

Feasibility Study Protocol: Investigating The Impact of Bleed Events On Anticoagulated Patients Diagnosed With Atrial Fibrillation Using Patient Reported Outcome Measures

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Study Protocol

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Abstract

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Oral anticoagulation therapies (OATs) are often prescribed in conjunction with medications to restore normal heart rate rhythm which can limit the risk of an AF-related stroke and systemic thromboembolism. However, they are associated with the serious side effect of bleeding. Both clinically relevant non-major bleeding (CRNMB) and major bleeding while anticoagulated are believed to have a significant impact on patient quality of life (QoL). There is currently limited research into the effect bleeding has on QoL. The aim of this study is to evaluate the feasibility of identifying and recruiting patients diagnosed with AF, who are taking OATs and have recently experienced a bleed and collecting information on their QoL.

Methods

We will recruit a minimum of 50 patients to this cross sectional, observational study. We will recruit from general practices, secondary care and through an online AF forum. We will ask participants to complete three validated patient-reported outcome measures (PROMs: EQ5D, AFEQT and PACT-Q), approximately four weeks following a bleed and again 3 months later. We will randomly select a subset of 10 participants (of those who agree to be interviewed) to undergo a structured interview with a member of the research team to explore the impact of bleeding on their QoL and to gain feedback on the three PROMs used. We will undertake a descriptive analysis of the PROMs and demographic data. We will analyse the qualitative interviews thematically to identify key themes.

Discussion

We aim to establish if it is possible to recruit patients and use PROMs to collect information regarding how patient QoL is affected when they experience either a CRNMB or major bleed, while taking OATs for the management of AF. We will also explore the appropriateness or otherwise of the three identified PROMs for assessing quality of life following a bleed.

Trial registration

The trial has been adopted onto the NIHR Portfolio (I.D. #47771) and registered with www.ClinicalTrials.gov (#NCT04921176) retrospectively registered in June 2021.

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia. The overall prevalence of AF is reported to be near 3% (Hill et al, 2019). However, many clinicians debate the true global prevalence, stating that it is likely to be underestimated as many individuals are asymptomatic and possibly undiagnosed (Nileshkumar et al, 2018). The prevalence of AF is also highest in patients aged over 60 (Darby-Stewart et al, 2012). Previous studies have concluded that for males aged 75–79, prevalence of AF doubled in

comparison to those aged 65–69 (Chugh et al, 2014). As the general population continues to age, AF is likely to become much more of a public health burden (Xue et al, 2017), with predicted numbers of AF patients estimated to reach a minimum of 1.3 million patients in the UK by 2060 (Deirdre et al, 2017). Despite this prediction, Public Health England has already reported that between 1.3–1.5 million patients were diagnosed with AF in 2020 and it is likely that another 300–500,000 are yet to be diagnosed (Public Health England, 2021).

Patients can develop AF-related complications, for example significant risks of stroke and systemic thromboembolism and increased mortality (Hansen et al, 2018; Kannel et al, 1998). AF-related stroke as a result of untreated AF is a major complication in patients and is associated with significant morbidity and mortality (Barra & Fynn, 2015).

The general symptom burden on AF patients and the subsequent reduced ability to undertake daily activities has been widely examined in numerous studies (Montbleau et al, 2017; Thrall et al, 2006; Spertus et al, 2011). People living with AF have a much lower quality of life (QoL) than patients who do not have the disease (Barra & Fynn, 2015).

With the steady increase in AF prevalence and its impact on patients, it is important 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 (National Clinical Guideline Centre, 2014), as treating the cause may be enough to treat and rectify the related AF. Once a detailed history of the type of AF (e.g paroxysmal or permanent) and stroke risk in the patient is established, a treatment plan should then be considered (Xu et al, 2016). Treatment plans usually involve controlling the heart rate or rhythm.

