expected[1], stratified into major and minor bleeds[2]. Depending on recruitment efficacy, a maximum of 200 patients will be enrolled.

Limitations/Strengths:

The main limitation of the study is the lack of access to a suitable PROM, which specifically captures the true impact of bleeding on quality of life (QoL). The study will instead utilise previously validated generic and disease specific health-related quality of life (HRQoL) measures and compare them with population norms.

As this is a feasibility study it is unknown how successful chosen recruitment strategies will be for the study in the study sites and populations selected.

This study will enhance currently limited research into how bleeding specifically affects QoL in patients diagnosed with AF.

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1 INTRODUCTION

1.1 Study Rationale

Atrial Fibrillation (AF) is the most common cardiac arrhythmia. The overall prevalence of AF is reported to be 0.4-1%[3]. However, many clinicians debate the true global prevalence, stating that it is likely to be underestimated as many individuals are asymptomatic and possibly undiagnosed[4]. Rates of AF are also highest in patients aged over 60[5]. Previous studies have concluded that for males aged 75-79, rates of AF doubled in comparison to those aged 65-69[6]. As the general population continues to age, AF is likely to become much more of a public health burden[7], with predicted numbers of AF patients estimated to reach a minimum of 1.3 million patients in the UK by 2060[8].

Patients can develop further AF-related complications, for example, significant risks of stroke and systemic thromboembolism and increased mortality[9 10]. Strokes triggered as a result of AF are a major complication in patients and are associated with significant morbidity and mortality [11].

The general symptom burden on AF patients and the subsequent reduced ability to undertake daily activities has been widely examined in numerous studies[12-14]. People living with AF have a much lower quality of life (QoL) than patients who do not have the disease[11 15].

With the steady increase in AF prevalence and its impact on patients, it is becoming increasingly necessary to deliver adequate treatment and/or therapies, which can improve health related quality of life (HRQoL) in patients. Identifying any underlying causes of AF may be the first step in any treatment plan[16], as treating the cause may be enough to treat and rectify the related AF. Once a detailed history of the form[17] [18] and significance of AF in the patient is established, a treatment plan should then be considered[19]. Treatment plans usually involve controlling the heart rate or rhythm.

Oral anticoagulation therapies (OATs) (for example warfarin and apixaban) are prescribed in conjunction with rate management in order to limit the risk of stroke and systemic thromboembolism. They are, however, associated with the serious side effect of bleeding. These bleeding complications include intracranial, gastrointestinal, genitourinary and respiratory tract bleeding haematuria[20]. Bleeding risk can be determined using calculated risk scores such as HAS-BLED[21]. A higher HAS-BLED score indicates that the patient is more at risk of a major bleed, which has previously influenced patient and clinician decisions not to offer or to withdraw anticoagulant treatment[22]. However, the European Society of Cardiology 2016 guidelines advise that it is s better to treat with OATs (despite the risk of bleeding) than not use OATs [23].

Bleeding while anticoagulated is believed to have a significant impact on patient quality of life (QoL)[24]. Quality of life and health status are considered to have a colinear relationship, but this is typically difficult to define. There are already a multitude of validated measures which attempt to quantify Health Related Quality of Life (HRQoL)[25-27]. HRQoL tools can also be disease- or injury-specific and aim to capture both benefits and undesirable aspects of different diseases from a patient perspective, including consequences of living with the disease[28]. More and more focus is being directed towards improving patient reported quality of life when delivering quality and value-based healthcare[29 30.]

There is currently limited research into how bleeding events impact QoL in AF patients, especially those who experience minor bleeds, for which no medical care is sought (as per Bleeding Academic Research Consortium (BARC) definition)[31]. Likewise, there are no existing and/or validated patient-reported outcome measures (PROMs) developed for use in assessing how bleeding influences patient QoL.

This feasibility study will examine how patient QoL is affected when they experience either a major or minor bleed, defined by the International Society on Thrombosis and Haemostasis (ISTH)[32], while taking OATs for the management of AF.

1.2 Feasibility Questions

- Can sufficient numbers of patients with AF be identified and recruited onto a study to investigate the impact of bleeding events, related to anticoagulant use, on quality of life?
- Can quality of life impact be measured for patients who are prescribed anticoagulants and experience bleeding as a side effect?

