CLINICAL TRIAL PROTOCOL

NOAH - AFNET 6

*N*on-vitamin K antagonist *O*ral anticoagulants in patients with *A*trial *H*igh rate episodes

An Investigator-driven, Prospective, Parallel-group, Randomised, Double-blind, Multi-centre Trial initiated by the European Society of Cardiology and AFNET

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This protocol has been written in accordance with current applicable guidelines (ICH-GCP and EU-Directive 2001/20/EC) as well as all other relevant additional references, medical and legal ones.

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1. Summary

TITLE	***N***on-vitamin K antagonist ***O***ral anticoagulants in patients with ***A***trial ***H***igh rate episodes (NOAH - AFNET 6)
INTERNATIONAL CHIEF INVESTIGATOR	Professor Paulus Kirchhof, Hamburg and Münster, Germany
SPONSOR	Kompetenznetz Vorhofflimmern e.V. (AFNET) [Atrial Fibrillation NETwork]
BACKGROUND AND RATIONALE	Atrial fibrillation (AF) is a common cause of stroke, especially ischemic stroke. So far, all available data that demonstrate a beneficial effect of oral anti-coagulation for stroke prevention have been collected in populations with AF documented by conventional ECG recordings. It is well established that a large proportion of AF episodes remain undiagnosed ("silent AF"), and many of these patients present with a stroke as the first clinical sign of AF. Earlier initiation of anticoagulation could prevent such events. Continuous monitoring of atrial rhythm by implanted devices could close this diagnostic gap. Pace-makers, defibrillators, cardiac resynchronisation devices, and insertable cardiac monitors already provide automated algorithms alerting to the occurrence of highly organised atrial tachyarrhythmia episodes, also called "subclinical atrial fibrillation" or, more commonly, "atrial high rate episodes" (AHRE). Data from large prospectively followed patient cohorts demonstrated that stroke rate is increased in patients with AHRE. A sizeable portion of these patients develops clinically detected AF over time. In these patients, AHRE can be considered as an early manifestation of paroxysmal AF. A few AHRE patients do not develop clinically overt AF, and the absolute stroke rates are lower in patients with AHRE when compared to stroke rates in patients with clinically diagnosed AF. In light of the bleeding complications associated with oral anticoagulant therapy, there is thus uncertainty about the optimal antithrombotic therapy in patients with AHRE. The Non-vitamin K antagonist Oral anticoagulants (NOACs) provide similar or slightly better stroke prevention, and appear slightly safer compared to vitamin K antagonists (VKAs). In addition, no individual therapy adjustment of NOACs has to be performed. Edoxaban, a newly introduced NOAC, at a dose regime of 60 mg once daily (OD) has a favourable profile compared to dose-adjusted VKA therapy: In the ENGAGE-TIMI 48 trial, edoxaban prevented strokes at least as effectively as VKA therapy but caused less major bleeding events than VKA therapy.
STUDY OBJECTIVE(S)	To demonstrate that oral anticoagulation with the NOAC edoxaban is superior to current therapy (antiplatelet therapy or no therapy depending on cardio-vascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE but without overt AF and at least two stroke risk factors leading to a modified CHA_2DS_2VASc score of 2 or more.
STUDY DESIGN	Investigator-initiated, prospective, parallel-group, randomised, double-blind, multi-centre trial. Although it can be argued that the indication tested is within the registered label of edoxaban, NOAH – AFNET 6 will be conducted as a phase IIIb study.
STUDY POPULATION Medical condition / Main selection criteria	The following main criteria must be present for eligibility into the study: ▪ Pacemaker, defibrillator or insertable cardiac monitor implanted for any reason with feature of detection of AHRE, implanted at least 2 months prior

	to randomisation ▪ AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration) documented by the implanted device ▪ Age ≥ 65 years ▪ In addition, **at least one** of the following cardiovascular conditions leading to a modified CHA_2DS_2VASc score of 2 or more: ✓ Age ≥ 75 years, ✓ heart failure (clinically overt or LVEF < 45%), ✓ arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mmHg), ✓ diabetes mellitus, ✓ prior stroke or transient ischemic attack (TIA), ✓ vascular disease (previous myocardial infarction, peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram [TEE]). Patients with history of overt AF or atrial flutter, patients with a clear contraindication for oral anticoagulation, patients with a clear need for oral anticoagulation, and patients with indication for long-term antiplatelet therapy other than acetylsalicylic acid (ASA) or a need for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy (DAPT) are not suitable for NOAH - AFNET 6.
Number of patients Expected number of sites	NOAH - AFNET 6 is an event-driven trial with a planned number of randomised and treated patients of n=2,538 and an anticipated number of primary endpoints of n=220. Patient recruitment is expected to be completed after 71 months. Approximately 200 to 250 sites in Europe with adequate experience in follow-up of implanted pacemakers, defibrillators or insertable cardiac monitors in clinical routine.
INVESTIGATIONAL INTERVENTIONS	Investigational medicinal product (IMP) being tested: edoxaban IMP used as a comparator: acetylsalicylic acid or placebo (depending on the indication for use of antiplatelet therapy) Edoxaban will be used in NOAH - AFNET 6 at the therapeutic dose approved for stroke prevention in non-valvular AF, i.e. 60 mg OD with a reduction of dose to 30 mg OD in patients with one of the following characteristics: ✓ Impaired renal function (CrCl 15-50 ml/min), or ✓ low body weight (≤60 kg), or ✓ patients receiving the p-glycoprotein inhibitors cyclosporin, dronedarone, erythromycin, or ketoconazole.
PRIMARY OUTCOME PARAMETERS	Time from randomisation to the first occurrence of stroke, systemic embolism, or cardiovascular death. A detailed definition of these outcome events is provided in Appendix III.
SECONDARY OUTCOME	▪ Components of the primary outcome ▪ Major Adverse Cardiac Events (MACEs: cardiovascular death, myocardial

PARAMETERS	infarction, acute coronary syndrome (ACS), PCI, CABG) ▪ Stroke or systemic arterial embolism ▪ All-cause death ▪ Major bleeding events according to the ISTH definitions ▪ Quality of life changes at 12 and 24 months compared to baseline ▪ Patient satisfaction at 12 and 24 months compared to baseline ▪ Cost effectiveness and health resource utilisation ▪ Patient autonomy changes at 12 and 24 months compared to baseline including chronic consequences of stroke (aphasia, hemianopia (“mild stroke”)) ▪ Cognitive function at 12 and 24 months compared to baseline
ASSESSMENT SCHEDULE	1. Enrolment and randomisation 2. Scheduled clinical follow-up at months 12, 24 and 36 after randomisation 3. “Drug/device visits” for dispensing of study drug and upload of device interrogations derived from the implanted device at months 6, 18, and 30 (continued in 6 months intervals after 36-months visit, if necessary) 4. Final end of study visit after the required number of primary outcome events has been accrued and verified
STATISTICAL CONSIDERATIONS	The main aim of the proposed study is to test the null hypothesis that the hazard rate, which is assumed to be constant during the study period, is identical in the two groups (usual care and NOAC). Based on the stroke and death rates of published trials (MOST, ASSERT, Medtronic AT500 data set, SOS), an annualised rate of stroke, systemic embolism, or cardiovascular death of 5.3% in the control group is expected. The primary analysis is in the modified intention-to-treat population, consisting of all randomised patients with a qualifying AHRE and intake of at least one dose of study drug. Patients who develop overt AF during the trial period will be censored at that point in time but followed according to protocol until the global end of the trial. All other patients who will not reach the endpoint by the end of the study will be censored at that time point. Cumulative incidence curves and corresponding p-values from competing risk analysis as well as tables with estimated (cause-specific) hazard ratios, confidence intervals, and corresponding p-values will be provided. The Cox-proportional hazards model will be used to estimate the (cause-specific) hazard ratio of edoxaban versus usual care. Safety analysis will be performed with all patients enrolled.
DURATION OF STUDY PERIOD	Duration per patient: Mean expected follow-up time of 42 months with a minimum follow-up time of 12 months and an expected maximum follow-up time of presumably 83 months. Every patient will be followed-up until global end of study. The exact duration of follow-up will be determined by the accrual of events (event-driven trial). The trial will be terminated after 220 evaluable primary outcomes have occurred. The total study duration of 90 months (around 7.5 years) was adapted based on an interim analysis.

2. Abbreviations

ACS	Acute coronary syndrome
AE	adverse event
AF	atrial fibrillation
AFNET	Atrial Fibrillation NETwork
AHRE	atrial high rate episodes
ALT	alanine transaminase
ASA	Acetylsalicylic acid
aPCC	activated prothrombin complex concentrate
aPTT	activated Partial Thromboplastin Time
AST	aspartate transaminase
CABG	coronary artery bypass graft surgery
CrCl	creatinine clearance
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
DAPT	dual antiplatelet therapy
ECG	electrocardiography
e-CRF	electronic case report form
EHRA	European Heart Rhythm Association
EQ-5D	Euroquol 5D questionnaire
ERC	Endpoint Review Committee
FU	follow-up
GCP	Good Clinical Practice
HF	heart failure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IIT	Investigator Initiated Trial
INR	International Normalised Ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention-to-treat
LVEF	left ventricular ejection fraction

MACES	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MoCA	Montreal cognitive assessment
mITT	modified intention-to-treat
NIHSS	National Institutes of Health Stroke Scale
NOAC	Non-vitamin K antagonist oral anticoagulants
NYHA	New York Heart Association
OD	once daily
PACT-Q	Perception of AntiCoagulant Treatment Questionnaire
PCC	Prothrombin complex concentrate
PCI	percutaneous coronary intervention
PE	physical examination
PI	principal investigator
QoL	Quality-of-life
RBSMP	Risk Based Study Monitoring Plan
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse event
TEE	transesophageal echocardiogram
TIA	transient ischemic attack
VKA	vitamin K antagonist

The terms “trial” and “study” as well as “study drug” and “study medication” are being used interchangeably throughout this protocol.