Oral anticoagulation therapies (OATs) are sometimes prescribed in conjunction with medications to restore normal heart rate rhythm in order to limit the risk of AF-related stroke and systemic thromboembolism. They are, however, associated with the serious side effect of bleeding. These bleeding complications most commonly include haematuria, intracranial, gastrointestinal, genitourinary and respiratory tract bleeding (Levine & Goldstein, 2014; Wallis et al, 2017). Bleeding risk can be determined using calculated risk scores such as HAS-BLED (Gorman et al, 2016). 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 (Dar et al, 2017). However, the European Society of Cardiology 2020 guidelines advise that the benefit of anticoagulating in reducing stroke far outweighs the risk of bleeding (Hindricks et al, 2021).

Bleeding while anticoagulated is believed to have a significant impact on patient quality of life (QoL) (Res et al, 2019). 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) (Herdman et al, 2011; Ware et al, 1999; Badia et al, 2007). 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 (Xiao-Jun

et al, 2013). Extensive focus is being directed towards improving outcomes that matter to patients and their reported quality of life when delivering quality and value-based healthcare (Porter, 2013; Bae, 2015; Riva & Pravettoni, 2016).

There is currently limited research into how bleeding events impact QoL in AF patients, especially those who experience CRNMB, for which no medical care is sought (as per Bleeding Academic Research Consortium (BARC) definition) (Mehran et al, 2011). Likewise, there are no existing and/or validated patient-reported outcome measures (PROMs) developed for use in assessing how bleeding influences patient QoL.

Objectives

- To test the feasibility of identifying patients with both CRNMB major bleeds as a result of anticoagulant treatment for AF and evaluating their QoL through both primary and secondary care settings.
- To describe and interpret the observed differences in QoL by type of bleed experienced.
- 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 OATs.
- To evaluate the 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 OATs

Methods/design

Participating sites

We will utilise three recruitment pathways for the study:

- Primary care – A large city general practice cluster made up of 8 practices in Swansea, UK
- Secondary care – A large University teaching hospital with an emergency department in Swansea, UK.
- Direct patient – An online forum and database through the Arrhythmia Alliance & AF Association Newsletter/e-card and forums

Study population

Adult patients (≥ 18) who have AF and are actively prescribed OATs and have experienced bleeds, up to a maximum of 4 weeks prior to enrolment. We will apply no upper age limit, but patients must match all other inclusion/exclusion criteria. For this feasibility study, we will select patients from the Swansea area only, who attend/have attended either anticoagulation clinics within the Swansea City Health Cluster,

Morrison Hospital emergency department or have been admitted to wards at Morrison Hospital due to a bleed. Lastly, we will engage with people who have signed up to an online forum and support group for those diagnosed with AF, via a survey link in a circulatory newsletter and using online forums/social media.

Inclusion criteria

- Adult patients (≥ 18 years old)
- Patients who have a fluent understanding of English and can therefore comprehend 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

Exclusion Criteria

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

Patient Recruitment & Study Sites

Our 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, we will identify eligible patients from regular searches in secure databases in both primary (GP surgeries) and secondary care (ward/emergency department [ED]). We will send letters of invite to patients who appear eligible via primary and secondary care. No on-site visits will take place due to restrictions surrounding COVID-19 and social distancing. We will subsequently approach patients 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, we will post study information to patients with AF who may not have recently visited clinics, wards, or emergency department (ED). Where appropriate, we will place study posters in locations such as general practice (GP) clinics to display information about the study. We will ensure that they are written in lay terms, to encourage discussion with GPs concerning all recent minor bleeds (as defined by ISTH), which the patient may not have thought relevant enough to mention otherwise. We will provide patient information sheets (PIS) and study cards, which will allow potential participants to take away study information for consideration, including discussion by friends and family members. We will instruct those patients interested in participating in the study to contact the clinical research team directly to streamline screening and enrolment process, and to limit time burdens on healthcare staff.

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.

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. We will recruit a maximum of 200 patients.