We hypothesise that there is a considerable and sustained impact on AF patient's quality of life (QoL) when they experience a bleed while anticoagulated, whether that bleed is major or minor in severity. Understanding the nature and extent of this impact on patients' QoL is expected to guide physicians' risk assessment when seeking to effectively anticoagulate patients with AF.

2 OBJECTIVES

2.1 Primary Objectives

To test the feasibility of i) identifying and recruiting patients with both minor and major bleeds[32] as a result of anticoagulant treatment for AF associated events, and ii) measuring their QoL in both primary and secondary care settings.

2.2 Secondary Objectives

- To describe and interpret the observed differences in QoL by type of bleed.
- To describe the treatment received and the nature of the bleed experienced by the patient.
- To undertake structured qualitative interviews to gain detailed insight into issues from a patient perspective, for those who live with AF and have experienced a recent bleed while taking anticoagulants.
- To observe appropriateness of three chosen PROMs (EQ5D, AFEQT and PACT-Q, part 2) in capturing QoL data, specifically post a bleeding event for AF patients who are taking anticoagulants.

3 STUDY DESIGN

3.1 Overview of Study Design

A descriptive evaluation of the QoL of patients with AF experiencing a bleed, both in primary care and secondary care settings (hospital wards and the emergency department (ED)).

Patient Recruitment & Study Sites

All patients will be targeted based on strict inclusion and exclusion criteria, as detailed further below (Section 3.2.1 & 3.2.2). Recruitment strategies will vary considerably in order to limit unconscious recruitment bias (for example, taking care not to direct all efforts only towards those patients who are more disposed to seek medical care when experiencing bleeds). Initially, eligible patients will be identified from regular searches in secure databases in both primary (GP surgeries) and secondary care

(ward/emergency department [ED]). JCRF staff will provide recruitment support by regular screening of A&E databases at Morriston hospital. Letters of invite will be sent out to patients who appear eligible via secondary care. NO on-site visits will take place by JCRF staff due to restrictions surrounding COVID-19 and social distancing. Patients will be subsequently approached about the study by means of a face-to-face referral in clinics where viable, in line with current consultation arrangements during the COVID-19 period, or, alternatively, study information will be posted to capture patients with AF who may not have recently visited clinics, wards, or emergency department (ED). Where appropriate, study posters will be placed in optimal locations such as general practice (GP) clinics to display information about the study, in lay terms, to encourage discussion with GPs concerning all recent minor bleeds (as defined by ISTH32), which the patient may not have thought relevant enough to mention otherwise. Leaflets and study cards will be provided, which will allow potential participants to take away study information for consideration, including by friends and family members. Patients interested in participating in the study will be instructed to contact the clinical research team directly to streamline screening and enrolment process, and to limit time burdens on healthcare staff.

Based on data provided by anticoagulation clinics within the Swansea City Health Cluster (eight general practices in the Swansea area), it is estimated that there are approximately 500 patients with AF who are currently taking prescribed anticoagulants. All eligible patients identified within the Health Cluster, will be contacted via post and, if willing, asked to report on any bleeds within the recruitment period. A further recruitment drive will take place synchronously in hospital settings, where all patients who attend the emergency department (ED) of Morriston Hospital or admitted to the wards due to bleeds, will be approached for participation in the study. These patients will be identified following admission, but existing in-patients at study outset will be approached if it is appropriate to do so. Lastly, e-cards will be sent to specific patient groups as required, on forums, social media, web site and newsletters run by online AF support networks. Finally, patients will be informed of the study via online AF support groups on forums, social media pages and from a large database of patients, managed by the support group. Approximately 60,000 patients are held on the database in total, which will be accessed and filtered to identify eligible AF patients. Consent will be received digitally and an online link to the questionnaires will be sent to those who wish to participate. Follow-up data collection for these patients will also be conducted digitally.

Recruitment is anticipated to commence in September 2020 and will continue for 6 months – a key decision made in light of the COVID-19 outbreak. Although the study will aim to recruit between 50 and

80 patients in the first instance, all suitable patients who are willing to partake in the study will be included. A maximum of 200 patients will be permitted to enroll if successfully screened.

The research team will not have any contact with the patient unless the patient registers their interest in the study or if they reply following invitation from the healthcare provider.