3. Introduction

3.1 Background Information

Atrial fibrillation (AF) is a common cause of stroke, especially ischemic stroke. Unlike strokes of other aetiology, which can be prevented by antiplatelet therapy, strokes in patients with AF require oral anticoagulation for adequate stroke prevention (1). Recently, four new, non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced into clinical practice that provide alternatives to vitamin K antagonist (VKA) therapy (2-6). Edoxaban is one of these NOACs. The NOACs including edoxaban provide similar or slightly better stroke prevention, and appear slightly safer compared to VKAs (7), but seem easier to use than VKAs. The NOAH - AFNET 6 trial will only commence in countries where edoxaban has been approved for stroke prevention in atrial fibrillation.

So far, all available data that demonstrate a beneficial effect of oral anticoagulation for stroke prevention have been collected in populations with AF documented by conventional ECG recordings (8). Studies in other populations in the absence of AF, e.g. heart failure, had outcomes whereby slight reductions in stroke were counterbalanced by increased bleeding (9). This illustrates the need to target anticoagulant therapy to patients at high risk for stroke events related to AF.

It is well established that many AF episodes remain undiagnosed (“silent AF”; 1). Often, a potentially preventable stroke is the first clinical manifestation of AF in patients with undiagnosed silent AF. Therefore, better techniques to detect silent AF are needed. Published and ongoing studies suggest that systematic intermittent ECG screening, using patient-operated devices (10, 11), “opportunistic screening” (1, 12), or Holter ECG recordings, e.g. in survivors of a stroke (3, 14), are capable of detecting additional patients with hitherto undiagnosed, silent AF. Although these non-invasive techniques increase the diagnostic yield of patients with silent AF, they will still miss many patients (15).

Continuous monitoring of atrial rhythm by implanted devices could close this diagnostic gap (15). While dedicated implanted rhythm monitoring devices are currently evaluated, most modern pacemakers, defibrillators, cardiac resynchronisation devices, and insertable cardiac monitors already provide automated algorithms alerting to the occurrence of highly organised atrial tachyarrhythmia episodes, also called “subclinical atrial fibrillation” or, more commonly, “atrial high rate episodes” (AHRE; 16, 18, 19). Data from large prospectively followed patient cohorts demonstrated that stroke rate is increased in patients with AHRE (16, 17). Indeed, a sizeable portion of these patients develops clinically detected AF over time, but often only after the first stroke (16, 42). Thus, AHRE can be assumed an early manifestation of paroxysmal AF.

On the other hand, the absolute stroke rates are lower in patients with AHRE when compared to stroke rates in patients with clinically diagnosed AF, and automated detection algorithms of AHRE by implanted devices have a good sensitivity, but not a sufficient specificity to distinguish AF from other arrhythmias or artefacts when compared to Holter ECG recordings analysed by specialists (18). In light of the bleeding complications associated with oral anticoagulant therapy, there is thus uncertainty about the optimal antithrombotic therapy in patients with AHRE, and more studies are needed to determine whether oral anticoagulation should be recommended for these patients (1, 19).

3.2 Study Rationale

The NOACs provide similar or slightly better stroke prevention, and appear slightly safer compared to VKAs (7, 45). Edoxaban at a dose regime of 60 mg once daily (OD) with a planned dose reduction to 30 mg OD in patients with reduced edoxaban elimination as outlined in the edoxaban Summary of Product Characteristics [SmPC] has a favourable profile compared to dose-adjusted VKA therapy: In the ENGAGE-TIMI 48 trial (6), edoxaban prevented strokes at least as effectively as VKA therapy (hazard ratio 0.8 (0.63 – 0.99), $p<0.0001$ for non-inferiority; (6)). Furthermore, importantly for the design of NOAH - AFNET 6, an edoxaban dose regime of 60 mg OD caused less major bleeding events than VKA therapy in the ENGAGE trial (hazard ratio 0.8 [0.71 – 0.91], $p<0.0001$). Thus, an edoxaban 60 mg OD therapy regimen provides an intervention that is safer than VKA (20% less major bleeding events, CI 9% – 37%), and at least as effective in preventing

strokes in non valvular AF patients. This intervention is expected to prevent clinical and subclinical strokes and thereby improve quality of life, and maintain cognitive function.

This randomised trial, therefore, tests the hypothesis that oral anticoagulation with the NOAC edoxaban used in a 60 mg OD dose regime is superior to antiplatelet therapy (or no therapy depending on cardiovascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE, but without AF, and with at least two stroke risk factors.

If combined with another similarly sized trial (ARTESIA, NCT01938248), the data are likely to change clinical practice in this patient group, with benefits for a large number of patients with AHRE. The NOAH - AFNET 6 Steering Committee plans combined analyses of the results of these two trials. The results of NOAH - AFNET 6 may also inform future guidance on the management of patients with atrial arrhythmias detected by implantable ECG monitors.

3.3 Benefit-risk Assessment

General risk assessment of the NOAH - AFNET 6 trial: All study drugs are market approved for prevention of stroke in patients with non-valvular AF. Although AHRE are presently not considered equal to AF documented by conventional ECG recordings, VKA and NOACs are currently used for patients with AHRE in clinical routine (off-label use), and the documentation of short-lasting arrhythmias that resemble atrial fibrillation is considered “non valvular AF” by many clinicians, although data supporting the use of anticoagulants in general are lacking in this population. Other clinicians will strive to document AF in the usual way in AHRE patients. Thus, there is true clinical equipoise for the use of anticoagulation in patients with AHRE. In view of the potential benefits for stroke prevention in this population, this is a clinically important issue that calls for resolution in a controlled clinical trial.

The other patient characteristics of the NOAH – AFNET 6 population and the use of edoxaban in the trial mirror the European label of edoxaban to ensure that the use of edoxaban is limited to patients in whom safety information exists from the completed phase III programme leading to the market authorisation of edoxaban in Europe (6). The sponsor of NOAH – AFNET 6 and the scientific partner, the European Society of Cardiology, have carefully considered how to define the phase of this investigator-initiated trial, also in view of the fact that edoxaban has been evaluated in a large clinical trial program in patients with very similar characteristics compared to those to be enrolled in NOAH – AFNET 6, and in view of the conduct of a similar trial (ARTESIA, NCT01938248) as phase IV. Reflecting the equipoise of anticoagulation and the uncertainty whether AHRE represent an early form of AF, NOAH – AFNET 6 will be conducted as a phase IIIb study.

All concomitant study procedures are standard care procedures according to applicable medical guidelines used within the recommended indications. All participating study sites have to document sufficient experience in the management of patients with implanted pacemakers, defibrillators, cardiac resynchronisation devices or insertable cardiac monitors and of patients with AF.

Thus, the overall risk level of the NOAH – AFNET 6 trial is expected to be low.

Assessment of the individual risk of study patients: The risk of therapy within NOAH - AFNET 6 seems acceptable in view of the favourable safety profile of an edoxaban 60 mg OD regime in the ENGAGE-TIMI 48 trial compared to warfarin. In light of existing data for apixaban and warfarin, the bleeding risk on edoxaban may only slightly exceed that of acetylsalicylic acid therapy (3, 23). Thus, the individual risk of study patients in the group randomised to treatment with NOAC will not differ from the risk of therapy in clinical routine treatment for prevention of stroke in patients with non-valvular AF. Patients randomised to treatment with NOAC have an increased risk for bleeding events compared to patients randomised to the group that undergoes usual care. Event rates for AHRE patients do not exist and will be generated in NOAH - AFNET 6. Based on the observed baseline stroke rates in AHRE patients (refer to section 12), similar effect differences are expected for NOAH - AFNET 6.

