# TRIAL PROTOCOL

# ABBRUPT

A randomised controlled trial to investigate clinical and cost effectiveness of Amiodarone vs Beta Blockade for new onset atrial fibRillation in icU - a Pragmatic sTudy

**This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)**

| | |
|---|---|
| **Version Number:** | **4.0** |
| **Version Date:** | **20th January 2025** |

# PROTOCOL DEVELOPMENT

## Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version. Amendments to the protocol will be made in collaboration with the TMG and the Sponsor will decide if the amendment is substantial or non-substantial. Amendments will be communicated to MHRA &/or REC as appropriate by completion of the amendment tool and approvals will be emailed to Trust's R&D departments. The amendment history will be tracked within the protocol using the table below.

| Amendment number | Date of amendment | Protocol version number | Type of amendment | Summary of amendment |
|---|---|---|---|---|
| 1 | 16th May 2024 | 2.0 | Substantial | Correction of minor typographical errors and administrative updates throughout.<br>Change of wording to magnesium exclusion criteria.<br>Amalgamation of two inclusion criteria.<br>Addition of sepsis as an expected SAE.<br>Removal of amiodarone loading dose.<br>Removal of list of beta blockers.<br>Remove decreased libido from list of AEs.<br>Removal of NHS number and Chi number.<br>Removal of National Opt-Out register.<br>Removal of EQ-5D-5L at baseline in Health Economics analysis. |
| 2 | 30th July 2024 | 3.0 | Substantial | Correction of minor typographical errors and administrative updates throughout.<br>Addition of PPI members to TMG<br>Addition of ACCPs to Section 4.3: confirmation of eligibility<br>Change of wording to Section 7.7.2: packaging and labelling |

| | | | | |
|---|---|---|---|---|
| 3 | 20th January 2025 | 4.0 | Substantial | Interim change of CI to Dr Dhruv Parekh<br>Amendments to inclusion/exclusion criteria:<br>I. Add definition of NOAF<br>II. Amended wording to inclusion criteria<br>III. remove exclusion 'in receipt of amiodarone or beta blocker within previous 24 hours'<br>IV. remove 'other thoracic surgery that ingresses the thorax<br>V. Remove 'A serum magnesium value below the index hospital laboratories lower limit of normal'<br>Remove paper EQ5D<br>Add streamlined eligibility and randomisation process<br>Removal of sub-study<br>Remove SmPCs and refer to RSI instead |


## Funding and support in kind

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The Funder of the trial has had no role in the trial design, data collection, data analysis or data interpretation.

This project is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## PROTOCOL SIGN OFF

### Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial 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 stated in this and any subsequent approved protocol will be explained.

| | |
|---|---|
| Trial name: | ABBRUPT |
| Protocol version number: | Version: 4.0 |
| Protocol version date: | 20 / January / 2025 |
| | |
| CI name: | Dr Dhruv Parekh |
| Signature and date: | _____ __ __/__ __/__ __ __ __ |

### Sponsor statement

By signing the IRAS form for this trial, the University of Birmingham, acting as sponsor, confirm approval of this protocol.

### Compliance statement

This protocol describes the ABBRUPT trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the ABBRUPT trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

## Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise patient safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

| | |
|---|---|
| Trial name: | ABBRUPT |
| Protocol version number: | Version: 4.0 |
| Protocol version date: | 20 / January/ 2025 |
| | |
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| Name of Site: | |
| Signature and date: | _____ __ __ / __ __ / __ __ __ __ |

## ADMINISTRATIVE INFORMATION

| **Reference Numbers** | |
|---|---|
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| ISRCTN reference number | 59775011 |
| IRAS reference number | 1007930 |

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| Mrs Teresa Melody | As above |
| Dr Joyce Yeung | As above |
| Jim Hyland | PPI |
| Sue Boex | PPI |

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| *Independent Members* | |

| | |
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| Gerrit Eichner | Statistician, Justus-Liebig-University of Giessen, Germany |
| Duncan Young | Professor of Intensive Care Medicine (retired) |

## ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ACCP | Advanced Critical Care Practitioner |
| AE | Adverse Event |
| AF | Atrial fibrillation |
| BCTU | Birmingham Clinical Trials Unit |
| BNF | British National Formulary |
| DCF | Data Clarification Form |
| DMC | Data Monitoring Committee |
| DSA | Data Sharing Agreement |
| CEA | Cost-effectiveness Analysis |
| CEAC | Cost-effectiveness acceptability curve |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CRP | C-Reactive Protein |
| CTIMP | Clinical trial of an investigational medicinal product |
| CUA | Cost-utility analysis |
| DCF | Data Clarification Form |
| DSUR | Development Safety Update Report |
| GCP | Good Clinical Practice |
| HR | Heart Rate |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment Programme |
| ICF | Informed Consent Form |
| ICU | Intensive Care Unit |
| ISF | Investigator Site File |
| IV | Intravenous |
| ITT | Intention to Treat |

| | |
|---|---|
| MI | Myocardial infarction |
| NHS | National Health Service |
| MAP | Mean Arterial Pressure |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health and Care Research |
| NOAF | New-onset atrial fibrillation |
| PI | Principal Investigator |
| PIS | Patient Information Sheet |
| PSS | Personal Social Services |
| QALY | Quality-adjusted life year |
| REC | Research Ethics Committee |
| RGT | University of Birmingham Research Governance team |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TSC | Trial Steering Committee |
| UoB | University of Birmingham |
| WCBA | Women of child-bearing age |

## TRIAL SUMMARY

**Title**

A randomised controlled trial to investigate the clinical and cost effectiveness of Amiodarone vs Beta Blockade for new onset atrial fibRillation in icU - a Pragmatic sTudy.

**Objectives**

To conduct a multi-centre, randomised trial comparing two commonly used treatments (beta blocker and amiodarone) for new onset Atrial Fibrillation (NOAF) in intensive care.

To perform clinical and full economic evaluation to compare treatment with beta blockers and amiodarone.

**Trial design**

Open-label interventional multi-centre two-arm randomised controlled trial with internal pilot and economic evaluation.

**Patient population and sample size**

Patients (≥16 years) requiring a high level of care with NOAF or a new episode of AF within this acute admission for which therapeutic intervention with either beta blockers or amiodarone is planned by the clinical team. In total, 2560 patients (1280 per arm) will be randomised.

**Setting**

Critical care units in NHS Trusts/ Health Boards within the UK

**Eligibility criteria**

**Inclusion criteria**

- Adult Patients (age ≥16 years)
- Monitored in an area of higher care with the ability to deliver the interventions
- Onset of NOAF or a new episode of AF during the acute illness (A&E, deterioration on ward, after surgery) where there is a clinical indication to treat with amiodarone or beta blockers as determined by the attending clinician/ACCP or equivalent.
- Usual electrolyte management with potassium and magnesium has taken place according to site practice

**Exclusion criteria**

- Treatment with anticoagulants or antiarrhythmics for the treatment of AF before the current hospital admission *anticoagulants or antiarrhythmics used for any other purpose can be included
- Current concomitant medication that are contraindicated with the intervention / comparator medications (e.g. Ciclosporin, Itaconazole, Letermovir)
- Serum Potassium of < 4 mmol $^{L-1}$ (measured either on Point-of-Care Testing or Laboratory)
- Patients having undergone cardiac surgery during the current hospital admission, defined as any surgery including lung resections, stent procedures such as percutaneous coronary interventions or other angioplasty procedures done on the heart muscle, valves or thoracic arteries including the thoracic part of the aorta
- Thyrotoxicosis
- Withdrawal of life support therapy within 24 hours
- Any other known contraindication or known sensitivity to beta-blockers or amiodarone
- Known pregnancy or patients currently known to be breast-feeding

**Interventions**

Intervention: Amiodarone

Comparator: Beta-blockade

*Both the intervention and comparator should be applied for as long as is usual in your local practice.*

**Outcome measures**

**Primary outcome**

- 90-day mortality

**Secondary outcomes**

*Clinical Outcomes:*

- ICU and hospital mortality
- Rates of cardiovascular events including stroke, myocardial infarction or thromboembolism up to 90-days
- Rate of established AF by the end of ICU stay / death / Day 90