Screening & Enrolment

The study will aim to enroll all patients who have AF and are anticoagulated, and who have experienced a bleed within a maximum of 30 days at point of enrolment. Patients experiencing bleeds over 30 days prior to enrolment will not be considered for the study at this stage. Numbers of minor and major bleeds reported will be monitored to ensure equal numbers of patients experiencing both types of bleeds are included, as far as feasible. Should an unequal proportion of n numbers occur between type of bleed, patients will not be turned away if they are willing to participate. Researchers will monitor numbers closely and attempt to achieve an equal proportion of minor and major bleed patients. If a balance of major and minor bleeds cannot be achieved within the chosen study population, it will be noted for informing study design of any related future studies.

Patients who meet all study criteria will undertake an informed consent process, where they will be provided with full study details in a patient information sheet (PIS) and asked to sign appropriate documentation to indicate agreement to take part. Patients will have at least 24 hours to deliberate if needed and will have the opportunity to ask any questions before consenting to take part. For surveys which are completed online via a survey link, e-consent will be received according to HRA advice. Patients must agree to provide current contact details for the study team to be kept confidentially by the study team for follow-up purposes. Basic patient demographic information will be collected by qualified research nurses and recorded on case report forms (CRFs), along with details of any bleed(s) experienced. Additional anecdotal questions will be asked relating to ongoing patient management of atrial fibrillation during the current pandemic of Coronavirus, such as the ease of seeking medical care in a situation of a lockdown and social distancing where visits to anticoagulation clinics are limited or entirely stopped. All study documentation will comply with Good Clinical Practice (GCP) guidelines and General Data Protection Regulation (GDPR).

Patient Questionnaires

All patients will be asked to complete three questionnaires for the study: EQ-5D-5L, Perception of Anticoagulant Treatment Questionnaire, **Part 2 only** (PACT-Q, Part 2) and Atrial Fibrillation Effect on QualiTy-of-life (AFEQT), which should take no longer than 30 minutes in total to complete[23, 39]. Considerations have been made, as far as possible, to minimize impact on patient's time. Questionnaires will be conducted at two time-points for this study; an initial round will be completed at point of consent/enrolment and a second identical set of questionnaires at 90±14 days post-enrolment. Patients will complete the initial round of questionnaires immediately after consent process, to ensure that loss to follow-up is controlled. An option to take part in a further qualitative interview, after the 90-day follow up, will be included in both questionnaire sets. Initial questionnaires will be provided electronically via tablet devices or on paper copies, if patients prefer. Follow-up questionnaires will be sent out either through the post 3 weeks prior to the 90-day follow-up date, along with a stamped addressed envelope for ease of return or enrolled patients who prefer to complete data collection electronically will be sent a survey link. Patients will be asked in an accompanying letter to complete and return the questionnaires within the 90±14 day time-frame. If no reply is received within 2 weeks of first correspondence, a reminder letter along with a second copy of all questionnaires will be delivered.

The PROMs for the study have been carefully selected based upon study requirements and desired outcomes as far as possible, in lieu of having access to a validated bleed-specific QoL questionnaire. Data collected using the chosen questionnaires will also allow comparable analysis with more substantial databases, as data will line up with previously collected QoL data in AF patients, where identical questionnaires have been widely used.

Patient Interviews

To capture valuable, emotive data in the form of patient thoughts and feelings in relation to the study objectives, a small subset of patients will complete short, structured interviews, which will be conducted by research staff at Swansea Trials Unit. It is anticipated that 10 interviews will be sufficient to identify key themes from patients. Interviews will stop if saturation is reached before then and no new themes are identified; interviewees will be randomly selected from all patients who have indicated that they would be willing to take part. Any patient who has consented to be interviewed *and* completed initial questionnaires **as a minimum**, will be contacted (i.e. patients who fail to complete a second set of questionnaires at 90±14 days can still take part in study interviews, if contacted successfully). However, patient interviews will only take place **after** the 90-day follow-up point post-enrolment. Interview

questions will be designed in close collaboration with the study's consultant haematologist to ensure that appropriate questions are asked in a concise and respectful way. Patients will be asked to expand more specifically on bleeding events and consequent level of impact on quality of life **at time of event (bleed)** in comparison to the effect **3 months (90 days) later**. Additionally, patients will be asked to give opinions on the chosen study PROMs on relevance to the true burden of AF and if the questionnaires have overlooked any important quality of life concerns for patients with AF. Recall bias will be managed as far as conceivable by ensuring that interviewers are sufficiently experienced in conducting interviews efficiently and interview questions are impartial. Any information given by patients during an interview will be verified where possible.