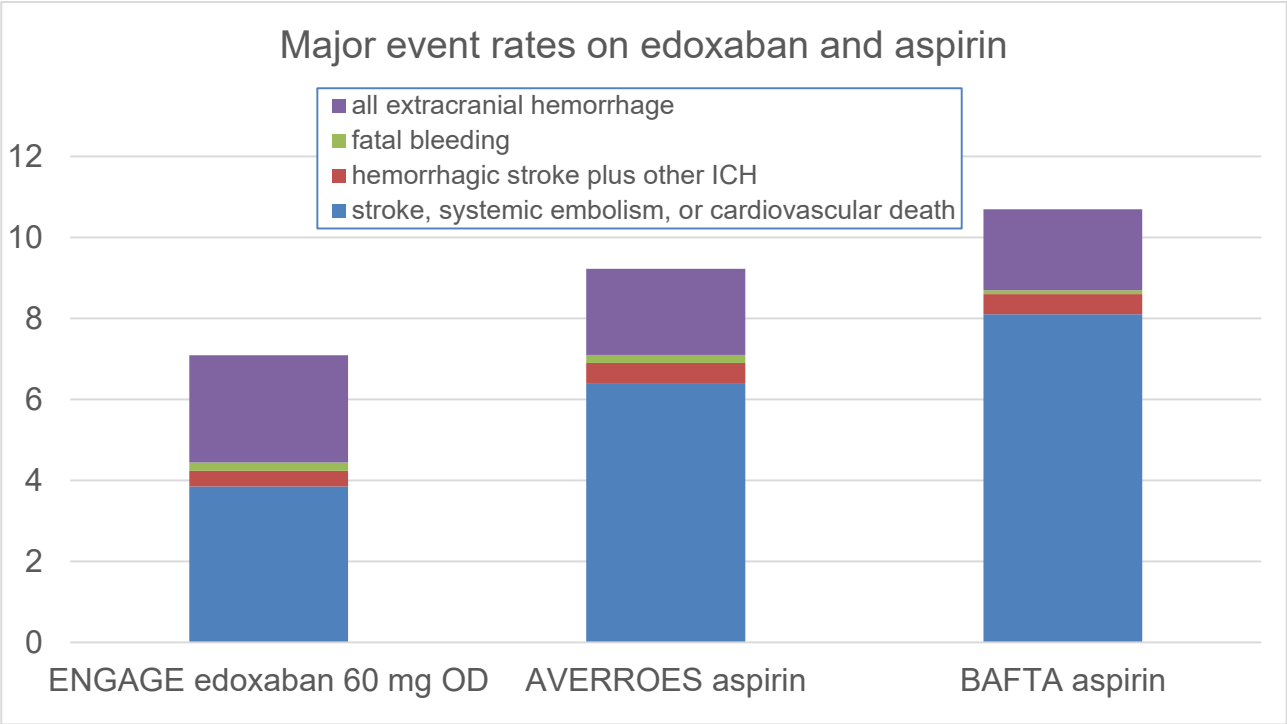

Figure 1: Major efficacy and safety event rates for AF patients randomised to an edoxaban 60 mg OD regime in the ENGAGE-TIMI 48 trial compared to event rates reported in patients randomised to acetylsalicylic acid in the AVERROES and BAFTA trials (3, 6, 23). All events are given as annualised rates in percent. This figure is replicated in the sample size estimation section.

General benefit of study patients: All patients participating in NOAH - AFNET 6 will have the added benefit of careful standardised monitoring of their anticoagulant treatment by their study physicians as well as of additional quality management by the CRO, the sponsor, the independent Data and Safety Monitoring Board and the Steering Committee.

Individual benefit of study patients: Patients randomised to edoxaban will receive a treatment that has been shown to be safer with a reduced annualized rate of major bleedings (hazard ratio 0.80) compared to VKA and slightly more effective to prevent stroke or systemic embolism than VKA with reduced annualized rates of these events (hazard ratio 0.79) in general AF populations (6). VKA therapy in general AF patients itself was demonstrated to be three times more effective in preventing stroke or systemic embolism compared to antiplatelet therapy (22). Based on the existing literature, it is likely that a similar benefit will be conveyed by edoxaban in patients with AHRE detected by pacemaker. By participating in the NOAH - AFNET 6 trial, patients will receive this safe anticoagulant earlier than in usual care, i.e. when atrial arrhythmias are documented by the implanted device rather than by the ordinary ECG, with the potential for added stroke prevention.

4. Study Objectives

To demonstrate that oral anticoagulation with the NOAC edoxaban is superior to current therapy (antiplatelet therapy or no therapy depending on cardiovascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE but without overt AF (Appendix I) and at least two stroke risk factors leading to a modified CHA2DS2VASc score of 2 or more.

4.1 Primary Outcome Parameters

The primary outcome parameter of NOAH - AFNET 6 is defined as the time from randomisation to the first occurrence of stroke, systemic embolism or cardiovascular death. A detailed definition of these outcome events is provided in Appendix III.

4.2 Secondary Outcome Parameters

The secondary outcome parameters are defined as

- components of the primary outcome,
- Major Adverse Cardiac Events (MACEs: cardiovascular death, myocardial infarction, acute coronary syndrome (ACS); PCI, CABG),
- stroke or systemic arterial embolism
- all-cause death,
- major bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) definitions (60, 61), (Appendix IV)
- quality of life changes at 12 and 24 months compared to baseline (assessed by EQ-5D including its visual-analogue scale and by the Karnofsky scale),
- patient satisfaction at 12 and 24 months compared to baseline (assessed by modified EHRA score (36) and PACT-Q (43))
- cost effectiveness and health resource utilisation estimated by quantification of relevant events, interventions, nights spent in hospital and cardiovascular therapies,
- changes of autonomy status only in patients with stroke during study participation, potentially assessed at each clinical follow-up visit by modified Rankin scale; a maximum of 2 subsequent assessments in follow-up per patient with stroke should be performed,
- cognitive function (MoCA) at 12 and 24 months compared to baseline.

5. Study Design

NOAH - AFNET 6 is an investigator-initiated, prospective, parallel-group, double-blind, randomised, multicentre trial. The trial tests whether oral anticoagulation using the NOAC edoxaban is superior to current therapy to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE. The trial will be conducted in several European countries (details of study sites are provided in a separate document).

NOAH - AFNET 6 is an event-driven trial with a planned number of randomised and treated patients of n=2,538 and an anticipated number of primary endpoints of n=220. The total duration of the trial is an estimate based on observed outcome rates in other large trials with similar populations. The total number of events in the trial is depending on the observed hazard rates and on the time at risk, which is the follow-up time of all patients. In practice, the event-driven design may result in slight variation of the expected trial duration and of the total number of patients enrolled if observed event rates do not exactly match the assumed rates. All patients will be followed until the global end of the trial.

5.1 Flow Chart

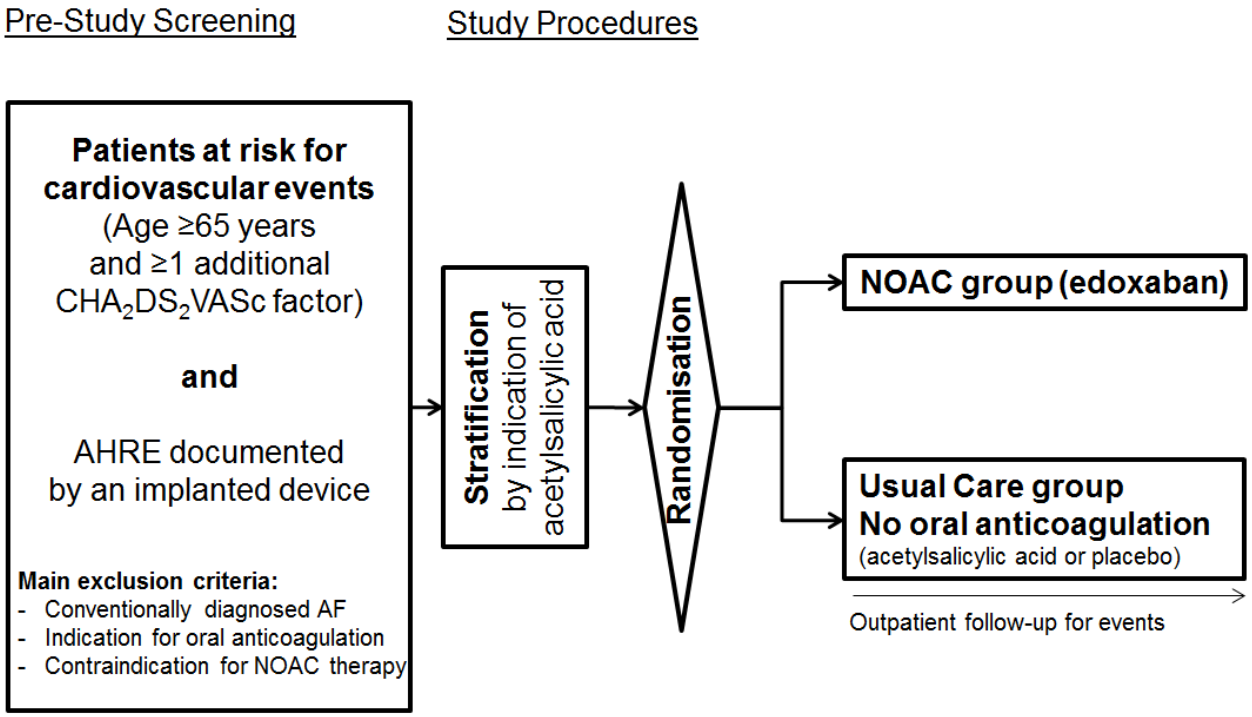

Figure 2: Study flow chart

6. Selection of Patients

6.1 Informed Consent

A signed, ethics committee (EC) /institutional review board (IRB) approved informed consent form, written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (Appendix IX) and the applicable laws for research using medical devices and drugs, will be obtained from every patient prior to any study-related procedure. All clinical data needed to evaluate the potential eligibility of a patient before study inclusion, e. g. recent laboratory results, ECG recordings or other technical parameters, are considered to be performed during clinical routine and are therefore not considered to be part of study related procedures. Participants will be advised that their quality of life and satisfaction data are collected for research purposes and will not be used to guide clinical care.

The investigator or responsible medical staff will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

Should there be any modifications to the protocol, such that this would directly affect the patient’s participation in the study, e.g. a change in any procedure, an addendum to the informed consent form specifying the modification must be compiled and the patients must agree to sign this addendum indicating that they re-consent to further participate in the modified study.

A signed copy of the patient’s informed consent form must be maintained in the study file on site. The patient’s permanent medical records should indicate the patient's study participation. A patient information sheet will be handed out to the patient unless declined by him/her.