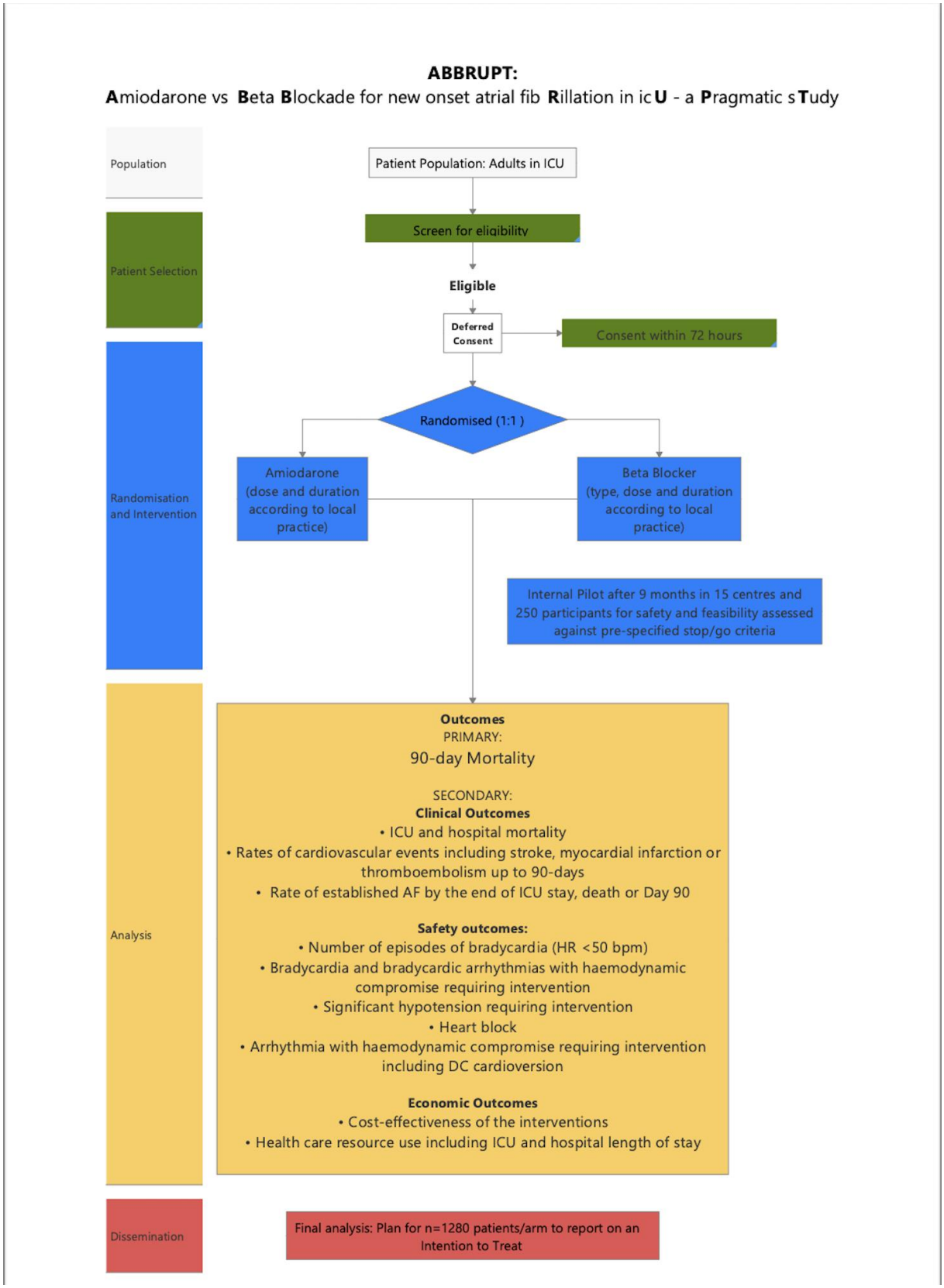
*Safety outcomes:*

- Number of episodes of bradycardia (HR <50 bpm) whilst in hospital and being prescribed the intervention
- Bradycardia and bradycardic arrhythmias with haemodynamic compromise requiring intervention
- Significant hypotension requiring intervention (not including temporarily stopping the trial medication) whilst in ICU
- Heart block
- Arrhythmia with haemodynamic compromise requiring intervention including DC cardioversion

*Economic Outcomes:*

- Cost-effectiveness of the interventions
- Health care resource use including ICU and hospital length of stay

## TRIAL SCHEMA



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# 1 BACKGROUND AND RATIONALE

## 1.1 Background

Atrial Fibrillation (AF) is a supraventricular tachyarrhythmia resulting from irregular, disorganised electrical activity and ineffective contraction of the atria (1); New Onset AF (NOAF) does not have a widely accepted definition, but for the purposes of this trial, ABBRUPT, we will define NOAF as AF during the acute illness (A&E, deterioration on ward, after surgery) where there is a clinical indication to treat with amiodarone or beta blockers as determined by the attending clinician/ACCP or equivalent. Patients having received anticoagulation or antiarrhythmics for the treatment of AF before the current hospital admission do not fall under this definition however, anticoagulants or antiarrhythmics used for any other purpose than for treating AF can be included. AF occurs in approximately 5-26% of Intensive Care Unit (ICU) patients (2,3), depending on age, sex, obesity, co-morbidities and the reason for ICU admission (2). The risk of AF increases in the presence of sepsis with one systematic review reporting an incidence of 46% (4). Although AF often resolves, AF recurs in up to 18% (5) of cases and is associated with severe complications such as death, stroke or myocardial infarction (MI) in the longer-term. A 2021 review (6) reported higher mortality in hospital and during the first 90-days after ICU discharge (adjusted odds ratio 2.32, 95% CI 2.16 to 2.48; adjusted Hazard Ratio 1.46, 95% Confidence Interval 1.26 to 1.70, respectively) in patients with NOAF. Re-admission rates for stroke and heart failure (adjusted cause-specific Hazard Ratio 1.47, 95% Confidence Interval 1.12 to 1.93; and adjusted cause-specific Hazard Ratio 1.28, 95% Confidence Interval 1.14 to 1.44, respectively) were also higher in patients with NOAF.

There are no prospective randomised studies comparing amiodarone with beta blockade reporting long term, clinically relevant outcomes. A retrospective analysis of the 38,159-patient MIMIC III dataset reported (7) that, compared with those who did not develop AF, there was significantly higher 90-day and hospital mortality (20.8% versus 15.3%) and beta blocker use had a protective effect (Hazard Ratio 0.59, 95% Confidence Interval 0.53–0.65, p<0.001). Amiodarone was associated with a higher mortality (Hazard Ratio1.16, 95% Confidence Interval 1.05–1.29, p=0.004). There are no information about the application of the treatment used and potential confounders, such as concomitant medications or whether amiodarone was used in patients with higher inotrope and vasopressor use.

Work by our own group (8) and others (9) has reported that the majority of intensivists use amiodarone to treat AF in the critically ill. Given the results from MIMIC and the analysis by Chean et al (8), there is a clear need to distinguish whether there is a difference in outcome in patients managed with amiodarone compared with beta blockade. ABBRUPT is a comparison of amiodarone and beta blockade to establish which management of AF is best to avoid harm and achieve optimal outcomes.

## 1.2 Trial rationale

The impact of developing AF in the ICU has been studied in a number of large retrospective analyses. ICU/Hospital Mortality: Several papers (10-13) have reported ICU mortality but are best summarised in 2019 systematic reviews and meta-analyses of 12 papers in NOAF only and excluding papers reporting established AF (14). There were significant differences in hospital mortality in ICU patients with NOAF compared with patients without (Odds Ratio 2.70; 95% Confidence Interval 2.43-3.00) (14), and a subgroup analysis of patients with sepsis or septic shock showed a significant association between NOAF and hospital mortality (Odds Ratio 2.32; 95% Confidence Interval 1.88-2.87) (14).

In a study of 3334 critically ill patients, NOAF was associated with increased in-hospital mortality and 1-year mortality. The mortality within the first year after being discharged from the hospital alive was 4.6% in patients with no AF, 11.6% in the patients with known AF and 26.0% in patients with NOAF

(15). A study of 1841 critically ill patients reported that there was higher post-ICU risk of death in the ICU survivors with AF (Hazard Ratio 2.2, P < 0.001) (14) compared to those without AF.

Excess mortality in patients with sepsis and septic shock: Meierhenrich reported a hospital mortality rate of 44% in those with NOAF versus 22% for those who did not in surgical ICU patients; hospital mortality was 45% for individuals with NOAF versus 16% for those without (16).

NOAF is also associated with increased morbidity. Studies report that patients with sepsis who develop NOAF have a greater risk for in-hospital stroke (2.6% versus 0.6%) (17), and subsequent hospitalisation for heart failure (11.2% versus 8.2%) compared with those who do not (18). Moreover, NOAF may not resolve; up to 18% of patients have been reported to have been discharged from ICU with persistent AF (5).

Although the prognostic significance of NOAF in ICU is established, what is not known is whether different treatment strategies can modify the associated morbidity and mortality that comes with it. Patients with AF require more vasopressor and inotropic support. Shaver (12) reported in 1770 patients, that those with AF were more likely to be treated with vasopressors or inotropes compared with patients who did not develop AF in the ICU (59.7% vs. 43.2%, p<0.001) and were treated with vasopressors for longer (1.7 ± 1.5 days in NOAF vs. 1.0 ± 1.3 days without AF, p<0.001). The requirement for additional vasoactive support may be a factor in adverse clinical outcomes. This is a current active area of study by our group and supported by the NIHR in the STRESS-L study (19) (NIHR EME - 14/150/85).

ICU survivorship leads to chronic ill health, morbidity and mortality. NOAF is also associated with significant on-going costs in terms of disability, care and treatments (20). ICU clinicians need to understand the best treatments to apply at the time of critical illness to optimise “good survivorship” – that is a long and healthy post-ICU recovery. In surveys from 2017 and 2021 (8,9), we have observed a trend in treatment preferences away from amiodarone towards beta blockade, but without the evidence of the benefit for either. Physicians’ growing awareness of NOAF as a major determinant of longer-term ICU outcome together with a lack of evidence on how to treat it, suggests that there is now an opportunity to determine best treatment options.

ABBRUPT will investigate important clinical outcomes, but will also provide an ideal opportunity for further, separately funded, mechanistic studies.

### 1.3 Justification for patient population

The development of NOAF in ICU is associated with a several unwanted side effects including an increased risk of myocardial events, stroke and death in the twelve months following ICU discharge. Retrospective studies suggest that management with amiodarone (when compared with beta blockade) is associated with worse outcomes. There is however concern that these data are biased as patients who are cardiovascularly stable could have been excluded from receiving beta blockers. The ABBRUPT trial will study the widest possible population of critically ill patients in ICU as the impact of NOAF management on 90-day mortality is unknown.

### 1.4 Justification for design

The CAFÉ report (6) noted that beta-blockers and amiodarone appear to be similarly effective in achieving cardiovascular control, but digoxin and calcium channel blockers appear to be inferior. The majority of intensivists use amiodarone to treat AF in the critically ill (8,9) but the proportion who use beta blockade is increasing. There are no studies available to define the optimal administration route, time and dose for either of the study drugs nor are there studies demonstrating that one particular beta blocker is superior to another. With the wide range of available drugs, route of administration

(IV or oral) and duration of treatments, a robust clinical trial is required to determine evidence based practice for intensities using amiodarone and/or beta-blockers for treating NOAF.

A randomised study such as ABBRUPT is necessary to inform ICU clinicians whether amiodarone or beta blockade is better to avoid 90-day mortality for the drug management of NOAF in ICU.

## 1.5 Justification for choice of intervention(s)

Despite being used as an anti-arrhythmic agent since the 1970s, amiodarone is relatively understudied in the ICU, and there are only few studies that have measured either beneficial or harmful associations with its use. An extensive systematic literature review was not able to define the superiority of amiodarone or beta-blockers as anti-arrhythmic agents for rhythm or rate control in NOAF (21). In addition, there are very few laboratory studies on the effects of amiodarone. However, in one animal study (22), amiodarone affected both phagocytic function and cell-mediated immunity possibly through the inhibition of phospholipase C. This may represent an immunomodulatory effect. The clinical impact of such immunomodulation on morbidity and mortality is unclear.