All interviews will be recorded upon patient consent and transcribed at a later date. Interview questions will be identical across all patients.

Data Handling & Storage

Paper copies of CRFs and questionnaires will be transcribed into the study database, where the data will be checked for consistency and accuracy, alongside other data collected electronically.

Data will be hosted securely on the REDCap data management system (licensed to Swansea Trials Unit (STU)). Study data will be held anonymously within REDCap and any identifying data (including protected characteristics) will be kept separately, secured by access restrictions.

Data Analysis and Reporting

Descriptive analysis of QoL reported by AF patients following a minor or major bleed while anticoagulated. Comparison to age-adjusted population norms may be insightful but no comparisons with controls are planned for this feasibility assessment.

A brief thematic analysis (Braun and Clarke, 2006[33]) will be conducted on transcribed interview data, to draw out important common themes relating to the study question, which will not be directly captured through the chosen PROMs. Specific qualitative data analysis software, NVivo 12, will be used for additional insight and to identifying trends in unstructured data captured during study interviews.

A final report will be submitted to the funder, BMS, in month 18 of the study. Alongside this, publications in the form of at least one conference presentations and one peer-review publication will be prepared and submitted between months 16 and 20.

Project timescales

Start date: **01st January 2020**

First Patient First Visit (anticipated):**01st September 2020**

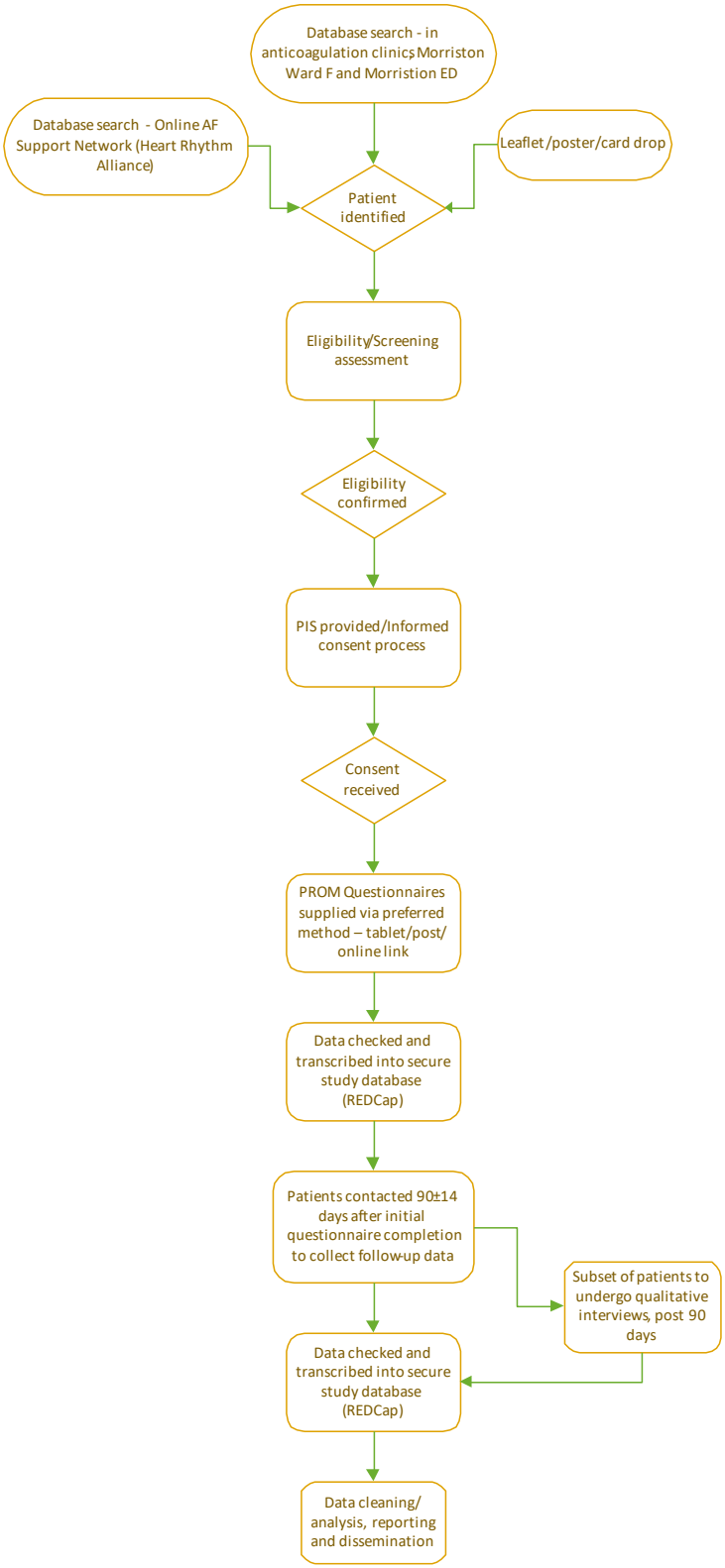
End date: **01st September 2021**

Duration: 20 months (16 months data collection, analysis and study report, 4 months peer review publication and dissemination)

EQUAL-AF Project timescales- Phase 1 feasibility study

TASK	**Months**																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Work Package 1																				
Identify appropriate PROMs, arrange licenses for PROM use, finalise protocol, completion of IRAS application for Ethics and R&D approvals																				
RedCap database development, production of tablet and app versions of questionnaires, CRF design																				
Site set up -Primary care, ED and ward (delay due to COVID-19)																				
Work Package 2																				
Patient recruitment (delayed in light of COVID-19 outbreak)																				
Work Package 3																				
Database cleaning and locking																				
Data analysis																				
Final report to BMS																				
Publications, peer review reporting and dissemination																				

Study Flowchart



3.2 Study Population

Adult patients (≥18) who have AF are actively prescribed oral anticoagulant therapies (OATs) and have recently experienced bleeds, up to a maximum of 4 weeks prior to enrolment. No upper age limit will be applied, but patients must match all other inclusion/exclusion criteria (section 3.2.1). Patients will be selected from the Swansea area only, who attend/have attended either anticoagulation clinics within the Swansea City Health Cluster, Morriston emergency department or have been admitted to wards at Morriston Hospital due to a bleed.