6.2 Study Population

The intended population for this study consists of patients who have documented AHRE but no history of overt AF at the time of randomisation and a risk for stroke fulfilling the inclusion criteria as listed below, i.e. approximating a modified CHA_2DS_2VASc score of 2 or more. This population has a clinical risk profile that would make patients with ECG-documented AF eligible for oral anticoagulation. In view of the uncertainty around event rates in patients with documented AHRE, a blind assessment of event rates is planned during the trial. It will be considered to adjust the trial population should event rates be lower than anticipated (see below for details). Patients will be recruited by contracted study sites only. The aim is to activate approximately 200 to 250 sites in Europe with adequate experience in follow-up of implanted pacemakers, defibrillators or insertable cardiac monitors in clinical routine and in treatment of patients with AF. Patient recruitment is expected to be completed after 71 months.

6.2.1 Number of patients

A total of 2,538 patients will be randomised and treated throughout Europe. Patients who develop overt AF during the trial period will be censored at that time point but followed according to protocol until the global end of the trial. The hazard of developing overt AF is assumed to remain constant and it is estimated at 0.287. The sample size may be adapted once in a blinded manner as described in the statistics section (refer to section 12).

6.2.2 Inclusion criteria

I1. Pacemaker ,defibrillator or insertable cardiac monitor implanted for any reason with feature of detection of AHRE, implanted at least 2 months prior to randomisation.

I2. AHRE detection feature activated for adequate detection of AHRE (refer to Appendix XIII).

I3. AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration) documented by the implanted device.
Any AHRE episode recorded is potentially eligible, but AHRE episodes detected in the first 2 months after implantation of a new device involving placement or repositioning of atrial electrodes are not eligible. AHRE episodes recorded in the first two months after a simple “box change” operation, i.e. exchange of a pacemaker or defibrillator device without exchange or repositioning of atrial electrodes, are eligible.

I4. Age ≥ 65 years.

I5. In addition, at least one of the following cardiovascular conditions leading to a modified CHA_2DS_2VASc score of 2 or more:

- Age ≥ 75 years;
- Heart failure (clinically overt or LVEF < 45%);
- Arterial hypertension (chronic treatment for hypertension, estimated need for continuous antihypertensive therapy or resting blood pressure > 145/90 mmHg);
- Diabetes mellitus;
- Prior stroke or transient ischemic attack (TIA);
- Vascular disease (previous myocardial infarction, peripheral, carotid/cerebral, or aortic plaques on transesophageal echocardiogram [TEE]).

I6. Provision of signed informed consent.

6.2.3 Exclusion criteria

General exclusion criteria

E1. Any disease that limits life expectancy to less than 1 year.

E2. Participation in another controlled clinical trial, either within the past two months or still ongoing.

E3. Previous participation in the present trial NOAH - AFNET 6.

E4. Drug abuse or clinically manifest alcohol abuse.

Exclusion criteria related to a cardiac condition

E5. Any history of overt AF or atrial flutter.

E6. Indication for oral anticoagulation (e.g. deep venous thrombosis).

E7. Contraindication for oral anticoagulation in general.

E8. Contraindication for edoxaban as stated in the current SmPC.

E9. Indication for long-term antiplatelet therapy other than acetylsalicylic acid or a need for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy (DAPT). Patients with a transient requirement for DAPT (e.g. after receiving a stent) will be eligible when the need for DAPT is no longer present.

E10. Acute coronary syndrome, coronary revascularisation (PCI or bypass surgery), or overt stroke within 30 days prior to randomisation.

Exclusion criteria based on laboratory abnormalities

E11. End stage renal disease (creatinine clearance (CrCl) < 15 ml/min as calculated by the Cockcroft-Gault method, refer to 7.1.1.).

Legal exclusion criterion (applicable in countries where legally required)

E.12. All persons exempt from participation in a clinical trial by law.

6.2.4 Adequate detection of AHRE

An adequate detection of AHRE by the implanted device is essential for screening of eligible patients to be included in NOAH - AFNET 6. Device interrogations derived from the implanted device containing the index AHRE episode that led to inclusion will be digitally uploaded for central review by an independent core analysis centre. The results of review will not lead to post-hoc exclusion of the patients if criteria of AHRE are not met but will detect protocol violations relevant for stability measures of final analysis and will lead to training of corresponding study sites to prevent future violations and therefore assure a standard quality of adequate AHRE detection.

The following paragraph outlines adequate settings of devices for adequate identification of AHRE episodes in patients who are potentially eligible for NOAH - AFNET 6:

- The intracardiac electrogram (IEGM) storage should be activated while the atrial tachycardia detection rate should be set to 170 bpm. Episodes at lower atrial rates are not qualifying episodes for NOAH - AFNET 6. Higher rate thresholds are acceptable, but may miss some episodes that would make patients eligible for NOAH - AFNET 6. Although false atrial tachyarrhythmia detection due to repetitive non-re-entrant ventriculo-atrial synchrony is rare for episodes greater than 6 minutes in duration, this phenomenon can be diagnosed by checking the stored IEGMs and can be eliminated by avoiding very long programmed AV delays and/or by increasing the post-ventricular atrial refractory period.
- For pacemakers and implantable cardioverter-defibrillators (ICDs) with programmable atrial electrogram configuration, the latter should be programmed Atip-Aring, in order to avoid noise detection and the use of short tip-to-ring spacing atrial leads (<10 mm) is strongly recommended.

- Finally the devices should be optimally programmed according to the individual patient and to the most recent practice guidelines (25, 26, 27), ensuring as far as possible optimum hemodynamic and avoiding unnecessary ventricular pacing.

Cardiac rhythm management device manufacturers use different detection algorithms and settings for the most accurate device diagnostics and EGM recordings. Detailed information will be provided in a separate instruction document “Appendix VIII: Suggestions for optimal programming of devices for adequate detection of AHRE” (see Appendix VIII).

6.2.5 Randomisation

Study patients will be randomised to one of two parallel groups in a 1:1 design, designated as “NOAC” and “Usual Care”. Randomisation will be stratified by indication for use of antiplatelet therapy as assessed by the responsible investigator at the time of randomisation.

Randomisation will be done per study site in blocks of variable size to allow minimising potential confounders related to different healthcare practice. A randomisation list will be created by the responsible study statistician before study start, and imported into the randomisation server of the e-trial management system. During the trial, randomisation will be performed by each site personnel within the e-CRF of the e-trial management system according to the imported randomisation list. The investigator has to document several clinical items prior to randomisation to verify eligibility of the patient for randomisation and to determine the stratum. The e-trial management system displays the medication number to be used, not the random group, and asks for confirmation by authorised study personnel. The account ID of the person performing the randomisation in the e-trial management system and the corresponding time stamp will automatically be documented in an electronic audit trail.

7. Therapy

NOAH - AFNET 6 is a double-blind trial designed to evaluate the safety and efficacy of the NOAC edoxaban in comparison to usual care consisting of either ASA or no antithrombotic therapy depending on the indication for use of antiplatelet therapy. Patients will receive study medication OD for oral intake depending on the random group throughout the whole study duration.

Patients of the “NOAC” group will receive anticoagulation therapy with edoxaban. Patients in the “Usual Care” group will receive either acetylsalicylic acid (ASA) or no antithrombotic therapy depending on the indication for use of antiplatelet therapy (stratification at the time of randomisation). All patients will receive identical number and form of study medication using the “double-dummy” technique:

- In the “NOAC” group one edoxaban tablet plus one placebo tablet matching in colour, weight, form and size to ASA 100 mg will be administered per day irrespective of stratum according to indication for use of antiplatelet therapy. The use of edoxaban eliminates the necessity of parallel intake of ASA 100 mg in case of an indication for use of antiplatelet therapy.
- In the “Usual Care” group either one tablet of ASA 100 mg plus one placebo tablet matching in colour, form and size to edoxaban 60 mg or one placebo tablet matching in colour, weight, form and size to ASA 100 mg plus one placebo tablet matching in colour, form and size to edoxaban 60 mg will be administered per day depending on the indication for use of antiplatelet therapy as assessed by the responsible investigator.
- A documented change of indication for use of antiplatelet therapy in follow-up will lead to blinded exchange of double-dummy study drug according to actual indication. In case of a new indication for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy (DAPT), blind treatment with study drugs has to be terminated and adequate treatment according to medical guidelines has to be provided by the treating physician. The patient will remain in regular study follow-up until the global end of the trial.

7.1 Study Drugs / Investigational Medicinal Products

An investigational medicinal product is defined as follows by the European Commission (The rules governing medicinal products in the European Union, Volume 10, Clinical Trials, 2006):

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketed authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

In this protocol, investigational products are:

- edoxaban 60 mg tablets,
- edoxaban 30 mg tablets,
- ASA 100 mg tablets, and
- matching placebo tablets.

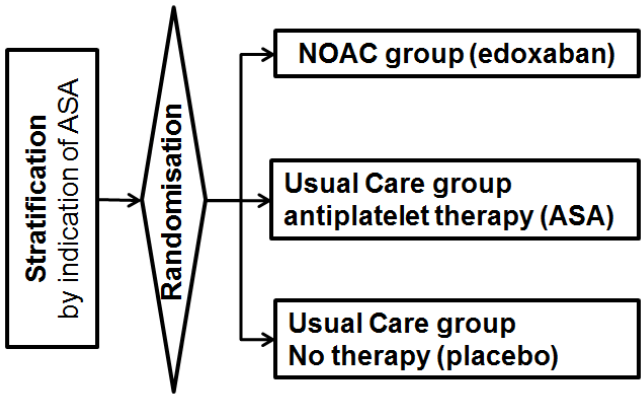

Figure 3: Drug supply schema.
The usual care group is divided into antiplatelet and placebo therapy defined (stratified) by indication of antiplatelet therapy existing at inclusion into NOAH - AFNET 6.