Beta blockers, on the other hand, have been widely studied in a variety of animal and cell studies. Beta blockers may have effects in the critically ill beyond cardioversion and heart rate (HR) control which are currently under investigation by our group (19). Clinically, HR control with beta blockers have been associated with improved outcomes in a variety of conditions including myocarditis, liver failure, multiple myeloma, traumatic brain injury, trauma, septic shock and burns (reviewed (23)). However, a meta-analysis of the use of beta blockers peri-operatively (24) reported that beta blockade prevented non-fatal MI but increased the risk of stroke, death, hypotension, and bradycardia. None of these studies has been replicated with amiodarone which has a wide variety of actions including some ability to block beta receptors. The potential side-effects of amiodarone are hypotension during infusion and an increased risk of chronic interstitial pneumonitis and organizing pneumonia (25) the impact of which remain unknown.

## 1.6 Justification of choice of primary outcome

NOAF in the ICU is associated with short-term and long-term mortality. Studies (6) have found that the rates of conversion to sinus rhythm are similar between amiodarone and beta blockade, but there is a possibility of an increase in long-term morbidity and mortality associated with either of the study interventions. The primary outcome in ABBRUPT is to determine if there is a difference in 90-day mortality rates between amiodarone and beta blockade.

# 2 AIMS AND OBJECTIVES

## 2.1 Internal pilot objectives

The success of the internal pilot will be based upon the following factors: patient recruitment, commencement of an alternative treatment, study drop-out and data completeness.

The number of patients to be recruited in the 9-month internal pilot will be 250 from at least 15 recruiting sites, assuming staggered site opening and for each site to recruit on average 2 patients per month. The decision for the trial to continue will be decided by pre-defined progression criteria below:

- Green: Recruitment rate 100%, alternative treatment rate <5%, drop-out rate <5%, data completeness ≥90%. If all criteria are met; continue the trial with protocol unchanged.
- Amber: Recruitment rate 75-99%, alternative treatment rate 5-10%, drop-out rate 5-10%, data completeness 80-89%. If one or more of our amber criteria are met, then the study will need review to see what changes (if any) could be made to improve whichever criteria are not at the "green" level.
- Red: Recruitment rate <75%, alternative treatment rate >10%, drop-out rate >10%, data completeness <80%. If one or more of these criteria are met, we will discuss with the Trial Steering Committee (TSC) and the funder regarding feasibility of the study continuing.

**Length of internal pilot phase: 9 months**

| Progression criteria | Red | Amber | Green |
|---|---|---|---|
| % Threshold | <75% | 75-99% | ≥100% |
| Alternative treatment rate | >10% | 5-10% | <5% |
| Drop-out rate | >10% | 5-10% | <5% |
| Data completeness | <80% | 80-89% | ≥90% |
| Recruitment rate/site/month | <1.5 | 1.5-1.9 | 2 |
| Number of sites opened | <12 | 12-14 | 15 |
| Total number of patients recruited | <172 | 172-249 | 250 |

## 2.2 Main trial objectives

### 2.2.1 Clinical aims and objectives

To conduct a multi-centre, randomised trial comparing two commonly used treatments (beta blocker and amiodarone) for NOAF in ICU.

### 2.2.2 Economic aims and objectives

The economic evaluation will compare beta blocker with amiodarone from a National Health Service (NHS) and Personal Social Services (PSS) perspective. A within-trial cost-effectiveness (CEA) and cost-utility analysis (CUA) will be conducted at 90-days follow up. If the trial demonstrates a difference between strategies, a model-based CUA will extrapolate beyond the endpoint of the trial.

# 3 TRIAL DESIGN AND SETTING

## 3.1 Trial design

ABBRUPT is a multi-centre, randomised, controlled open label trial comparing amiodarone with beta blockade for the treatment of NOAF, or a new episode of AF, in the ICU. It will study a total of 2560 patients.

- For the purposes of the trial, NOAF is defined as AF during the acute illness (A&E, deterioration on ward, after surgery) where there is a clinical indication to treat with amiodarone or beta blockers as determined by the attending clinician/ACCP or equivalent.

## 3.2 Trial setting

At least 60 ICUs across the UK.

## 3.3 Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

Type A = No higher than the risk of standard medical care

# 4 ELIGIBILITY

## 4.1 Inclusion criteria

- Adult Patients (age ≥16 years)
- Monitored in an area of higher care with the ability to deliver the interventions
- Onset of NOAF, or a new episode of AF, during the acute illness (A&E, deterioration on ward, after surgery) where there is a clinical indication to treat with amiodarone or beta blockers as determined by the attending clinician/ACCP or equivalent.
- Usual electrolyte management with potassium and magnesium has taken place according to site practice

## 4.2 Exclusion criteria

- Treatment with anticoagulants or antiarrhythmics for the treatment of AF before the current hospital admission *anticoagulants or antiarrhythmics used for any other purpose can be included
- Current concomitant medication that are contraindicated with the intervention / comparator medications (e.g. Ciclosporin, Itaconazole, Letermovir)
- Serum Potassium of < 4 mmol $^{L-1}$ (measured either on Point-of-Care Testing or Laboratory)
- Patients having undergone cardiac surgery during the current hospital admission, defined as any surgery including lung resections, stent procedures such as percutaneous coronary interventions or other angioplasty procedures done on the heart muscle, valves or thoracic arteries including the thoracic part of the aorta
- Thyrotoxicosis
- Withdrawal of life support therapy within 24 hours
- Any other known contraindication or known sensitivity to beta-blockers or amiodarone
- Known pregnancy or patients currently known to be breast-feeding

## 4.3 Confirmation of eligibility

The Medicines for Human Use (Clinical Trials) Regulations state that 'the decision whether a subject is eligible for entry into a clinical trial is considered to be a medical decision and must be made by a medically qualified doctor the medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist' (Part2 (11) of Schedule 1 to SI 2004/1031). However, within the critical care setting, the role of Advanced Critical Care Practitioners (ACCPs) or equivalent e.g. Advanced Nurse Practitioners (ANPs), Clinical Nurse Specialists (CNSs) have developed into autonomous practitioners; their skills include non-medical prescribing, assessment, diagnosis and the management of patients' health needs and complex clinical decision making. (26)

Thus, it is appropriate in ABBRUPT (as a Type A CTIMP) to take a risk proportionate approach to the assessment of eligibility. Confirmation that a patient is eligible to be randomised into ABBRUPT may be confirmed by either a medically qualified doctor or an ACCP (or equivalent), working under the supervision of a medically qualified doctor. In all instances, those confirming eligibility must be trained on the ABBRUPT trial procedures and have been delegated the task of confirming eligibility by the PI, either by being added to the delegation log or by being provided with the link to the eligibility and

randomisation training by the PI. The name of the person who has confirmed eligibility will be recorded in the patient's medical notes and will also be captured on the Randomisation Form.

## 4.4 Co-enrolment

The Trial Management Group (TMG) will consider requests for co-enrolment into other trials in accordance with best practice recommendations (27). Co-enrolment to other trials will be considered on a case-by-case basis by the ABBRUPT TMG. Prior to co-enrolment being agreed, the following will be reviewed and considered: study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; patient considerations and logistical and organisational issues. Co-enrolment to Clinical Trials of Investigational Medicinal Products (CTIMPs), will be restricted to those assessed to be 'Type A' that are comparable to the risk of standard medical care, where the intervention(s) would commonly be used in the treatment of the patient, and where no biological interactions or additional safety reporting will be required for concomitant administration of the intervention(s).

For co-enrolment to occur, an agreement will be reached between the respective trials team prior to the patient being considered for inclusion. A log of all patients co-enrolled will be maintained by the ABBRUPT Trial Office.

# 5 CONSENT

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each patient. This task can be delegated by the PI to other members of the local research team, if local practice allows and this responsibility has been documented in the site signature and delegation log.

NOAF can be a life-threatening condition requiring urgent treatment. The vast majority of eligible patients will be sedated and mechanically ventilated and will therefore lack capacity to consent for themselves. Furthermore, owing to the need for urgent treatment, it would be clinically unjustifiable to delay treatment until informed consent can be obtained from a legal representative. Even if such a representative were immediately available, the emotional distress of the situation is such that they would be unlikely to make an informed decision in the minimal time available. Consequently, ABBRUPT cannot be conducted on the basis of prospective informed consent.

Patients who are incapable of giving consent in emergency situations are an established exception to the general rule of informed consent in clinical trials. This is clearly acknowledged in the Declaration of Helsinki 2008. Under UK law, emergency care is permitted under the terms of The Medicines for Human Use (Clinical Trials; Amendment No.2) Regulations 2006. Specifically:

- Having regard to the nature of the trial and the particular circumstances of the case, it is necessary to take action for the purpose of the trial as a matter of urgency
- It is not reasonably practicable to obtain informed consent prior to entering the subject
- The action to be taken is carried out in accordance with a procedure approved by the research ethics committee

## 5.1 Patient consent (*after* trial intervention)

An assessment will be made at site to determine whether the patient has regained capacity and is able to consent for themselves. Where this is found to be the case, a Patient Information Sheet (PIS) will be provided to facilitate this process. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the patient. They will also explain that their continued participation is voluntary and that they are free to decide to withdraw from the trial at any time. The patient will be given adequate time to read, or have read to them, the PIS and to discuss their participation with others outside of the site research team. The patient will also be given the opportunity to ask questions before signing and dating the latest version of the Informed Consent Form (ICF). If the patient then confirms that they are willing to continue participating in the trial, they will be asked to sign and date the latest version of the ICF. The PI or delegate will then sign and date the ICF. Where a patient is physically unable to sign the ICF, a witness will be able to sign on their behalf. A copy of the ICF will be given to the patient, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). The patient's trial number will be entered on the ICF. In addition, the patient will be asked to confirm that they understand that a copy of the signed ICF will be transferred to BCTU for review.