3.2.1 Inclusion Criteria

- Adult patients (>= 18 years old)
- Patients who can understand all study information and literature to provide fully informed consent
- Atrial fibrillation (AF) as the primary diagnosis
- Having a major or minor bleed up to a maximum of 30 days prior to point of enrolment
- Receiving oral anticoagulation therapy for AF

3.2.2 Exclusion Criteria

- Pregnant women
- Patients with active cancer
- Patients unable to consent for themselves
- Patient on concomitant antiplatelet therapy

3.3 Data Source/Data Collection Process

Data sources

As part of this feasibility study, we will explore the most appropriate mechanism to identify patients who have experienced recent minor and major bleeds. We will extend recruitment across both primary and secondary care, including wards and the ED. Patients attending anticoagulation clinics at the Swansea City Health Cluster (made up of eight separate general practices) will be identified by the practice pharmacist or nurse. They will be given information about the study and will consent for a research nurse to contact them to complete the study questionnaires. Research nurses based in Swansea University's Joint Clinical Research Facility (JCRF) will undertake regular exploration of Morriston Ward F audit data (Stroke ward) to identify patients who have experienced a recent bleed. Our GP investigator will also identify patients from ED records at Morriston hospital. Lastly, e-cards will be sent to specific patient groups on forums, social media, web site and newsletters, which are run by online AF support networks.

Outcomes

Quality of life and the impact of the anticoagulation treatment will be collected via validated patient-reported outcome measures (PROMs). We will also include a small number of additional relevant questions regarding when the bleed occurred, the nature of the bleed, and current treatment for the patient. We will also collect the documented cause and location of bleed as identified in discharge summary (for secondary care) in patients with major bleeds. Patient reported bleeds will be posthumously classified into minor or major bleeds by a clinician.

Exposure

Oral anticoagulant to prevent stroke following diagnosis of AF.

Data collection

Cases will be identified from i) routine anticoagulation clinics in primary care, ii) from hospital records for ward patients and from ED records. QoL data will be collected directly from patients via questionnaires. We envisage that data will be collected from patients via an electronic tool, ideally via patients' phones or tablets. We will also produce paper versions of questionnaires for patients who do not have access to a smartphone/tablet or would prefer this method of questionnaire completion. In order to maximise data collection, we will collect data directly from patients attending primary or secondary care if feasible or by phone or post.