7.1.1 Description of edoxaban

Edoxaban has been tested in large trials and will be applied in NOAH - AFNET 6 at the therapeutic dose approved for stroke prevention in non-valvular AF, i.e. 60 mg OD with a reduction of dose to 30 mg OD in patients with one of the following characteristics:

1. Impaired renal function (CrCl 15-50 ml/min*), or
2. Low body weight (≤60 kg), or
3. Patients receiving the p-glycoprotein inhibitors ketoconazole, ciclosporin, erythromycin, or dronedarone.

If conditions for reduced dosage of edoxaban are not anymore fulfilled during the study, dosage of edoxaban should be increased as stated in the SmPC.

The e-trial management system will automatically identify those conditions if adequately documented by the study site personnel and supply an appropriate medication box containing either 60 mg or 30 mg tablets in patients randomised to edoxaban. However, the investigator finally needs either to confirm the calculated dosage or adjust the dosage according to his medical decision and provide a reason for doing so.

* calculated by the Cockcroft-Gault method:
For male: ((140 - age [years])/ Serum creatinine value [mg/dl])* (weight[Kg] / 72)
For female 0.85 * ((140 - age [years])/ Serum creatinine value [mg/dl])* (weight[Kg] / 72)

7.1.2 Description of acetylsalicylic acid (ASA)

ASA has been used for decades as standard therapeutic agent for antithrombotic therapy according to corresponding medical guidelines. Within NOAH - AFNET 6 either tablets of 100 mg ASA will be applied or matching placebo tablets. The e-trial management system will automatically identify the indication for use of antiplatelet therapy as assessed by the responsible investigator, if adequately documented, and supply an appropriate medication bottle.

7.1.3 Description of placebo

Matching placebo tablets will be applied which are comparable in size, weight, shape and colour to

- edoxaban 60 mg tablets,
- edoxaban 30 mg tablets,
- ASA 100 mg tablets.

7.1.4 Identification of study drugs

The following investigational medicinal products will be provided by the manufacturer of edoxaban:

Product	**Potency**
Edoxaban tablets + matching placebo	60 mg
Edoxaban tablets + matching placebo	30 mg
ASA tablets + matching placebo	100 mg

Table 1: Investigational medicinal products

All study drugs will be packed in study-specific blisters. The sponsor will assure that adequate labelling, storage, and distribution including import of study drugs to study sites on demand is provided by drug suppliers. All quality management requests related to manufacturing, labelling, storage, distribution and reporting defined in applicable international and national standards will be followed by the drug suppliers subcontracted by the sponsor.

7.1.5 Storage condition

Due to the double-blind design, the different storage conditions for edoxaban, ASS or placebo cannot be followed individually but the most restrictive has to be considered. Thus, all study drugs have to be stored continuously between 2 and 25° C. Temperature has to be controlled and documented, e.g. by means of temperature logger provided by the sponsor. Detailed instructions for handling of temperature logging will be provided. In case of exceedance (<2°C or > 25°C) the investigator has to inform the CRO and report the duration of the exceedance and the peak temperature. The CRO will subsequently inform the sponsor who will give advice on actions to be taken in cooperation with the manufacturer of the study drugs.

7.2 Non-investigational Products

Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products.

7.3 Compliance with Study Drugs, Dispensing and Return

The study drugs will be supplied to the study sites in sufficient quantity according to local needs, e. g. expected recruitment rate. The respective time of drug supply will be determined by the CRO but supply itself will be provided by the Drug Supplier.

The logistics of study drug distribution will be managed and tracked centrally in the e-trial management system. Each study medication unit will be supplied with a unique medication number together with a corresponding unique verifier printed on study specific labels. A list of all unique medication numbers together with the corresponding unique verifiers of the provided study medication will be hosted in the materials tool of the e-trial management system.

Labelling follows requirements as specified in Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products. National requirements will be taken into consideration. The Drug Supplier responsible for labelling and delivery of study drug to study sites receives automated supply orders via e-mail from the e-trial management system as soon as a pre-defined minimal number of study drugs in stock at the study site is reached. Triggers for supply orders are individually defined for the different types of study drugs. Tracking of study drugs to be sent to study sites will be performed in the e-trial management system revealing information on medication numbers and verifiers, date of shipment and recipient by study site. Receipt of study drug has to be tracked in the e-trial management system by the receiving site staff by entering the verifier printed on each label.

When a patient is randomised, the e-trial management system displays the medication numbers to be used. Site staff has to confirm dispense of the pre-defined study drugs to the patient by entering in the e-trial management system the corresponding verifiers printed on each label of the study drugs. By doing so, the investigator documents each dispensing of study medication to a patient with the patient's ID, study site ID and the date of dispensing (automatically allocated by the e-trial management system). Comparable procedures will be performed at each drug/device visit in follow-up.

Patients will be asked to bring all unused or partly used medication at each visit in follow-up. The investigator will assess patients' compliance with study drug by asking the patient about medication intake and by pill count during every clinical visit and at the end of follow-up. In case the patient did not take the assigned study drugs for a period of more than 7 consecutive days the date, duration and reason for interruption has to be documented.

Compliance with study drug is defined as following (percentages refer to the period between the last documented follow-up visit and the next, ideally 6 months):

- Intake of study drugs < 80% of the number of pills calculated for the corresponding time period: non-compliance.
- Intake of study drugs 80% to < 90% of the number of pills calculated for the corresponding time period: acceptable compliance.
- Intake of study drugs 90% or more of the number of pills calculated for the corresponding time period: good compliance.

In case of non-compliance the investigator has to instruct the patient about importance of regular drug intake.

Any unused or partly used study medication has to be returned to the drug supplier periodically or latest at the end of the trial in the corresponding study site, depending on the amount of such medication in local stock. Returned study medication will be tracked by the investigator in the e-trial management system in a way comparable to the procedures at study medication dispense. The shipment of returned or unused study medication to the drug supplier will be managed by the CRO but performed by the investigator.

7.4 Blinding/Unblinding

To maintain blinding of study treatment, all study drugs will be prepared in tablets matching edoxaban and ASA tablets in form, size and colour. Patients, investigators and staff of study sites, committee members, and the sponsor's and CRO's staff conducting the study, will not have access to individual patient treatment assignments. The members of the Data and Safety Monitoring Board (DSMB) will have access to such assignments on demand.

Blinding is critical to the integrity of this clinical trial. However, the patient's treatment may be revealed by the investigator in a medical emergency, in which knowledge of the investigational product would be instrumental for further treatment decisions. A newly occurring indication for change of dosage of the study drugs or for initiation or termination of antiplatelet therapy is not a valid reason for unblinding since procedures for blinded change of dosage and antiplatelet therapy are offered. Before breaking the blind of an individual patient's blinded treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the patient's immediate management. In many cases, particularly when the emergency is clearly not study drug-related, the situation may be managed by assuming that the patient is receiving active product without unblinding.

Every patient will be provided with an alert card. The alert card:

- indicates that the patient is participating in a double-blind clinical trial,
- provides the trial number and acronym,
- will note that the patient may be receiving either edoxaban or ASA or placebo, and
- includes the investigator's name and phone number for providing information to emergency medical personnel.

Unblinding: In a medical emergency and if knowledge of the patient's randomised treatment assignment would have a meaningful impact on individual management, the patient's treatment assignment can be unblinded. However, whenever possible, the need to break the blind should first be discussed with the CRO's medical advisor or project director.

Information regarding patient's treatment assignment should be provided only to those who are caring for the patient and as few other people as possible. Thus, bias will be minimised by assuring that the Endpoint Review Committee (ERC) remains blinded to treatment assignment, even if the investigator has been unblinded.

Unblinding of a patient's treatment will be managed and tracked centrally in the e-trial management system. The investigator who is breaking the blind has to document date and reason for code break in the e-CRF and in the patient's medical records. The CRO will receive an automated email containing all necessary information on the code break (however without information regarding treatment) at the same time of the data being documented in the e-CRF. In case the e-CRF system is not reachable the investigator has to contact the CRO's hotline to induce unblinding.

7.5 Temporary or Permanent Discontinuation of Study Drugs

In case of newly occurring

- clinical indication for oral anticoagulation (such as new diagnosis of overt AF), or
- contraindications as given in the current SmPC of edoxaban or of ASA, or
- clinical indication for long term treatment (> 6 months) with any antiplatelet agent in addition to study medication, especially dual antiplatelet (DAPT) therapy, or
- contraindications for oral anticoagulation in general, or
- patient's request of permanent study drug discontinuation,

therapy with blinded study medication should be stopped permanently and other adequate, open-label therapy should be started according to applicable medical guidelines.

In case of clinical indication for temporary treatment with antiplatelet agent in addition to study medication (≤ 6 months duration), study medication should not be stopped permanently but discontinued temporarily, only, for the duration of prescription of any antiplatelet agent in addition to study medication.

Date and reason of discontinuation of study drugs have to be documented (refer to section 9.3.3). Be aware of the fact that overt AF can only reliably be diagnosed by external ECG recordings according to ESC guidelines 2010, (Appendix VII).