Details of the informed consent discussions will be recorded in the patient's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the patient, version number of ICF signed and date consent received.

Throughout their participation in the trial, the patient's willingness to continue in the trial will be ascertained and documented in the medical notes. The patient will have the opportunity to ask questions about the trial. Any new information that may be relevant to the patient's continued participation will be provided. Where new information becomes available which may affect the patient's decision to continue, they will be given time to consider and if happy to continue they will

be re-consented. Re-consent will be documented in the medical notes. The patient's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the ABBRUPT Trial Office and these should be presented on the headed paper of the site.

## 5.2 Patients who lack capacity to consent for themselves

Where a patient is found to still lack capacity following administration of the loading dose, consent from a legal representative will be sought as soon as practically possible. Sites should aim to obtain consent within 72 hours of the patient being randomised into the trial.

In the first instance, the local research team will work to identify a **personal legal representative** as defined below:

> *A personal legal representative is a person independent of the trial, who by virtue of their relationship with the trial patient is suitable to act as their legal representative for the purposes of the trial and who is available and willing to act for those purposes.*

The personal legal representative will be approached and will be provided with the Research Ethics Committee (REC) approved personal legal representative information sheet explaining the trial and the options for the patient's continuing involvement, including the need for them to give consent on behalf of the patient. The personal legal representative will then have time to consider the information provided, after which, a member of the local research team will ask when the personal legal representative would like them to come back and discuss participation further and potentially receive consent.

In the event that a personal legal representative cannot be identified, or it is deemed inappropriate to approach the potential personal legal representative, the local research team will work to identify a **professional legal representative** as defined below:

> *A person independent of the trial, who is the doctor primarily responsible for the medical treatment provided to that adult. Or a person nominated by the relevant healthcare provider.*

Informed consent given by a professional legal representative shall represent the patient's presumed will. Where a professional legal representative gives consent, should a personal legal representative subsequently be identified they will be informed at the earliest opportunity and consent for the patient to continue in the trial will be sought from them.

If face-to-face consent is not possible, remote written consent may be undertaken. The informed consent discussions will proceed as above but by telephone, videoconference or equivalent. This written process will be undertaken in the presence of a witness who will initial the boxes on the ICF in response to discussions between the member of the research team and the legal representative. The member of the research team will then sign and date the ICF as will the witness. A copy of the completed ICF will be given to the patient and can be provided to the legal representative upon request. As above, a copy of the ICF will also be filed in the patient's medical notes, a copy will be sent to BCTU and the original placed in the ISF.

Should the legal representative decide that the patient would not want to take part, the patient will be withdrawn from the trial and no further data collected.

If the patient does regain capacity during the follow-up period, they will be asked to give consent for themselves using the process outlined in Section 5.1.

**The patient's wishes (consent or refusal) will in all cases, supersede the legal representative's consent.**

## 5.3 Patients who do not survive

The most challenging ethical consideration in this trial relates to the inevitable death of some patients. Actively seeking out and informing relatives of trial participation is transparent and avoids potential distress were the family to discover at some future point that their relative had been involved in a clinical trial. However, informing the relatives/ friends of trial participation in the immediate aftermath of their relative/ friend's death will impose an additional emotional burden at a time of great distress. Previous and ongoing critical care trials have used passive information approaches, placing information in publicly accessible locations and in sites likely to be visited by relatives of the deceased (hospitals, GP surgeries, the offices of the Registrars of Births and Deaths). Such information contains brief details of the trial and contact details for those wishing to seek further information. This allows a relative to make an individual decision as to whether to seek further information regarding their relative/ friend, at a time of their choosing. This is the approach that we will take with the ABBRUPT trial and a REC approved poster will be placed in appropriate locations of participating sites.

Whilst every effort should be made to obtain consent as soon as possible following randomisation, there remains a risk that a patient may die prior to consent being obtained. In this instance, only a minimal, pseudoanonymised (trial number and age) dataset comprising of variables captured as part of standard of care will be transferred to BCTU. A Change of Status Form will also be completed for these patients.

## 5.4 Patients transferred to non-ABBRUPT sites during follow-up

There may be some situations where patients recruited to the ABBRUPT Trial have to be transferred to other hospitals. In these circumstances, with the patient's and/or legal representative's consent, the CI, ABBRUPT Trial Office and/or the research team at site shall engage with the non-ABBRUPT site to request a minimal dataset for the patient. The dataset requested will comprise both patient safety and compliance data.

# 6 ENROLMENT, RANDOMISATION AND BLINDING

## 6.1 Identification

Patients with NOAF will be identified by their existing clinical care team. As this may occur at any time of the day or night, sites should make efforts to ensure that a system exists whereby patients may be recruited and randomised at any time of the day and any day of the week. The local research team at site should be made aware of the randomisation at the first opportunity.

## 6.2 Screening and enrolment

Details of all patients approached about the trial will be recorded in REDCap ANNEX.

Prior to randomisation, a **medically qualified doctor or ACCP**, the name of whom will be captured on the Randomisation Form, **must** confirm eligibility.

## 6.3 Randomisation

Randomisation will be provided by BCTU using a secure online system thereby ensuring allocation concealment. Unique login usernames will be provided to those who wish to use the online system and who have been delegated the role of randomising patients into the trial as detailed on the ABBRUPT Trial Site Signature and Delegation Log. These unique login details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. Clinical team members who have been provided with the link to eligibility and randomisation training by the PI, will have a site-specific link provided to them on completion of the training to access the online randomisation system. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. In the event of the online system not being available, a back-up telephone toll-free randomisation service (0800 953 0274) is available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

## 6.4 Randomisation process

After eligibility for randomisation has been confirmed, the patient can be randomised into the trial using the online system. All questions and data items on the online Randomisation Form must be answered prior to a patient being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the PI and other delegates.

The site should add the patient to the ABBRUPT Patient Recruitment and Identification Log which links patients with their Trial Number. PIs must maintain this document securely and it must not be submitted to the ABBRUPT Trial Office. The ABBRUPT Patient Recruitment and Identification Log should be held in strict confidence.

## 6.5 Randomisation method

Patients will be randomised at the level of the individual in a 1:1 ratio to either Amiodarone or Beta-Blockade. A minimisation algorithm will be used within the randomisation system to ensure balance in the intervention allocations over the following variables:

- Hospital
- Age (≤ 60 years, >60 -<80, ≥ 80 years)

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

## 6.6 Blinding

This an open label trial with no blinding of the treatment allocation. Blinding is not possible as within the intervention arms, the choice of dose (and in the case of beta-blockade, the type) rests with the site.

## 6.7 Informing the patient's GP

With the patient's/their legal representative's permission, the patient's GP should be notified that they are participating in the ABBRUPT trial, using the ABBRUPT trial GP Letter.

# 7 TRIAL INTERVENTION

## 7.1 Trial interventions and dosing schedule

Patients will be randomised to either the intervention group (amiodarone) or the control group (beta-blockade). For the purposes of the trial, amiodarone and beta-blockers are defined as Investigational Medicinal Products (IMPs)

For those patients randomised to the intervention group, amiodarone will be prescribed according to the local treatment pathway and practice for AF. The treating clinician choosing the route of administration, dose and duration in accordance with local practice.

For those patients randomised to the control group, clinicians will prescribe the beta-blocker which aligns with their local treatment pathway and practice for AF. The beta-blocker choice should reflect local availability and familiarity. They may be administered enterally or intravenously; dosing should be according to local practice.

Patients will be treated with the allocated intervention until sinus rhythm has been maintained for 24 hours. Clinicians should then consider stopping the intervention according to local practice.

Compliance for ICU patients will be assessed from the observation and medication charts. The dosage of the intervention (amiodarone or beta-blocker) will be recorded up until Day-7 on the corresponding case report form (CRF).

## 7.2 Drug interaction or contraindications

As with all medications, there are common side effects with both beta-blockers and amiodarone. These are provided below:

Beta-blockers:

- Dizziness
- Headache
- Bradycardia
- Fatigue
- Gastrointestinal disorders

Amiodarone:

- Hypothyroidism
- Bradycardia
- Sleep disorders
- Eczema
- Decrease in blood pressure

Amiodarone has a long half-life; meaning there is potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped.

## 7.3 Concomitant medication(s) / intervention(s)

Amiodarone can prolong the QT interval and therefore treatment with other drugs capable of prolonging the QT interval should be used with caution.

Antihypertensive agents should be used with caution in patients treated with beta blockade.

Clinicians should bear in mind that catecholamine-depleting agents or anti-sympathomimetic agents (e.g. clonidine, dexmedetomidine, reserpine) may have an additive effect when concomitantly administered with beta blockade with marked hypotension and bradycardia.

Rescue medication for refractory AF that requires treatment is at the discretion of the treating physician. Any treatment given should be recorded on the drug log within the follow up CRFs.

The addition of calcium-channel blockers to beta blockers is permitted as long as the patient is on ICU and monitored for cardiodepression.

## 7.4 Prohibited medication(s) / intervention(s)

Both interventional treatments should be avoided in severe conduction disturbances (unless pacemaker fitted); in sinus node disease (unless pacemaker fitted); sino-atrial heart block (except in cardiac arrest); sinus bradycardia (except in cardiac arrest), atrio-ventricular blocks grade II or III, torsade de points.

Amiodarone should be avoided in iodine sensitivity and thyroid dysfunction.

Concomitant administration of beta blockade with verapamil or diltiazem is not recommended in patients with atrioventricular conduction abnormalities.

## 7.5 Intervention modification or discontinuation

Local Clinicians should monitor the patients and modify dosing or discontinue treatment should adverse effects become apparent. In particular, patients in both arms should be monitored for bronchospasm, bradycardia and higher degree heart block. Amiodarone may prolong the QT interval.

If an alternative treatment to the randomised intervention is commenced as part of standard of care, the participant will no longer be on the trial drug and will be followed up as Intention to Treat (ITT). This information will be captured on the subsequent CRFs.

## 7.6 Continuation of intervention after the trial

It is anticipated that patients will be treated until sinus rhythm has been maintained for 24 hours. Clinicians should then consider stopping the intervention according to local practice.