A subset of patients with AF will also be invited to participate in structured interviews in order to capture emotive data and to draw out any common themes in issues relating to burden of side effects, specifically higher bleeding risks, from anticoagulants. Interview questions have been informed by public and patient representatives who have close experience with those who have AF or live with the condition themselves. Additionally, questions have been designed with input from relevant clinical staff, including a consultant hematologist. In order to limit any potential bias, each interviewer selected to perform patient interviews will be experienced in delivering qualitative interviews in similar settings and will also be mindful of possible potential bias when delivering the interview questions, such as refraining from asking leading questions. Each patient will be asked an identical set of questions, which will be void of emotive language and closed questions where possible. Questions have been chosen and approved based upon clinical guidance based upon previous information given by patients with AF who experience bleeds while prescribed anticoagulants.

3.3.1 Patient Reported Outcome (PRO) Measures

An extensive literature search at the outset of study design confirmed that there is currently no known validated Patient Reported Outcome Measure (PROM) which specifically captures impact of bleeding on Quality of Life (QoL). In lieu of having access to such PROM, three previously validated and widely used PROMs will be used to allow for comparisons with larger databanks. The questionnaires that will be completed for the study consist of:

- EQ-5D-5L;
- Perception of Anticoagulant Treatment Questionnaire (PACT-Q); and
- Atrial Fibrillation Effect on QualiTy-of-life (AFEQT).

<u>EQ-5D-5L</u>

The EQ5D has been developed by the EuroQoL group for use in clinical studies as a patient reported outcome measure, commonly used for reporting the current health status of an individual. Patients rate their health from 1 to 5 based on 5 components: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A 5-digit number will be generated (e.g. 11111), giving an indication of the patients' current health status. The 5L version of EQ5D has been selected for use in this study as it is considered to

have improved sensitivity compared with the 3L version when capturing quality of life issues in patients living with different health conditions[34]. The 5L version has also been accepted for use in previous studies investigating quality of life in patients with atrial fibrillation taking oral anticoagulants[35].

As part of the EQ5D assessment, patients will also indicate pain levels using a visual analogue scale (VAS) which asks the patient to place a cross over a graduated line from 0 (no pain) to 100 (worst pain imaginable).

PACT-Q

PACT-Q is a two-part PROM, which is used in AF studies to capture patients' perception of treatments before and after initiation. The questionnaire comprises of 7 items for Part 1 (treatment expectations) and 20 items in Part 2 (convenience, burden of disease and treatment, anticoagulant treatment satisfaction, taking an average of 20 minutes total to complete (10 minutes per section). Patients are asked to mark answers on a Likert scale from 1 to 5. For the purpose of this study, only **Part 2** will be completed by all patients.

AFEQT

The AFEQT is a self-reported measure which directly measures impact of atrial fibrillation (AF) on quality of life. The aspects of quality of life aspects covered in the questionnaire detail impact of AF on hobbies, relationships, activities including walking or sports, mental health, and side effects from treatment (including side effects such as nosebleeds, bleeding gums, heavy bleeding from cuts and bruising), over the last 4 weeks prior to point of completion. Patients will answer each question on a Likert scale from 1-7. The AFEQT consists of 20 items in total.

3.4 Definitions of Study Variables

As defined by the International Society for Thrombosis and Haemostasis[2 32] for non-surgical patients

Major bleed

1. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome.

2. Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

Minor bleed

All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not. Some examples of minor bleeds include but not limited to:

- Nose bleeds
- Bloody stools
- Small, manageable cuts (e.g shaving cuts)
- Noticeable and/or persistent bruising

Clinically Relevant Minor Bleed

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission or attendance at A&E for bleeding, or
- A physician guided medical or surgical treatment for bleeding, or
- A change in antithrombotic therapy (including interruption or discontinuation of oral anticoagulant).

Other variables collected in the study will be the following:

- Recruitment pathway
- Medication type
- Co-morbidity/ies, if present
- Location of bleed
- Impact of COVID-19 pandemic and resulting restrictions and closures on ability to seek medical care for a bleed

Collecting the above confounding variables, each of which also has the potential to have some impact on QoL for patients with AF who experience bleeding (while anticoagulated), will allow researchers to reflect on and account for any resulting confounder bias. Confounding variables will be reported on within the end of study descriptive analysis.

3.4.1 Outcomes/Endpoint Variables

Quality of life data and the impact of the anticoagulation treatment will be collected via validated patient-reported outcome measures (PROMs). We will also include a small number of additional relevant questions regarding when the bleed occurred, the nature of the bleed and their current treatment. We will also collect the documented cause and location of bleed as identified in discharge summary (for secondary care) in patients with major bleeds.