The initiation of oral anticoagulation should follow local clinical practice in patients who develop overt AF or another indication for oral anticoagulation. The study medication should be stopped just prior to initiation of effective oral anticoagulation. Compared to usual care, where the patient is not anticoagulated prior to AF detection, this will provide the same timing and effectiveness of oral anticoagulation in patients randomised to usual care (ASA or no therapy), and a better anticoagulation (edoxaban) until initiation of oral anticoagulation in the patients randomised to edoxaban. This regime applies to all patients. For details refer to Appendix VI.

If anticoagulation must be temporarily discontinued for medical reasons, e.g. in case of bleeding or to reduce the risk of bleeding during surgical or other procedures, study medication should be stopped as soon as possible and preferably at least 24 hours before the procedure.

In case of non-life-threatening bleeding time is the most important antidote of the NOACs in view of the relatively short elimination half-lives. After cessation of treatment, restoration of haemostasis is to be expected within 12–24 h after the last taken dose, given plasma half-life of around 12 h for edoxaban. In addition, standard supportive measurements (such as mechanical compression, surgical haemostasis, fluid replacement, and other haemodynamic support) should be provided.

In case of life-threatening bleeding the administration of prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate (aPCC) can be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. Clinical trials and registry data with NOACs have shown that this is rarely needed. The choice between PCC and aPCC may depend on their availability and the experience of the treatment centre. However, the efficacy of PCC or aPCC in patients who are actively bleeding has not been firmly established and one has to balance the potential prothrombotic effects against the potential anticoagulant benefits.

For details on adequate therapy in case of bleeding please refer to chapter 9, page 20 ff. of the Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation attached as Appendix VI.

Date, duration and reason for interruption have to be documented in the corresponding AE or SAE form of the e-CRF. In deciding whether a procedure should be delayed until 24 hours after the last dose of study medication, the potentially increased risk of bleeding should be weighed against the urgency of the intervention. Study medication should be restarted after the surgical or other procedures as soon as adequate haemostasis has been established. If oral medicinal products cannot be taken during or after surgical intervention, consider administering a parenteral anticoagulant and then switch to oral study medication.

If the patient did not take the assigned study drugs for any other reason (intended or unintended) this has to be documented in the e-CRF as part of the compliance measure at each follow-up visit (refer to section 7.3).

Discontinuation of study drug, temporary or permanent, will not result in termination of study participation (intention-to-treat principle). In any case of discontinuation of study drug the patient will be followed according to study protocol until the global end of the trial.

7.6 Concomitant Medication

The concomitant use of antiplatelet agents is discouraged in all study patients, because the concomitant use of an oral anticoagulant and antiplatelet agents increases the risk of bleeding without known benefits. Patients who require treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy, at the start of the trial are not eligible for NOAH - AFNET 6 (refer to 6.2.3, exclusion criteria). If the indication for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy, appears after inclusion into the trial therapy with blinded study drugs should be stopped permanently and other adequate, open-label therapy should be started according to applicable medical guidelines (refer to 7.5, temporary or permanent discontinuation of study drugs). All other concomitant medication can be used within the NOAH - AFNET 6 trial if in line with the contraindications given in the current SmPC of edoxaban.

In the e-CRF, all concomitant drugs will be documented by generic name and dosage administered.

7.7 Post-study Treatment

It is at the discretion of the treating physician which kind of therapy will be prescribed to the patient once their participation in the study has ended (global study end or premature study discontinuation). It is recommended to strictly follow the applicable medical guidelines and the market authorisation of the intended drugs.

8. Adverse Event Reporting

As all study treatments in NOAH - AFNET 6 are marketed and in-line with clinical practice, even knowing that the administration of edoxaban in AHRE patients without overt non-valvular AF is not in-line with the approved label, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”).

8.1 Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A newly diagnosed concomitant disease is also considered an AE. However, onset of ECG-documented AF and subsequently confirmed diagnosis of AF after randomisation is not considered an AE and does not require documentation in an AE form in the e-CRF unless any criterion for seriousness is met. Onset of AF has to be documented in a special “AF onset form”.

Following the patient’s randomisation in the study, all AEs, whether related or not related to study drug, must be collected. However, within the context of the NOAH – AFNET 6 trial, no specific AEs and/or laboratory abnormalities are being considered as critical to safety evaluations. Thus, reporting of AEs not fulfilling any criteria of seriousness (refer to section 8.3) is not time critical.

All AEs will be documented by study site personnel in the relevant section of the e-CRF specifying:

- the type of AE
- the diagnosis of the underlying illness or disorder rather than its individual symptoms.
- the date of onset,
- the date of resolution,
- the outcome,
- the intensity,

- the causal relationship to study drug, and if related, the suspected study drug, and
- the action taken with regard to study drugs.

8.2 Adverse Drug Reactions

According to Directive 2001/20/EC, Adverse Drug Reactions (ADRs) are all untoward and unintended responses to an investigational medicinal product related to any dose administered, irrespective of its degree of seriousness. Events associated with placebo will usually not satisfy the criteria for a serious adverse drug reaction. For all ADRs an assessment of "expectedness" will be performed by the sponsor or its responsible subcontractors.

8.3 Serious Adverse Events

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that

- results in death or,
- is life-threatening
  (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe) or,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
  (defined as inpatient care of more than one calendar day [= at least one overnight stay]; see also **NOTE** below) or,
- results in persistent or significant disability/ incapacity or,
- is a congenital anomaly / birth defect, or
- is a medically important event
  (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation).

More than one of the above criteria can be applicable to each event.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

NOTE: The following hospitalisations are not considered SAEs:

- A visit to any hospital department or emergency room which does not result in an overnight stay (unless considered an "important medical event" or an immediate life-threatening event).
- Any non-emergency medical or surgical admission planned before signing consent.
- Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy).
- Any overnight hospital stay required only for overnight diagnostic procedure (e.g. sleep laboratory).
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

8.4 Recording and Reporting Serious Adverse Events

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected.

The investigator should specify and report in the e-CRF the nature of the sign or symptom leading to the SAE, the date of onset of the sign or symptom, the date of resolution (duration) of the specific event (not of the underlying disease), the intensity, interventions performed (if any), the relationship to study treatment, and the outcome.

All SAEs, whether related or unrelated to study drug, must be reported expeditiously to the CRO through the SAE section of the e-CRF within 24 hours of becoming aware of the event. An SAE form within the e-CRF should be completed for any event where doubt exists regarding its status of seriousness. As a minimum, the investigator has to fill out the following items of the internet-based SAE form:

- type of event,
- description,
- date of onset,
- criteria for seriousness,
- causal relationship to study drug, and if related, the suspected study drug.

As soon as further information regarding the event is available (e.g. discharge letter), the investigator should complete the documentation in the e-CRF and sign it electronically. Copies of the discharge letter, of all reports regarding examinations carried out and/or diagnostic findings should be faxed to the CRO. For laboratory results, the laboratory normal ranges should be included. All documents should be sent to the CRO after adequate blinding of patient identifiers, only.

Follow-up of any SAE that is fatal or life threatening should be provided within one additional calendar week.

Any SAE reporting (initial reporting and follow-up information on e.g. changes of an ongoing SAE's intensity or relationship to the investigational product or outcome) is done through the SAE section of the e-CRF and an automated email notification system within the e-trial management system, i.e. no extra SAE form needs to be faxed but the CRO will receive an automated email containing all necessary information on the SAE at the same time of the data being documented or changes of relevant SAE data being made in the e-CRF.

The sponsor will via contracted CRO forward all SAEs immediately after awareness to the pharmacovigilance department of the edoxaban manufacturer for inclusion in their global safety database. The relevant SAE data will be retrieved from data documented by the investigator within the e-CRF and sent to the edoxaban manufacturer digitally. Changes of relevant SAE data (including deletion of SAEs if relevant criteria are not met) will also be forwarded to the pharmacovigilance department of the edoxaban manufacturer. Patient identifying data will consist of patient ID number, year of birth, gender and site ID number, only.

According to legal requirements and international standards, annual safety reports will be prepared by the sponsor or its responsible subcontractors and forwarded to responsible authorities of all participating countries and to all corresponding ECs / IRBs.

8.4.1 Definition of intensity

Intensity	Definition
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities
Very severe	Signs/symptoms are debilitating, significantly incapacitate patient despite symptomatic therapy

8.4.2 Definition of causality

In accordance with Council of International Organisations of Medical Sciences (CIOMS), causality of an event will be assessed as:

not related: No causal relationship exists between the study treatment and the event but an obvious alternative cause exists, e.g. the patient's underlying medical condition or concomitant therapy.

or

related: There is a reasonable / plausible possibility that the event may have been caused by the study treatment (e.g. the event cannot be explained by concomitant disease(s) or other drugs/treatments).

8.5 Adverse Event Follow-up Procedures

The investigator should take all appropriate measures to ensure the safety of the patients, notably he / she should follow-up the outcome of any AE or SAE (clinical signs, laboratory values or other, etc.) until the return to normal or consolidation of the patient's condition.

In case of any SAE, the patient must be followed until clinical recovery is completed and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after termination of the trial, and that additional investigation may be requested by the CRO team.

8.6 Handling of Expedited Safety Reports

This applies to any SAE that is considered related to study drug and the nature or severity is not consistent with the applicable product information (suspected unexpected serious adverse event; SUSAR). The expectedness of an adverse reaction will be determined by the sponsor or its responsible subcontractors according to the Reference Safety Information (RSI) document of each study drug. The RSI will be clearly identified before global start of the trial and is the same in all participating countries.