Patient Questionnaires

We will collect basic patient demographic information on case report forms (CRFs), along with details of any bleed(s) experienced. We will ask patients additional questions relating to the ongoing management of their AF during the current Coronavirus pandemic. This will include the ease of seeking medical care in the situation of a lockdown and social distancing where visits to anticoagulation clinics are limited or entirely stopped. We will comply with Good Clinical Practice (GCP) guidelines and the General Data Protection Regulation (GDPR) in the conduct of the study and the collection of patient information.

We will ask all participants to complete three PROMs questionnaires for the study: the Euroqol 5 Dimensions-5 Levels (EQ-5D-5L) (EuroQol Group, 2009), Perception of Anticoagulant Treatment Questionnaire, Part 2 only (PACT-Q, Part 2) (Sanofi-Aventis, 2007) and Atrial fibrillation Effect on Quality-of-life (AFEQT) (Spertus et al, 2009). We have been mindful to reduce participant burden as far as possible and have estimated that completion of all study questionnaires should take no longer than 30 minutes. We will send the participant questionnaires 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. The purpose of the initial timepoint is to gather information about patient quality of life around the time of the bleed. The second time point will assess if their quality of life has changed 3 months later. We will ask participants to complete the initial round of questionnaires immediately after the consent process, to ensure that loss to follow-up is controlled. In both questionnaire sets, we will include an option for participants to take part in a further qualitative interview, after the 90-day follow up. We will send an electronic link to the initial questionnaires so the participant can access the questionnaires on a computer, tablet or phone or will provide paper copies, if requested. We will send follow-up questionnaires either through the post 3 weeks prior to the 90-day follow-up date, or we will send a survey link to participants. We will ask participants in an accompanying letter to complete and return the questionnaires within the 90 ± 14 day time-frame.

COVID-19 Impact

We designed the proposed study in line with current guidelines set out by the UK and Welsh Government for Coronavirus management. We will follow up to date Government guidance throughout the study (available online at <https://gov.wales/coronavirus>).

We acknowledge that the current COVID-19 pandemic, resulting restrictions and dramatic changes to patient lifestyle has the potential to cause additional adverse impact on QoL issues for the study population being investigated. We will not investigate QoL issues directly caused by the global Coronavirus pandemic as part of this study. However, we will collect anecdotal information about how

patients manage their diagnosis of AF during relevant clinic closures, lockdown environment and social distancing restrictions.

Data Handling & Storage

We will enter paper copies of CRFs and questionnaires into the study database. Questionnaires completed electronically will be saved directly into the study database. All data will be checked for consistency and accuracy.

We will host the data securely on the REDCap data management system (licensed to Swansea Trials Unit (STU)). We will hold study data anonymously within REDCap and any identifying data (including protected characteristics) will be kept separately, secured by user access restrictions.

Data Analysis and Reporting

We will focus our analysis of the questionnaire data primarily on our feasibility outcomes and present descriptive data. We will present summary information on patient demographics, mode of recruitment and levels of missing data. We will present descriptive summaries of PROMs scores reported by AF patients following a minor or major bleed while taking OATs, but we will not undertake any formal statistical comparisons. We will compare PROMs scores to age-adjusted population norms where available.

We will undertake a brief thematic analysis (Braun & Clarke, 2006) 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. We will use specific qualitative data analysis software, NVivo 12, for additional insight and to identify trends in unstructured data captured during study interviews.

Ethical considerations

This study has received ethical approval from the London Research Ethics Committee. All patients will undergo fully informed consent and have the right to withdraw at any point of the study. We recognise that participants may become distressed or emotional during completion of study questionnaires by the recollection of previous experiences associated with bleeds. Patients may also experience low mood or anxiety associated with their AF. Our 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 we will encourage them to discuss this with their primary or secondary care researcher and the participant will be signposted to local relevant services or advised to contact their GP. All data collected in the study will be stored securely within a password protected Clinical Data Management System (REDCap) while the study is conducted and anonymised for analysis purposes.