4 STATISTICAL ANALYSIS

Due to the feasibility aspect of the study and the low number of cases, a full statistical analysis is not planned. A descriptive analysis of QoL reported by AF patients following a minor and/or major bleed, while anticoagulated, will be performed. Patients who experience multiple bleeds over the course of study participation and consequently report these to research staff will be included, and multiple bleeds will be posthumously categorised into minor or major bleeds by a clinical professional and included as part of the descriptive analysis. Recorded treatment type (anticoagulant used) will be compared with type of bleed (minor/major) to determine if there is any possible linkage which could warrant further testing. Comparison to age-adjusted population norms may be insightful but no comparisons with controls are planned for this feasibility assessment.

A brief thematic analysis (Braun and Clarke, 2006)[33] will be conducted on transcribed interview data, to draw out important common themes relating to the study question, which will not be directly captured through the chosen PROMs. Specific qualitative data analysis software, NVivo 12, will be used for additional insight and to identifying trends in unstructured data captured during study interviews.

Lastly, CRF's and online survey links will include sections for eligible patients to provide open-ended feedback regarding each of the PROMs used in this study and how far the PROM captured bleed-specific QoL issues for anticoagulated AF patients. As previously stated, this information will not be used to

conduct a full statistical analysis but will allow researchers to gauge each PROM performance in capturing QoL post-bleed(s) for these patients.

4.1 Progression Criteria

The feasibility of the trial methods, recruitment strategies, and its potential to be further developed and into a full qualitative study will be measured on key progression criteria. These criteria have been approved by our Trial Steering Committee and study managers, where applicable:

- Minimum requirements met for recruitment (50 eligible patients)
- Retention of at least 50% of enrolled patients at follow-up
- 70% PROMs data completion at baseline and 40% completion of PROMs at follow-up

5 STUDY LIMITATIONS/STRENGTHS

The study will enhance limited, existing knowledge of the level of impact that bleeding while anticoagulated have on patients who have been diagnosed with AF taking anticoagulants.

As this is a feasibility study, it is difficult to predict how successfully eligible patients will be identified and subsequently enrolled, based on the study inclusion/exclusion criteria. There is also uncertainty around optimal ways to promptly identify patients within the primary care and hospital settings. Patients who experience minor bleeds do not always routinely discuss these events with GPs and identifying these patients could prove challenging. Recruitment measures will be tested during this pilot study to inform best strategies for a possible larger-scale study in the future.

As yet, there is no known validated PROM which specifically investigates the impact of bleeding on quality of life which would be suitable for use with AF patients. The study will instead utilize three previously validated general and disease-specific HRQoL measures EQ-5D, Perception of Anticoagulant Treatment Questionnaire (PACT-Q) and Atrial Fibrillation Effect on QualiTy-of-life (AFEQT).

6 STUDY CONDUCT

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

The required approval from the <<name of committee>> Research Ethics Committees, and Swansea Bay University Health Board R&D approvals will be obtained before study site initiation. All approvals will be sought through Health and Care Research Wales using the Integrated Research Application System (IRAS). The study research governance sponsor will be Swansea University (researchgovernance@swansea.ac.uk).

6.1.2 Informed Consent

In accordance with local regulations, subjects should provide written consent before enrollment into the study. Investigators must ensure that patients, are clearly and fully informed about the purpose of the study, potential risks, and the patient's rights and responsibilities when participating in this study.

6.2 Responsibilities within the Study

The Principal Investigator (PI) of this study is Professor Hayley Hutchings, Swansea Trials Unit (STU). Swansea University (SU). Swansea University will be the Sponsor of this study under the UK Policy Framework for Health and Social Care Research. BMS have agreed to fund the study and will provide oversight of the scientific quality and value for money of the protocol.

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and authorised by, the study sponsor Swansea University and the funder BMS.

6.2.1 Sponsor Roles and Responsibilities

The Sponsor will assume overall responsibility for the study design, conduct, analysis and interpretation, as well as report writing and dissemination of results.

A representative from the funder, will sit on the Trial Steering Committee and will ensure that the protocol is well designed, scientifically valid and provides value for money.

6.2.2 Principal Investigator Roles and Responsibilities

The PI is ultimately responsible for the conduct of the study as a whole, regardless of dissemination of study tasks. The PI will ensure that the study is conducted in accordance with the protocol and that tasks are delegated appropriately. The PI will oversee research staff and ensure wellbeing of study participants.