The sponsor will act in strict compliance with all applicable laws and regulations and will ensure that any delegate strictly abides by the same. The sponsor or its responsible subcontractors will notify the competent authorities, corresponding ECs / IRBs and all principal investigators concerned of any SUSAR in-line with applicable regulatory requirements. In addition, the sponsor or its responsible subcontractors will inform the marketing authorisation holder of the study drug of the previous notification to the competent authorities.

Before notification of a SUSAR to the competent authorities and corresponding ECs / IRBs, unblinding for this patient must be performed by the sponsor or its responsible subcontractors, however blinding should be maintained for the investigator and for the biostatisticians responsible for data analysis and interpretation. Unblinding of a patient's treatment will be managed and tracked centrally in the e-trial management system. The person performing code break has to document date and reason in the e-CRF.

9. Study Schedule

All data and assessments described in the following sections have to be documented as defined in the e-CRF, even if not described in detail in the study protocol.

9.1 Visit Schedule

The expected timing and assessment of the study are outlined in the following table:

Assessment	**Baseline Visit** Day 0	**Drug/Device Visit*** Month 6	**Clinical Visit*** Month 12	**Drug/Device Visit*** Month 18	**Clinical Visit*** Month 24	**Drug/Device Visit*** Month 30**	**Clinical Visit*** Month 36	**Final Visit*****
Signed ICF (medical informed consent)	X							
Check inclusion & exclusion criteria	X							
Physical examination (PE) / medical history	X		X		X		X	
Karnofsky score	X		X		X			
Modified Rankin scale			X[1]		X[1]		X[1]	
12-lead ECG	X	X	X	X	X	X	X	X
Number of AHRE, upload of device interrogations from implanted device	X	X	X	X	X	X	X	X
Laboratory parameters (blood sample)	X[2]		X[3]					
Cognitive function test (MoCA)	X		X		X			
Quality-of-Life questionnaire (EQ-5D)[4]	X		X		X			
Patient ’s satisfaction and symptom severity questionnaire[4] (mEHRA score, PACT-Q)	X		X		X			
Supply of study drug	X	X	X	X	X	X	X	
Return of study drug		X	X	X	X	X	X	X
Adverse event (AE) /serious adverse event (SAE)		X	X	X	X	X	X	X

Table 2: Study visit schedules

* Time window +/- 2 weeks
** or longer if required
*** within 3 months after confirmation that the required number of adjudicated endpoints has been reached (will be announced by CRO)
[1] Assessment of modified Rankin scale only in pts. with stroke during study participation; a maximum of 2 subsequent assessments in follow-up per patient with stroke should be performed
[2] Blood sample not older than 28 days at the date of randomisation (full blood cell count, serum creatinine, AST, ALT, bilirubin, aPTT, and INR) + extra blood sample for central analyses
[3] Extra blood sample for central analyses, only
[4] All Quality-of-Life measures and satisfaction questionnaires should ideally be completed prior to the clinical consultation.

9.2 Baseline Visit

A patient meets eligibility criteria of the study if all inclusion and exclusion criteria are fulfilled as described in the sections above. Prior to any trial related procedure a signed informed consent form has to be obtained from every patient to be included in NOAH – AFNET 6 and kept on file locally.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent;
- Document all inclusion and exclusion criteria (refer to section 9.2.1 for qualifying AHRE);
- Assess patients' medical history;
- Assess quality-of-life (EQ-5D questionnaire) prior to the main clinical consultation (refer to section 9.7);
- Assess patient’ s satisfaction and symptom severity (PACT-Q questionnaire and modified EHRA score) prior to the main clinical consultation (refer to section 9.7);
- Obtain a 12-lead ECG and digitally upload the ECG to a provided system (refer to section 9.5);
- Perform a physical examination including actual weight;
- Assess function of implanted device and AHRE detection settings, number of AHRE;
- Upload interrogations derived from the implanted device according to upload instructions (will be given as a separate instruction document);
- Obtain blood samples for laboratory assessments (refer to section 9.6);
- Collect a blood sample for storage in the central laboratory (separate informed consent required; refer to section 9.6);
- Assess cognitive function (MoCA test; refer to section 9.8);
- Assess performance status (Karnofsky score; refer to section 9.8);
- Initiate study therapy.

9.2.1 Documentation of the qualifying AHRE

Presence of AHRE is an essential inclusion criterion for NOAH - AFNET 6. Documentation of the qualifying AHRE is essential to monitor inclusion criteria. To allow meaningful assessment of the qualifying AHRE, a digital upload onto a provided system is mandatory to perform a central review. Description of events without documentation of the episode is not sufficient for documentation of the qualifying AHRE. The results of review will not lead to post-hoc exclusion of the patients if criteria of AHRE are not met but will detect protocol violations relevant for stability measures of final analysis and will lead to training of corresponding study sites to prevent future violations and therefore assure a standard quality of adequate AHRE detection.

If AHRE has not been confirmed (i.e. index condition for NOAH - AFNET 6 is not fulfilled),

- and no study medication has been administered, the patient will not remain in the study (refer to section 11.2);
- and at least one dose of study medication has been administered, the patient will remain in the study (principle of intention-to-treat) and has to be followed according to protocol until the end of the trial.

9.3 Follow-up

NOAH - AFNET 6 is an event-driven trial. All patients will be followed until the global end of the trial. Sample size has been estimated based on a minimal follow-up time of 12 months after the end of enrolment and assuming an enrolment time of 71 months.

Clinical follow-up visits will be performed at months 12, 24, and 36. Starting at month 6 and subsequently alternating to clinical follow-up visits, patients will come to the study site for dispensing study drug and up-load of device interrogations derived from the implanted device ("drug/device visit"). After month 36, no more scheduled clinical visits will take place but "drug/device visits" in 6-monthly intervals until end of study, only.

All patients will be followed for outcome and safety until global end of the trial. After the required number of primary outcome events has been accrued and verified, all patients will be seen for a final end of study visit.

For all scheduled follow-up visits, a time window of +/- 2 weeks is allowed.

9.3.1 Clinical visits (Months 12, 24, and 36)

At each visit, the investigator or designee will

- Assess the AHRE detection settings in the implanted device;
- Assess overall heart rhythm, number of AHRE, and history of AF since preceding visit;
- Upload device interrogations derived from the implanted device according to upload instructions (will be given as a separate instruction document);
- Perform a physical examination including actual weight;
- Obtain a 12-lead ECG and digitally upload the ECG to a provided system (refer to section 9.5);
- Assess for clinical events, AEs, SAEs, and contraindications for edoxaban or oral anticoagulation that occurred since the preceding visit / contact;
- Assess modified Rankin scale in patients with stroke during study participation; a maximum of 2 subsequent assessments in follow-up per patient with stroke should be performed
- Assess and document adherence to study therapy by asking the patient and by pill count;
- Dispense new study medication as far as required and collect remaining study medication.

At month 12 and 24 the investigator or designee will in addition:

- Assess quality-of-life (EQ-5D questionnaire) prior to the clinical consultation (refer to section 9.7);
- Assess performance status (Karnofsky score; refer to section 9.8);
- Assess patient' s satisfaction and symptom severity (PACT-Q questionnaire and modified EHRA score) prior to the main clinical consultation (refer to section 9.7);
- Assess cognitive function (MoCA test; refer to section 9.8).

At month 12 the investigator or designee will in addition:

- Obtain blood sample for central analyses (refer to section 9.6).

9.3.2 Drug/device visits (Months 6, 18, and 30 or longer if required)

At each drug/device visit, the investigator or designee will

- Record patients weight, dispense new study medication as far as required and collect used/empty study medication;
- Assess and document adherence to study therapy by asking the patient and by pill count;

- Obtain a 12-lead ECG and digitally upload the ECG to a provided system (refer to section 9.5);
- Upload device interrogations derived from the implanted device according to upload instructions (will be given as a separate instruction document);
- Assess for clinical events, AEs and SAEs that occurred since the preceding visit / contact.

9.3.3 Triggered visit „Discontinuation of study drug“

If the study drug needs to be discontinued for medical reasons (e.g. in case of clinical indication for anticoagulation or antithrombotic therapy such as new diagnosis of AF or in case of contraindications given in the current SmPC of edoxaban or for oral anticoagulation in general) or the patient's request of study drug discontinuation (refer to section 7.5) this has to be documented in the e-CRF and the investigator or his designee will

- Assess the AHRE detection settings in the implanted device;
- Assess overall heart rhythm, number of AHRE, and history of AF since preceding visit;
- Upload device interrogations derived from the implanted device according to upload instructions (will be given as a separate instruction document);
- In case of new diagnosis of AF as reason for discontinuation of study drug, upload first ECG available with documentation of AF;
- Assess for clinical events, AEs and SAEs that occurred since the preceding visit / contact;
- Document date and reason for discontinuation of study drug;
- Assess and document previous adherence to study drug by asking the patient and by pill count;
- Collect all study medication.

Although having discontinued study drug, these patients will be followed according to study protocol until global end of study (intention-to-treat).