Patients who do not revert to sinus rhythm should be treated according to local practice. Patients who remain in AF at the end of their ICU stay should be managed according to local practice.

It is expected that both the intervention and control arm will be stopped upon discharge from the ICU unless there is a clinical indication for continuing them.

## 7.7 Intervention supply and storage

### 7.7.1 Intervention supplies

Local pharmacies will use the standard preparations from their normal supply chain.

### 7.7.2 Packaging and labelling

Through the risk-adapted approach, a full risk assessment of the ABBRUPT trial has been conducted including the drug accountability requirements. Drugs will be used within their authorisation, and dispensed according to site's local practices from standard stock. The risk assessment has determined that an additional clinical trial label is not necessary (as covered by Regulation 46 (2) of SI 2004/1031).

### 7.7.3 Drug storage

The drugs in both arms of the trial will be used as per standard clinical practice, therefore there is no additional requirement, above that of local policy, to monitor temperature during storage. Drugs that have expired or are returned as excess drug should be destroyed in accordance with local practice.

### 7.7.4 Accountability

Drug accountability will be according to standard operating procedures and local policy guidelines at each participating NHS Trust.

Adherence in both trial arms will be documented on the Follow-Up CRFs using information available in the patient's medical notes.

# 8 OUTCOME MEASURES

## 8.1 Pilot Outcomes

- 250 patients recruited from at least 15 sites
- Alternative treatment to randomised arm of <5%
- Drop-out rate of <5%
- ≥90% data completeness of the primary outcome

## 8.2 Main trial outcomes

### Primary outcome

- 90-day mortality

### Secondary outcomes

#### Clinical Outcomes

- ICU and hospital mortality
- Rates of Cardiovascular events including stroke, myocardial infarction or thromboembolism at 90-days
- Rate of established AF by the end of ICU stay / death/ day 90

#### Economic Outcomes

- Cost-effectiveness of the interventions
- Health care resource use including ICU and hospital length of stay

#### Safety Outcomes

- The number episodes of bradycardia (HR <50 bpm) whilst in hospital and being prescribed the intervention
- Bradycardia and bradycardic arrhythmias with haemodynamic compromise requiring intervention
- Significant hypotension requiring intervention (not including temporarily stopping the trial medication) whilst in ICU
- Heart block
- Arrhythmia with haemodynamic compromise requiring intervention including DC cardioversion

# 9 TRIAL PROCEDURES

All data will be recorded in the CRFs.

The Visits will be at Baseline (D0), Day 1 (D1), Day 2 (D2), Day 3 (D3), Day 7 (D7), ICU discharge, Hospital Discharge, Day 60 (D60) (+/- 14 days) and Day 90 (D90) (+/- 14 days).

Adverse events should be recorded as soon as the Local Research Team become aware of them. Please see Section 11 **ADVERSE EVENT REPORTING** for further details.

Day 0 (D0)

- Demographics Data:
- Sex, age, height, weight, APACHE score, summary of the relevant medical history, date of admission to hospital and ICU should be recorded at randomisation
- Treatment Allocation:
- Treatment Arm
- Randomisation date and time
- Time and date of first AF will be recorded. The diagnosis of AF should be confirmed by a competent clinician.
- Components in order to calculate the SOFA score
- Clinical Data – Data for the 24 hours prior to randomisation should be recorded. This can be collected from the clinical records and may be collected retrospectively.
- *Cardiovascular*: time and date of onset of AF and HR, Mean Arterial Pressure (MAP), Inotrope and Vaospressor type and dose every 6 hours.
- *Biochemistry*: Sodium, Potassium, Urea, Creatinine, Magnesium and C-Reactive Protein (CRP).
- *Haematology:* White Cell Count, Lymphocyte, Monocyte, Neutrophil and Platelet count and the haemoglobin.

Day 1 (D1), Day 2 (D2), Day 3 (D3), and Day 7 (D7)

- Clinical Data – This can be collected from the clinical record and may be collected retrospectively
- *Cardiovascular*: time and date of onset of AF and HR, Mean Arterial Pressure (MAP), Inotrope and Vaospressor type and dose every 6 hours.
- *Biochemistry*: Sodium, Potassium, Urea, Creatinine, Magnesium and C-Reactive Protein (CRP).
- *Haematology:* White Cell Count, Lymphocyte, Monocyte, Neutrophil and Platelet count and the haemoglobin.
- Expected Serious Adverse Events:
- Death related to the underlying cause of ICU admission
- Cardiovascular failure, including the need for vasopressors/ inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic impairment as measured by Bilirubin rise of >100 µmol/L or Transaminases >1000 IU/L
- Acute Kidney Injury, including the need for renal replacement therapy
- Haematological / coagulation failure, including thrombocytopaenia and Disseminated Intravascular Coagulopathy (DIC)
- Delirium / confusion

Discharge From ICU

- Date of discharge from ICU
- Mortality status
- **Medication groups listed on CRF Drug Log** should be recorded especially those for risk reduction of stroke (such as anti-coagulation with Apixaban or Rivaroxaban or Warfarin or other) and the ongoing treatment with either of the study drugs. The INR should be recorded if known and if the patient is having their warfarin status monitored. All medication associated with Myocardial events should also be noted.
- Components in order to calculate the SOFA score
- AF resolution

Discharge from Hospital

- Date of hospital discharge
- Mortality status
- **All medications** should be recorded especially those for risk reduction of stroke (such as anti-coagulation with Apixaban or Rivaroxaban or Warfarin or other) and the ongoing treatment with either of the study drugs. The INR should be recorded if known and if the patient is having their warfarin status monitored. All medication associated with Myocardial events should also be noted.
- EQ-5D-5L
- AF resolution

Day 60 (D60) and Day 90 (D90) - Visit can be performed remotely.

- Mortality status
- **All medications** should be recorded especially those for risk reduction of stroke (such as anti-coagulation with Apixaban or Rivaroxaban or Warfarin or other) and the ongoing treatment with either of the study drugs. The INR should be recorded if known and if the patient is having their warfarin status monitored. All medication associated with Myocardial events should also be noted.
- All new contacts with health services including hospital admissions
- New Stroke, TIA, Myocardial or Thromboembolic (PE / DVT) events
- EQ-5D-5L
- Expected Serious Adverse Events:
- Death related to the underlying cause of ICU admission
- Cardiovascular failure, including the need for vasopressors/ inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic impairment as measured by Bilirubin rise of >100 µmol/L or Transaminases >1000 IU/L
- Acute Kidney Injury, including the need for renal replacement therapy
- Haematological / coagulation failure, including thrombocytopaenia and Disseminated Intravascular Coagulopathy (DIC)
- Delirium / confusion
- AF resolution

## 9.1 Schedule of assessments

**Table 1 - Schedule of Assessments**

| Procedure | Baseline (Day 0) | Day 1 | Day 2 | Day 3 | Day7 | ICU Discharge | Hospital Discharge | Day 60 (in hospital if necessary) (± 14 days) | Day 90 (± 14 Days) |
|---|---|---|---|---|---|---|---|---|---|
| Eligibility assessment | • | | | | | | | | |
| Consent | | | | • | | | | | |
| Randomisation | • | | | | | | | | |
| Prescription of IMP by clinical team | • | | | | | | | | |
| Demographics (medical records) | • | | | | | | | | |
| Medical history (medical records) | • | | | | | | | | |
| Cardiovascular | • | • | • | • | • | | | | |
| Biochemistry | • | • | • | • | • | | | | |
| AF resolution | • | • | • | • | • | • | • | | |
| Expected Serious Adverse Events and Serious Adverse Events | | • | • | • | • | • | • | • | • |
| Mortality and morbidity | | • | • | • | • | • | • | • | • |
| Medications | • | • | • | • | • | • | • | • | • |
| Quality of life questionnaires (EQ-5D-5L) | | | | | | | • | • | • |

# 10 WITHDRAWAL AND CHANGES IN LEVELS OF PARTICIPATION

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and patients should be asked about their ongoing willingness to continue participation at all visits. Patients should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time. A patient may wish to cease to participate in a *particular* aspect of the trial.

Patients found to be ineligible post-randomisation (i.e. they were eligible at the point of randomisation but became ineligible over the course of the trial) should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation.

The changes in levels of participation within the trial are categorised in the following ways:

**No trial intervention:** The patient would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments (i.e., the patient has agreed that data can be collected and used in the trial analysis).

**No trial related follow-up:** The patient does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits (i.e., the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis).

**No further data collection:** The patient is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason and category of status change) should be clearly documented in the source documents.

The Legal Representative and/or Researcher are also able to withdraw the patient for the above reasons.

# 11 ADVERSE EVENT REPORTING

## 11.1 Definitions

**Table 2 – Adverse event reporting definitions**

| | | |
|---|---|---|
| Severity Definitions | Mild | Awareness of signs or symptoms that do not interfere with the patient's usual activity or are transient and resolved without treatment and with no sequelae. |
| | Moderate | A sign or symptom, which interferes with the patient's usual activity. |
| | Severe | Incapacity with inability to do work or perform usual activities. |
| Adverse Event | AE | Any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this intervention.<br>*An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.* |
| Adverse Reaction | AR | All untoward and unintended responses to an IMP related to any dose administered.<br>*An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.* |
| Serious Adverse Event | SAE | Any untoward medical occurrence or effect that:<br>Results in death<br>Is life-threatening*<br>Requires hospitalisation or prolongation of existing hospitalisation<br>Results in persistent or significant disability or incapacity<br>Is a congenital anomaly/birth defect<br>Or is otherwise considered medically significant by the Investigator** |
| Serious Adverse Reaction | SAR | An AR which also meets the definition of a SAE. |

| | | |
|---|---|---|
| Unexpected Adverse Reaction | UAR | An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).<br>When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected. |
| Suspected Unexpected Serious Adverse Reaction | SUSAR | A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information.<br>A SUSAR should meet the definition of an AR, UAR and SAR. |

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.

### 11.2 Adverse event recording – general

The recording and reporting of adverse events (AEs) will be in accordance with the Principles of Good Clinical Practice (GCP) as set out in the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in **Table** 2 **– Adverse event reporting definitions** in Section 0.