6.2.3 Steering Committee

Trial Steering Committee (TSC)

Members of the trial steering committee will include sponsor representatives, study PI, research nurses, PPI representatives, trial manager and governance staff. The TSC will provide supervision of the study, make timely decisions on study set-up and conduct and monitor key milestones set out for the study. Meetings will occur monthly upon study set up (months 1-3) and quarterly (or as needed) for the remainder of the study.

Patient and Public Involvement

Two patient and public involvement (PPI) representatives will be selected at study outset and invited to contribute to study design, selection of appropriate data collection methods/tools and to attend study steering meetings. PPI's will be selected based on appropriate relatedness to the condition, such as those currently living with AF and prescribed anticoagulants and/or those involved with AF support groups (e.g. Heart Rhythm Alliance).

6.3 Confidentiality of Study Data

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

For the purposes of protecting a patient's identity, a unique study code will be assigned to each patient, such as a series of numbers and/or letters. The data that is recorded with the patient's assigned code is called "key-coded data". Key-coded study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the "study database"). Only the site staff will have access to the link

between patient's assigned code and the patient's identity. However, in case of an audit or inspection, subject to local laws and regulations, government officials, REC representatives and sponsor representatives may access this information at the study site. If the study requires on-site monitoring, subject to local laws and regulations, sponsor representatives will also access the primary data source at the study site (see section 6.4). Data that could directly identify the patient will not be collected in the "study database".

Data will be processed in accordance with the Data Protection Act (2018) and GDPR (2016). All information collected about participants will be kept strictly confidential.

6.4 Quality Control

Representatives of the study sponsor must be allowed to visit all study site locations to assess the data quality and study integrity. On site, they will review study files and, patient medical notes to compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

6.5 Database Retention and Archiving of Study Documents

The investigator must retain all study records and source documents for 10 years. The investigator must contact Swansea University prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report. Data will be securely stored and only accessible by the research team and will be carefully maintained and available for a minimum of ten years after completion of the study.

6.6 Registration of Study on Public Website

This study will be registered on ClinicalTrials.gov. The study will also be adopted into the NIHR CRN portfolio.

7 ADVERSE EVENT REPORTING

This study is not designed to capture safety events on any medicinal product and therefore, adverse event collection and reporting is not required.

Consideration has been taken for the possibility that patients may become distressed or emotional during completion of patient questionnaires by the recollection of previous experiences associated with bleeds. Patients may also experience low mood or anxiety associated with their condition. Both primary and

secondary care researchers have clinical experience of working with patients with low mood, anxiety and distress. If a participant reports, or shows signs of low mood, distress or anxiety they will be encouraged to discuss this with their primary or secondary care researcher and will be signposted to local relevant services or to contact their GP

Patients will have the right to withdraw at any point of the study. This will not affect their NHS care and this will be explained in the patient information sheet and any discussions. Should a distressed patient wish to continue participation, they will be given adequate time to complete questionnaires, taking into account any breaks the patient may wish to take. The patient information sheet contains contact details for researchers involved in the study and for the patient advice and liaison service (PALS) with information on how to contact both.

8 LIST OF ABBREVIATIONS

Term	Definition
A&E	Accident and Emergency
AF	Atrial Fibrillation
BARC	Bleeding Academic Research Consortium
BMS	Bristol-Myers Squibb
CRF	Case Report Form
EC	European Commission
ED	Emergency Department
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practice/General Practitioner
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
IRAS	Integrated Research Application System
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis

JCRF	Joint Clinical Research Facility
NYHA	New York Heart Association
OAT	Oral Anticoagulant Therapy
PI	Principal Investigator
PROM	Patient Reported Outcome Measure
QoL	Quality of Life
REDCap	Research Electronic Data Capture
STU	Swansea Trials Unit
TIA	Transient Ischaemic Attack
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

9 SCIENTIFIC PUBLICATIONS

Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor, funder and the external authors. No public presentation or publication of any interim results may be made by the PI, sub-investigator or any other member of the study team without the prior written consent of the Sponsor.

Authorship of publications for this study is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (i.e., ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (e.g., evaluable subjects with quality data or data generation), analysis, or interpretation of data for the work (e.g., problem solving, advice, evaluation, insights and conclusion); AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered for authorship of the publication.

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