Public and Patient Involvement

We will invite two patient and public involvement (PPI) representatives 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. Arrhythmia Alliance & AF Association). We will utilise advice and expertise from PPI members of the study team to appropriately disseminate study findings.

Discussion

We will aim to determine in this feasibility study if we are able to recruit and collect QoL data from patients who have experienced either a major bleed or CRNMB, while taking OATs for the management of AF.

As this is a feasibility study, it is difficult to predict if we will successfully identify eligible patients and subsequently enrol them, based on the study inclusion/exclusion criteria. There is also uncertainty around optimal ways to identify patients promptly within the primary care and hospital settings. Patients who experience CRNMB do not always discuss these events with GPs, and identifying these patients could prove challenging, however utilising an online forum allows additional opportunity for identification and recruitment. We will test recruitment measures in this feasibility study to inform best strategies for a possible larger-scale study in the future.

Abbreviations

AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
BMS	Bristol Myers-Squibb
COVID-19	Coronavirus Disease 2019
CRFs	Case Report Form(s)
CRNMB	Clinically Relevant Non Major Bleed
ED	Emergency Department
EQ5D	EuroQol-5D
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HAS-BLED	HTN (SBP>160), Age >65, Stroke , Bleeding history or predisposition, Liver and Kidney dysfunction, Elevated or unstable INRs, Drugs and Alcohol
HRQoL	Health-related Quality of Life
ISTH	International Society on Thrombosis and Haemostasis
OATs	Oral Anticoagulation Therapies
PACT-Q	Perception of Anti-Coagulant Treatment Questionnaire
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome Measure(s)
QoL	Quality of Life
REDCap	Research Electronic Data Capture

Declarations

Ethics approval and consent to participate

This protocol has received ethics approval from the London -Riverside Research Ethics Committee (20/PR/0479). All participants will provide written informed consent prior to taking part in the proposed study.

Consent for publication

Participants will provide written informed consent for their anonymised data and interview quotes where relevant to be used in any future publications.

Availability of data and materials

All data collection instruments are available following an appropriate request for use license. The structured interview format is available as an additional document. Anonymised versions of the dataset used will be available from the corresponding author upon reasonable request.

Competing interests

Hayley A Hutchings leads this independent research which has received funding from Pfizer and Bristol Myers Squibb.

Hamish Laing is an employee of Swansea University who has received a grant for a Value-Based Healthcare programme of work from Pfizer Ltd., which he leads and support to attend a meeting.

Steven Lister is an employee of BMS who are funding the independent research and holds stock in BMS and Pfizer.

Kevin Pollock is an employee of BMS who have provided funding for the research.

Julian Halcox has received funding to their instruction from Pfizer and Bristol Myers Squibb since initial planning of this work, has received research grants to institution from Pfizer and Bristol Myers Squibb, personal consulting fees and payments for lectures from Pfizer and Bristol Myers Squibb, Bayer and Boehringer Ingelheim and finally support from Pfizer and Bristol Myers Squibb for attending meetings including travel costs paid to meeting organizers/travel companies.

Gail Holland, Claire Fegan, Kirsty Lanyon, Arfon Hughes, Rhys Jenkins, Trudie Lobban, Lianne More, Diane Owen, Ceri Todd and Kathie Wareham declare that they have no conflict of interest.

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This study was sponsored by Pfizer and Bristol Myers Squibb, who will have oversight of all publications and conference presentations. A final report detailing the results of the study will be submitted to Pfizer and Bristol Myers Squibb upon its completion. The study is being conducted and managed through Swansea University who will act as the research governance study sponsor, independently of the Pfizer and Bristol Myers Squibb.

Authors' contributions

HAH is the Chief Investigator of the study. HAH and SL conceived the project and developed the initial protocol. KL is managing the study, developed the full protocol for ethics and governance approvals, and drafted the initial manuscript. GH provided input into protocol development and governance. All authors

provided input into the study development and confirmed accuracy and scientific value. All authors approved the final manuscript.

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