It is routine practice to record AEs in the patient's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

### 11.3 Adverse event reporting in ABBRUPT

The patients randomised into the ABBRUPT trial are likely to have significant co-morbidities and therefore the frequency of AEs is expected to be high. Most of the AEs occurring in ABBRUPT, whether serious or not, will therefore be anticipated in the sense that they are recognised and accepted complications/consequences of critical illness.

Sites therefore will only report AEs that meet the definition of 'serious', details of which are outlined in Section 11.4.

The reporting period for AEs in the ABBRUPT trial will be from the day of randomisation for 90 days.

### 11.4 Serious Adverse Advents (SAE) reporting in ABBRUPT

For all SAEs, the PI or delegate must do one of the following:

- **Record safety reporting-exempt SAEs in the medical notes** but not report them to the ABBRUPT Trials Office as per Section 11.5 11.5 Serious Adverse Events not requiring reporting to the ABBRUPT Trial Office.

- **Report SAEs to the ABBRUPT Trial Office in a non-expedited manner**. This can only be done for the pre-defined subset of SAEs as per Section 11.6 11.6 Serious Adverse Events requiring non-expedited reporting to the ABBRUPT Trial Office.
- **Report SAEs to the ABBRUPT Trial Office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above 2 categories must be reported as per Section 11.7 11.8 SAE Reporting process.

**Note**: when a SAE occurs at the same hospital at which the patient is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

### 11.5 Serious Adverse Events not requiring reporting to the ABBRUPT Trial Office

Participation in the trial will be for 90 days following randomisation. At whatever time they occur during the patient's participation, from the time the intervention started to the end of patient follow-up, the following are not considered to be critical to the evaluation of the safety of the trial:

- Known complications of the underlying cause of the patient's ICU admission (not including death; please refer to section 11.6).
- Pre-planned hospitalisation(s) following patient discharge

All events which meet the definition of serious must be recorded in the patient's notes, including the causality and severity, throughout the patient's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are 'safety reporting exempt'.

### 11.6 Serious Adverse Events requiring non-expedited reporting to the ABBRUPT Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the patient's underlying condition), and the SAE, may be known. That is, such events are protocol-defined as 'expected' (see Section 11.10 **11.11 Assessment of expectedness of an SAE by the** CI**)**.

Such events should still be recorded by the trial team in the patient's notes and reported to the ABBRUPT Trial Office on the appropriate follow-up CRF but it does not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified events has been pre-defined. These include:

- Death related to the underlying cause of ICU admission
- Cardiovascular failure, including the need for vasopressors/ inotropes
- Respiratory failure, including mechanical ventilation and acute lung injury
- Hepatic impairment as measured by Bilirubin rise of >100 µmol/L or Transaminases >1000 IU/L
- Acute Kidney Injury, including the need for renal replacement therapy
- Haematological / coagulation failure, including thrombocytopaenia and Disseminated Intravascular Coagulopathy (DIC)
- Delirium
- Sepsis ( as defined by The Third International Consensus Definitions for Sepsis and Septic Shock)

## 11.7 Serious Adverse Events requiring expedited reporting to the ABBRUPT Trial Office

All SAEs not listed in Sections 11.5 and 11.6 must be reported to the ABBRUPT Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

## 11.8 SAE Reporting process

On becoming aware that a patient has experienced a SAE the PI or delegate should report the SAE to their own Trust in accordance with local practice.

To report a SAE to the ABBRUPT Trial Office, the PI or delegate must complete, date and sign the trial specific CRF. The completed form together with any other relevant, appropriately anonymised, data should be submitted to the ABBRUPT Trial Office using the information below in accordance with the timelines given in Section 11.6 and 11.7.

**To report an expedited SAE, submit the SAE Form to:**

**ABBRUPT@trials.bham.ac.uk**

Where a SAE Form has been completed by someone other than the PI (or medically trained delegate who has been assigned "SAE causality and severity assessment" on the site delegation log) initially, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

On receipt of a SAE form, the ABBRUPT Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the ABBRUPT Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE are filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the ABBRUPT Trial Office.

## 11.9 Provision of SAE follow-up information

Following reporting of a SAE for a patient, they should be followed up until resolution or stabilisation of the event. Follow-up information for expedited SAEs should be provided using the SAE reference number provided by the ABBRUPT Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the ABBRUPT Trial Office and the original kept in the ISF.

**Follow up information for non-expedited SAEs is not expected.**

## 11.10 Assessment of causality of a SAE

When completing the SAE Form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see **Table** 3 **– Categories of causality** ) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE Form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table** 3 **– Categories of causality** , all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events

considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trials office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

**Table 3 – Categories of causality**

| Category | Definition | Causality |
|---|---|---|
| Definitely | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. | Related |
| Probably | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. | |
| Possibly | There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant events or medication) | |
| Unlikely | There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant events or medication). | Unrelated |
| Not related | There is no evidence of any causal relationship. | |

On receipt of a SAE Form, the ABBRUPT Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently* review the causality of the SAE. A SAE judged by the PI or CI or delegate to have a reasonable causal relationship ("Related" as per **Table 3 – Categories of causality** ) with the intervention will be regarded as a Serious Adverse Reaction (SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI, an independent clinical causality review will be performed.

### 11.11 Assessment of expectedness of an SAE by the CI

The CI or delegate will also assess all related SAEs for expectedness with reference to the criteria in

**Table** 4 **– Categories of expectedness** .

**Table 4 – Categories of expectedness**

| Category | Definition |
|---|---|
| Expected | An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the Summary of Products Characteristics (SmPC) Section 4.8. Clinicians are directed to the SmPCs for the drug used and should note adverse events requested in the Schedule of Assessments section 9.1. For the purposes of this trial, the Reference Safety Information (RSI) will be prepared and annually reviewed on the anniversary of the Development Safety Update Report (DSUR) by the ABBRUPT trials team. Sites will be informed and sent the latest version of any updated SmPCs for the duration of the trial. |
| Unexpected | An adverse event that is not consistent with known information about the trial related procedures. |

If the event is unexpected (i.e., it is not defined in the approved version of the RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

### 11.12 Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The ABBRUPT Trial Office will report details of all SARs (including SUSARs) to the MHRA, REC, and University of Birmingham (UoB) Research Governance Team (RGT) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

Additionally, the ABBRUPT Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA, REC, and RGT within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days of being notified.

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

### 11.13 Urgent Safety Measures

If any urgent safety measures are taken, the ABBRUPT Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken.

### 11.14 Follow-up of pregnancy outcomes for potential SAEs

Known pregnancy is an exclusion criterion as there is a risk of congenital anomalies or birth defects in the offspring of patients as a result of their participation in the trial. Pregnancy in this patient population is unlikely as women of child-bearing age (WCBA) have a much lower risk of AF whilst in the ICU. However, WCBA are tested for pregnancy as part of routine care upon admission to ICU and those found to be pregnant will be considered ineligible.

In the unlikely event that a pregnant patient is randomised into the trial or becomes pregnant during the follow up period, this will need to be reported using the trial-specific Pregnancy Notification Form. This form will capture the pregnancy outcomes. Where the following outcomes are reported, they will also be defined as a SAE and should be reported to the ABBRUPT Trial Office according to the process described in Section 11.8:

- Induced abortion (medical reason)
- Miscarriage
- Stillbirth
- Birth defects
- Neonatal unit admission
- Neonatal death

# 12 DATA HANDLING AND RECORD KEEPING

## 12.1 Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of patients, source data will be accessible and maintained.

Some data variables may be entered directly onto the CRF these are clearly identified and detailed below in Table **5** – Source data in **ABBRUPT .**

Source data is kept as part of the patients' medical records generated and maintained at site.

**Table 5 – Source data in ABBRUPT**

| Data | Source |
|---|---|
| Laboratory results | The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs. |
| Blood pressure | The routine clinic blood pressures at various time points will be available from the medical notes/electronic patient record system, which will be kept and maintained in line with normal local practice. The medical notes/electronic patient record system is the source and will be transcribed onto CRFs. |
| Imaging | The source is the original imaging usually as an electronic file. Data may be supplied to the ABBRUPT Trials Office as a password-protected, anonymised, copy of the electronic file, or as an interpretation of the imaging provided on a CRF. Where data is interpreted, the CRF onto which it is transcribed becomes the source. Copy of the CRF should be provided to the trial office. |
| Clinical event data | The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the patient, either in or out of clinic (e.g., phone calls), must be documented in the source documents. |
| Health economics data | Often obtained by interview directly with the patient for transcription onto the CRF. The CRF is source data. |
| Recruitment | The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system. |
| Withdrawal | Where a patient expresses a wish to withdraw, the conversation must be recorded in the source documents. |

## 12.2 Case Report Form (CRF) completion

The CRFs will include (but will NOT be limited to) the following Forms (see Table **6** – Case Report forms in **ABBRUPT** ABBRUPT).

**Table 6 – Case Report forms in ABBRUPT**

| Form Name | Schedule for submission |
|---|---|
| Consent | Within 72 hours of randomisation |
| Randomisation CRF | At the point of randomisation |
| Baseline and Follow-up CRFs including EQ-5D-5L | As soon as possible after each follow-up assessment time point<br>Where CRFs are used to report non-expedited SAEs, they must be submitted within a timely manner on the respective follow-up CRF. |
| Serious Adverse Event Form | If expedited: emailed within 24 hours of site research team becoming aware of event |
| Pregnancy Notification Form | As soon as possible after becoming aware of patient's pregnancy |
| Change of Status Form | As soon as possible after the point of reduced participation or death |

A CRF should be completed for each individual patient.

In all cases, it remains the responsibility of the PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI, or delegate(s). The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The delegated staff completing the CRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by signing and dating the CRF.

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried.

The following guidance applies to data and partial data:

- Only CRFs provided by the ABBRUPT Trial Office should be used.
- Where forms are completed on paper (SAE, Pregnancy Notification), true copies should be sent to the ABBRUPT Trial Office with originals filed in the ISF.
- Entries should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the **24-hour clock**
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible

- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the ABBRUPT Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the ABBRUPT Trial Office on discovery.

## 12.3 Patient completed questionnaires

The EQ5D-5L will be completed at hospital discharge, 60 days and 90-days.

Patients will be asked to complete the questionnaire with staff whilst in the hospital or over the telephone. The questionnaire should generally be completed by the patient alone but physical assistance in completing the form can be given by the research staff where appropriate. In such circumstances, questions are to be read to the patient verbatim and responses must not be led by research staff. EQ-5D-5L data will not be collected at baseline as it will not be possible for this patient population to complete the questionnaire on admission to hospital. Methods to account for this are outlined in section 17.

## 12.4 Data management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry and data queries of trial data.

Data entry will be completed by the sites via a bespoke BCTU trial database. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using Data Clarification Forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site within 2 weeks of receipt. Overdue data entry and data queries will be requested on a fortnightly basis.

## 12.5 Self-evident corrections

No self-evident corrections will be permitted within the ABBRUPT trial.

## 12.6 Data security

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). BCTU has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

**Physical security measures:** restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fireproof safe.

**Logical measures for access control and privilege management:** including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

**Network security measures:** including site firewalls, antivirus software and separate secure network protected hosting.

**System management:** the system will be developed by the Programming Team at BCTU, and will be implemented and maintained by the Programming Team.

**System design:** the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

**Operational processes:** the data will be processed and stored within BCTU.

**System audit:** The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

**Data Protection Registration:** UoB's Data Protection Registration number is Z6195856.

## 12.7 Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored securely and confidentially for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

# 13 QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the ABBRUPT Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

ABBRUPT is a trial comprising an emergency intervention and there is a need therefore to mitigate delays in delivering treatment. It is recognised that a critically ill, potentially eligible patient may present in ICU at any time of the day and that there are frequent staff changes within the department. Whilst it is essential that this trial is managed according to The Medicines for Human Use (Clinical Trials) Regulations 2004, it is not practical for all staff involved in delivery of the trial to have full GCP training. It is expected that the PI, associate PI (if applicable), lead Research Nurse/ Facilitator and Pharmacist at site are fully GCP trained and a copy of their up-to-date GCP certificate is required by the ABBRUPT Trial Office. However, through a risk-adapted approach, we have determined that it is appropriate for some site staff, with delegated trial duties, to receive 'targeted GCP training' which will be delivered as part of the overall ABBRUPT trial training package, provided this aligns with the site's policies and procedures. The ABBRUPT Trial Training Log must be completed and sent to the ABBRUPT Trial Office before undertaking any delegated duties. Table 7 outlines the trial related roles an ABBRUPT researcher can perform with 'targeted GCP training'.

**Table 7 - Permitted trial roles to be performed by ABBRUPT trial research members with Targeted GCP Training**

| **Role/ process** | **Minimum training required** |
|---|---|
| Medically qualified doctor/Advanced Critical Care Practitioner (or equivalent) confirming eligibility | ABBRUPT Trial Training<br>Targeted GCP training |
| Randomisation | ABBRUPT Trial Training<br>Targeted GCP training |
| CRF completion | ABBRUPT Trial Training<br>Targeted GCP training |
| Safety reporting | ABBRUPT Trial Training<br>Targeted GCP training |

In all instances, it remains necessary for the PI to delegate roles and responsibilities to the trial team at site and these should be documented using the ABBRUPT Delegation of Duties Log. Furthermore,

the above does not remove the need for the PI to have oversight of, and sign documentation off as required by the ABBRUPT Trial Protocol.

### 13.2 Out of hours eligibility and randomisation pathway for non-research clinical team members

Due to the pathophysiology of NOAF it can occur at any time during ICU admittance. Therefore, to align the trial with standard of care, members of the clinical team who do not participate in research, but would normally treat a patient with NOAF, for example, a medically trained individual or ACCP, might be required to confirm eligibility and subsequently randomise a patient to ABBRUPT.

To undertake these tasks, a bespoke online eligibility and randomisation training package must be completed, where upon completion a site-specific link will be provided via email to the randomisation system. When the patient is randomised, the PI and ABBRUPT trial team will receive confirmation of the randomisation to maintain oversite and ensure eligibility is being confirmed by a medically trained individual or ACCP.

### 13.3 Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

### 13.4 On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the ABBRUPT Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the ABBRUPT trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

### 13.5 Central monitoring

The ABBRUPT Trial Office will check received ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

### 13.6 Audit and inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The investigator will comply with these visits and any required follow-up. Sites are also requested to notify the ABBRUPT Trial Office of any relevant inspections or local audits.

## 14 NOTIFICATION OF SERIOUS BREACHES

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial, within 7 days of becoming aware of that breach. For the purposes of this regulation, a “serious breach” is defined a breach which is likely to affect the:

- Safety or physical or mental integrity of the patients of the trial;

- Scientific value of the trial

Sites are therefore requested to notify the ABBRUPT Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the ABBRUPT Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the ABBRUPT Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

# 15 END OF TRIAL DEFINITION

The end of trial will be 6 months after the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC, MHRA and the Sponsor within 90-days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA REC within 15 days of the end of trial. The Trial Office will provide the REC, MHRA and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

# 16 STATISTICAL CONSIDERATIONS

## 16.1 Sample size

Sample size calculation is based on a time-to-event superiority analysis. Literature (8) suggests that 90-day mortality in patients with NOAF was approximately 20%. A 5% absolute difference in mortality is considered a 'meaningful clinically important difference [MCID]' which equates to a hazard ratio of approximately 0.73. Using 90% power and a 2-sided alpha of 0.05 to detect a hazard ratio of 0.73 with event rate of 20% (or survival rate of 80%), a total of 426 events will be required. The enrolment of approximately 2430 patients would provide the required number of primary outcome events. Allowing for a 5% non-evaluable rate, a total of 2560 patients (1280 per group) will need to be recruited (rounded to nearest 10). We have allowed for a slightly higher non-evaluable rate as this study is recruiting critically ill patients undergoing an acute deterioration during their care.

## 16.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to Amiodarone versus those randomised to Beta blockade. All analyses will be based on the intention to treat principle, i.e., all patients will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. For all outcomes, appropriate summary statistics will be presented by group, (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). Intervention effects will be adjusted for the minimisation variables listed in Section 6.5 **ENROLMENT, RANDOMISATION and BLINDING** as fixed effects in the model (except site/hospital which will be included as a random effect). 95% confidence intervals and p-values will be presented for all outcomes. No adjustment for multiple comparisons will be made.

## 16.3 Primary outcome(s)

Differences in the primary outcome (90-day mortality) will be assessed by comparing time from randomisation to death from any cause between randomised groups, assessed up until the end of the follow-up period, where all patients will have a minimum of 90 days follow-up.

The primary outcome (90-day mortality) will be compared between treatment arms using survival analysis methods. Kaplan-Meier survival curves will be constructed for visual presentation of the data. A Cox proportional hazards model will be fitted to obtain an adjusted hazard ratio and corresponding 95% confidence interval with p-value.

## 16.4 Secondary outcomes

The secondary outcomes are a combination of time-to-event data, binary data, continuous data and count data.

**Time-to-event outcomes:** The secondary outcomes that are time-to-event data (e.g. ICU mortality and hospital mortality) will be analysed using the same methods as described for the primary outcome.

**Count data outcomes:** For secondary outcomes that are count data (e.g. Number of episodes of bradycardia (HR <50 bpm)), a Poisson regression model (or negative binomial mode if evidence of overdispersion) will be used for analysis. Time (in days) will be used as an offset in the model. Results will be presented as an adjusted incidence rate ratio with 95% confidence interval and p-value.

**Binary outcomes:** The secondary outcomes that are binary data (e.g. Rates of stroke and myocardial infarction) will be analysed using a Poisson regression model (with robust standard errors). Results will be presented as an adjusted relative risk with 95% confidence interval and p-value.

**Continuous outcomes:** The secondary outcomes that are continuous data (e.g. Hospital length of stay) will be analysed using a linear regression model. Results will be presented as an adjusted mean difference with 95% confidence interval and p-value.

## 16.5 Planned subgroup analyses

Subgroup analyses will be performed to the same variables used in the minimisation algorithm (except site/hospital) (see Section 6.5 – ENROLMENT, RANDOMISATION and BLINDING) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only. Any other subgroup analysis which are not part of the variables used in the minimisation algorithm will be defined ahead of database lock in the Statistical Analysis Plan.

## 16.6 Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study patients; it is thus anticipated that missing data will be minimal. Since the primary outcome is based on a time-to-event analysis, a sensitivity analysis to assess the impact of missing data will not be required since all patients will be included in the analysis and will be censored at the point where they have no further data.

There may be times when patients in both groups do not sufficiently adhere to their treatment, i.e. poor uptake of the drug, or may even be commenced on an alternative drug. To assess the impact of this, a per-protocol analysis for the primary outcome will be undertaken as a sensitivity analysis.

Full details will be included in the Statistical Analysis Plan.

### 16.7 Planned final analyses

The primary analysis for the trial will occur once all patients have completed the 90-day follow-up assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 90-day assessment and no further.

# 17 HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

### 17.1 Within-trial economic evaluation

The economic evaluation will compare the interventions from an NHS and Personal Social Services (PSS) perspective. A within-trial incremental cost-effectiveness (CEA) and cost-utility analysis (CUA) will be conducted at 90-day follow up to determine the cost per life year gained and cost per quality-adjusted life year (QALY) gained.

Resource use and costs: Health and social care resource use will be collected using study case report forms (using information from patient notes). Resource use will include intervention medication, number of days spent in hospital including length of stay in ICU, readmissions to hospital, including for acute clinical events such as stroke and MI. Resource use will be multiplied by unit costs obtained from standard (national) sources and healthcare providers.

Outcomes: The outcome measure for the cost-effectiveness analysis is survival at 90-days. For the cost-utility analysis, the EQ-5D-5L questionnaire will be administered to patients (or their carers) at hospital discharge, 60 and 90-days. EQ-5D-5L data will not be collected at baseline, as it will not be possible for this patient population to complete the questionnaire on admission to hospital. Therefore, we will use a previously published method and assume that the EQ-5D-5L score for all patients at baseline is zero, and the change in quality of life between baseline and hospital discharge is linear. Any patients who die within the 90-days will be assigned a utility of zero from date of death. The approach for estimating the baseline score will be explored in sensitivity analysis in two ways. Firstly, patients will be asked to provide their quality of life using the EQ-5D-5L at the 90-day data collection time point. Secondly, the utility value for unconscious will be assumed at baseline. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current National Institute for Health and Care Excellence (NICE) recommendations.

Analysis: As cost data is likely to have a skewed distribution (with high-cost outliers), a non-parametric comparison of means (using bootstrapping) will be undertaken. Where there are missing data on resource use or quality of life outcomes, multiple imputation techniques will be used to ensure that all trial patients are included in the final analysis. Adjustment for baseline covariates will focus on the same variables as outlined for the primary analysis. The robustness of the results will be explored using sensitivity analysis. Uncertainty will be explored through the use of cost-effectiveness acceptability curves (CEACs).

### 17.2 Model-based economic evaluation

A model-based CUA will extrapolate beyond the endpoint of the trial, taking into account the presence of AF long-term and related events such as stroke and MI. Markov decision modelling will extend the within-trial results beyond 90-days follow-up, utilising survival analysis methodology. The purpose of

the model is to extrapolate costs, outcomes and QALYs to calculate the long-term cost-utility with discounting of costs and outcomes at 3.5%. A scoping review of the literature on existing economic models in AF will be undertaken to inform the model structure, in consultation with the trial team. This will then allow a full description of the model structure and methods whilst the trial is ongoing. The Markov model health states will consider the presence of AF, and history of events (stroke, MI) that occurred within the 90-days. A further review will be undertaken to source parameter values, including those for natural history of AF, stroke and MI (e.g. mortality and recurrence of events), long-term health and social care resource use and costs, and utility values for different health states. The model will be subject to extensive deterministic sensitivity analysis by changing individual parameter values and changing model assumptions, and probabilistic sensitivity analysis to simultaneously incorporate all parameter uncertainty. Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented.

All reporting of the methods and results of the health economics analyses will be conducted in line with the recommendations in the CHEERS checklist (28).

# 18 TRIAL ORGANISATIONAL STRUCTURE

## 18.1 Sponsor

The Sponsor for this trial is the University of Birmingham (UoB).

## 18.2 Coordinating centre

The trial coordinating centre (ABBRUPT Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at UoB.

## 18.3 Trial Management Group

The Trial Management Group comprises individuals responsible for the day-to-day management of the trial: the CI, Co-CI, Statistician(s), Trials Management Team Leader, Trial Manager, Data Manager and Analyst Programmer. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard patients and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

## 18.4 Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress troubleshoot and plan strategically.

## 18.5 Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the ABBRUPT trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC). The TSC will operate in accordance with a trial specific TSC Charter.

### 18.6 Data Monitoring Committee

The role of the independent DMC is to monitor the trial data, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

### 18.7 Finance

The research costs of the trial are funded by the National Institute for Health and Care Research (NIHR), Health Technology Assessment (HTA) Programme (ref.: 150027) awarded to Prof Tony Whitehouse, and Prof Ingeborg Welters (Co-CI) with the University of Birmingham as the sponsoring institution. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events Cost Attribution Template (SOeCAT). These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

## 19 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004, and the Data Protection Act 2018.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any patients are randomised into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patient.

# 20 DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments).

For those patients where consent has been obtained, personal data categories that will be collected include patient's trial number, initials, age and sex. For those patients who die prior to consent being obtained only the following personal data categories will be collected and analysed: patient's trial number, age and sex.

Patients for whom we have received consent will only be identified by their unique trial identification number and initials on CRFs and on any correspondence with the ABBRUPT Trial Office. Where consent has not yet been obtained, patients will be identified by their unique identification number only. Patients will acknowledge the transfer and storage of their informed consent form to the ABBRUPT Trial Office. This will be used to perform central monitoring of the consent process.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the ABBRUPT Trial Office and sponsor may be required to have access to patients' medical records for quality assurance purposes, but patients should be reassured that their confidentiality will be respected at all times. The ABBRUPT Trial Office will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party.

# 21 FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

# 22 INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at UoB's discretion provide cover for non-negligent harm to patients.

With respect to the conduct of the trial at site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

UoB is independent of any pharmaceutical company and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

# 23 POST-TRIAL CARE

If there is a clinical indication for continuing treatment, the patient should be managed according to the discretion of the local clinical team and local practice.

# 24 ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated during this study will be considered by BCTU. Data will typically be available 6 months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

# 25 PUBLICATION PLAN

On completion of the trial, the data will be analysed, and a Final Study Report prepared. The final report will be published in a time defined by the contract between the Sponsor and the HTA. Outputs from this trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the writing group as defined in the trial publication plan. Manuscripts should be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review. The funder (HTA) will be acknowledged according to the HTA policy.

The results will be announced at an international meeting such as https://criticalcarereviews.com/ and placed on the trial website in both scientific and lay language.

The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) (29,30) guidelines. All publications and presentations relating to the study will be authorised by the Trial Management Group. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

In all publications, authors should acknowledge that the trial was performed with the support of the NIHR HTA Programme, UoB and BCTU. Intellectual property rights will be addressed in the Clinical Trial Agreement between sponsor and site.

We will work with the PPI Team to develop dissemination plans and materials in formats that are accessible to patients, communities and the wider public. We will organise a series of PPI meetings to report the trial and disseminate the results.

# 26 REFERENCE LIST

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257-354.

2. Wetterslev M, Haase N, Hassager C, Belley-Cote EP, McIntyre WF, An Y, et al. New-onset atrial fibrillation in adult critically ill patients: a scoping review. Intensive Care Medicine. 2019;45(7):928-38.

3. Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. J Intensive Care. 2015;3(1):19.

4. Kuipers S, Klein Klouwenberg PM, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: a systematic review. Crit Care. 2014;18(6):688.

5. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care. 2012;27(3):326.e1-8.

6 Bedford J, Drikite L, Corbett M, Doidge J, Ferrando-Vivas P, Johnson A, et al. Pharmacological and non-pharmacological treatments and outcomes for new-onset atrial fibrillation in ICU patients: the CAFE scoping review and database analyses. Health Technol Assess. 2021;25(71):1-174.

7. Qian J, Kuang L, Chen F, Liu X, Che L. Prognosis and management of new-onset atrial fibrillation in critically ill patients. BMC Cardiovascular Disorders. 2021;21(1):231.

8. Chean CS, McAuley D, Gordon A, Welters ID. Current practice in the management of new-onset atrial fibrillation in critically ill patients: a UK-wide survey. PeerJ. 2017;5:e3716.

9. Wetterslev M, Møller MH, Granholm A, Hassager C, Haase N, Aslam TN, et al. Management of acute atrial fibrillation in the intensive care unit: An international survey. Acta Anaesthesiologica Scandinavica. 2021;n/a(n/a).

10. Chen AY, Sokol SS, Kress JP, Lat I. New-onset atrial fibrillation is an independent predictor of mortality in medical intensive care unit patients. Ann Pharmacother. 2015;49(5):523-7.

11. Arrigo M, Ishihara S, Feliot E, Rudiger A, Deye N, Cariou A, et al. New-onset atrial fibrillation in critically ill patients and its association with mortality: A report from the FROG-ICU study. Int J Cardiol. 2018;266:95-9.

12. Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard GR, et al. Atrial Fibrillation Is an Independent Predictor of Mortality in Critically Ill Patients. Crit Care Med. 2015;43(10):2104-11.

13. Bedford JP, Ferrando-Vivas P, Redfern O, Rajappan K, Harrison DA, Watkinson PJ, et al. New-onset atrial fibrillation in intensive care: epidemiology and outcomes. European Heart Journal Acute Cardiovascular Care. 2022.

14. Kanjanahattakij N, Rattanawong P, Krishnamoorthy P, Horn B, Chongsathidkiet P, Garvia V, et al. New-onset atrial fibrillation is associated with increased mortality in critically ill patients: a systematic review and meta-analysis. Acta Cardiol. 2019;74(2):162-9.

15. Jacobs MS, Loef B, Reidinga AC, Postma MJ, Van Hulst M, Tieleman RG. Incidence, treatment and mortality of new-onset atrial fibrillation patients at the intensive care unit. Open Heart. 2020;7(1):e001226.

16. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. Crit Care. 2010;14(3):R108.

17. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. Jama. 2011;306(20):2248-54.

18. Walkey AJ, Hammill BG, Curtis LH, Benjamin EJ. Long-term outcomes following development of new-onset atrial fibrillation during sepsis. Chest. 2014;146(5):1187-95.

19. Lall R, Mistry D, Skilton E, Boota N, Regan S, Bion J, et al. Study into the reversal of septic shock with landiolol (beta blockade): STRESS-L Study protocol for a randomised trial. BMJ Open. 2021;11(2):e043194.

20. Hope AA, Munro CL. Understanding and Improving Critical Care Survivorship. Am J Crit Care. 2019;28(6):410-2.

21. Johnston BW, Chean CS, Duarte R, Hill R, Blackwood B, McAuley DF, et al. Management of new onset atrial fibrillation in critically unwell adult patients: a systematic review and narrative synthesis. Br J Anaesth. 2021.

22. Wilson BD, Clarkson CE, Lippmann ML. Amiodarone causes decreased cell-mediated immune responses and inhibits the phospholipase C signaling pathway. Lung. 1993;171(3):137-48.

23. Pemberton P, Veenith T, Snelson C, Whitehouse T. Is It Time to Beta Block the Septic Patient? Biomed Res Int. 2015;2015:424308.

24. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130(24):2246-64.

25. Bosch NA, Cimini J, Walkey AJ. Atrial Fibrillation in the ICU. CHEST. 2018;154(6):1424-34.

26. Advanced practice standards | Royal College of Nursing (rcn.org.uk)

27. Krige A, Pattison N, Booth M, Walsh T. Co-enrolment to intensive care studies – a UK perspective. JICS. 2013;14(2):103-6

28. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. BMJ.2022;376(e067975).

29. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. JAMA. 1996;276(8):637-9.

30. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. The Lancet. 2008;371(9609):281-3.

# 27 APPENDIX