9.3.4 Final visit (at global end of study)

The global end of study will be announced by the CRO after all necessary primary endpoints have been reached. All regular scheduled follow-up visits have to be cancelled after this point in time, but a final in person visit has to be scheduled for all patients still in follow-up at the time of global end of study. It is expected that this visit will be scheduled, performed and documented within 3 months after announcement by the CRO. At that visit, the investigator or his designee will

- Assess overall heart rhythm, number of AHRE, and history of AF since preceding visit;
- Upload device interrogations derived from the implanted device according to upload instructions (will be given as a separate instruction document);
- Obtain a 12-lead ECG and digitally upload the ECG to a provided system (refer to section 9.5);
- Assess for clinical events, AEs and SAEs that occurred since the preceding visit / contact;
- Assess and document previous adherence to study drug by asking the patient and by pill count;
- Terminate study medication intake and collect all remaining study medication;
- Document and start change management to therapy after end of study in each patient.

In patients with premature termination of study drug before global end of study the final visit might be performed as final phone call assessing for clinical events, AEs and SAEs, only.

After termination of study treatment it is at the discretion of the treating physician which kind of therapy will be prescribed to the patient. It is recommended to strictly follow the applicable medical guidelines and the market authorisation of the intended drugs.

9.4 Patient withdrawal from the study

Termination of treatment with study medication for any reason does not necessarily mean premature study withdrawal or termination of study procedures. Individual study participation is only terminated in case of death or patient's explicit wish. It is expected that a large proportion of patients wishing to withdraw consent for further study participation wish to avoid the time and effort of study-specific visits at the study site rather than completely withdrawing from study participation. All study patients wear an implanted device with the need of personal visits for periodic device checks in clinical routine. Patients expressing the wish to withdraw from the study will therefore be asked to maintain consent for minimal effort follow-up, allowing to use their clinical data achieved at the clinically indicated visits within the NOAH - AFNET 6 trial (modification of consent). All study patients wearing an implanted device with home monitoring capacity should be asked to consent for a follow-up allowing using their device data achieved by remote monitoring.

If a patient completely withdraws consent to any further study participation, the investigator should contact the patient and

- Assess overall heart rhythm, number of AHRE, and history of AF since preceding visit;
- Upload device interrogations derived from the implanted device according to upload instructions;
- Assess for clinical events, AEs and SAEs that occurred since the preceding visit / contact;
- Assess and document adherence to study therapy by asking the patient and by pill count;
- Collect all study medication

These data will be documented in the e-CRF in a withdrawal visit.

9.5 Electrocardiogram

All patients will undergo 12-lead ECG at baseline and as part of the clinical follow-up visits. Operators recording ECGs should ensure that chest leads are placed in the proper position and electrodes make good skin contact to minimize noise and artefacts. The reversal of limb leads and the switching of precordial leads are known to cause important alterations in ECGs.

All ECGs will be uploaded digitally onto a central server. This requires an ECG machine capable of exporting an adequate digital format that can then be uploaded. Details regarding upload of ECGs are described in a separate ECG upload manual.

The ECG recording should be digitally annotated with the date of recording, patient study ID and gender, only. No patient identifying annotations (e. g. last name, first name, date of birth) must be documented.

In case an ECG is only available as paper version, a copy has to be faxed or mailed to the CRO for further analyses to be performed by a central evaluation centre.

9.6 Blood Samples

Routine laboratory parameters obtained within clinical routine procedures are part of the standard work-up of the patient's status before study participation in order to verify the enrolment criteria and therefore not considered to be part of study related procedures. If these parameters can be assessed from a blood sample not older than 28 days at the date of inclusion, blood sampling and analysis do not have to be repeated within the study baseline visit. Parameters include a full blood cell count, serum creatinine, AST, ALT, bilirubin, aPTT, and INR. All blood parameters will be determined at the local laboratory of the study sites provided

their analytical laboratories are certified. The e-CRF will collect laboratory values and information whether the value is normal or abnormal.

At baseline and at clinical visit month 12, a study-specific blood sample will be collected (20 ml whole blood) and sent to a central laboratory for archiving for later analysis (analyses of factors and mechanisms of AF, stroke, and bleeding, including genetic markers) which will be performed either in the central laboratory of the trial or within scientific collaborations. All analyses will be supervised by the Steering Committee. Patients will provide a separate signed informed consent to obtain this extra blood sample. Details regarding handling and shipment of these blood samples are described in a separate manual.

9.7 Quality of Life, Experience, Symptoms and Cognitive Function

All patients will be requested to complete quality-of-life, symptom and experience questionnaires and undergo cognitive function testing at baseline, 12 and 24 months. It is hypothesised that the intervention will lead to improved quality-of-life, reduce symptoms, improve patient experience and maintain cognitive function. This hypothesis is based on the observation that AF, including “asymptomatic” forms, is associated with reduced quality of life (44). Observational data suggest that small cerebral emboli are common in patients with short AF episodes (51, 55) and can contribute to reduced quality of life (56, 57). Based on the assumption that AHRE are a very early form of AF conveying a risk of stroke including silent brain lesions, it is expected that quality of life and cognitive function in AHRE patients will also be reduced. Furthermore, the collection of EQ-5D information will provide a valid basis to compare the intervention tested in NOAH - AFNET 6 to other interventions in terms of utility and cost effectiveness. This will inform payers and providers of health care services and allow to put the findings of NOAH - AFNET 6 into a broader health care perspective (58, 59). Significant benefits should be observed within 12 months of treatment and be maintained thereafter. All assessments will be conducted in accordance with the QOL Site Training Manual (will be given as a separate instruction manual) prior to the main clinical consultation.

9.7.1 Patient Reported Outcomes: quality of life, experience and symptoms

Quality of life will be assessed using the EuroQoL EQ-5D L questionnaire. The EQ-5D is a self-administered, validated, generic preference-based measure of health status that comprises a 5-question multi-attribute questionnaire and a visual analogue self-rating scale (46, 47, 48). Patients are asked to rate severity of their current problems according to 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). Patients can therefore be classified into 3,125 possible health states which can be converted into an EQ-5D index score. On the visual analogue scale patients are asked to rate their own health state relative to full health (score=100) or worst imaginable health state (score=0).

Patients’ expectations of, and satisfaction with their anticoagulant treatment will be assessed using the Perception AntiCoagulant Treatment Questionnaire (PACT-Q). This is a validated tool which takes around 10 minutes to complete (49, 50).

Patient perception of the severity of their symptoms will be assessed using the modified EHRA score (36).

9.8 Clinical Assessment of Performance Status and Cognitive Function

Performance status will be assessed using the Karnofsky Performance Status Scale (52, 53). The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death, and has previously been used in AF patients (54):

100% – normal, no complaints, no signs of disease
90% – capable of normal activity, few symptoms or signs of disease
80% – normal activity with some difficulty, some symptoms or signs
70% – caring for self, not capable of normal activity or work
60% – requiring some help, can take care of most personal requirements
50% – requires help often, requires frequent medical care

40% – disabled, requires special care and help
30% – severely disabled, hospital admission indicated but no risk of death
20% – very ill, urgently requiring admission, requires supportive measures or treatment
10% – moribund, rapidly progressive fatal disease processes
0% – death

Cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA; 62); a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

9.9 Measures to be taken in case of a Pandemic

In case of a pandemic, actions should be taken by the study sites in order to support the safe continuation of the NOAH - AFNET 6 study and to protect the study population from harm. The goal is to keep as many patients as possible in the study without endangering their safety or health in order to allow a meaningful continuation of the study and not to jeopardize the quality of the study data. Measures will be taken by the sponsor to warrant the continued supply of study medication and medical care during study participation. Based on local requirements, the study team shall perform a risk assessment to determine whether the actions described below and potentially additional actions will be implemented at its site to assure the patients' safety.

- In case an increased risk due to progressive pandemic is foreseeable, patients should be invited to the study site early, regardless of the calculated visit date, to assure medication supply for the next 6 months.
- Study patients should be contacted by phone before a FU-visit, in order to clarify whether their state of health allows them to visit the study site without an increased risk to themselves or others.

If a personal FU-visit at the study site is possible:

- Examinations which are not relevant for the safety of the patient may be omitted to shorten the duration of the patient's stay at the site.
- To reduce the number of examinations, study medication may be dispensed based on patient records, consultation with the general practitioner or an interview with the patient.
- The study team shall adhere to local requirements and polices related to infection control for the pandemic.

In case of a lockdown or (self-)quarantine of study patients:

- FU-visits should be performed by phone with the focus on evaluation of any new adverse events as well as information necessary to determine safety aspects with regard to supply of the study drug.
- Study medication may be sent by taxi or courier after a FU-visit by phone. Date and time of dispatch as well as delivery to the patient has to be documented.
- Study patients with an implanted device with home monitoring capacity should be monitored remotely.
- Remote enrolment of study patients may be performed based on patient records and an interview with the patient. To reduce the number of assessments, examinations may be limited to those that are relevant for the patient's safety and the assignment of study medication.

Each action, especially deviations from the study protocol, needs to be documented for every patient affected.

10. Duration of Study Participation

10.1 Overall Duration of the Study

Screening and enrolment of patients is expected to be accomplished after 71 months. Based on the sample size estimation, it is expected that the required number of adjudicated / verified primary outcome events will be reached 12 months after enrolment of the last patient. Due to the time required to obtain follow-up information and to adjudicate events (about 3 months to perform a final study visit in all patients still in the trial plus 4 months for receiving SAE documents and adjudication by ERC to confirm that the required number of adjudicated endpoints have been reached), a total study duration of 71 + 12 + 3 + 4 = 90 months is expected. The total study duration of 90 months (about 7.5 years) was adapted based on an interim analysis.

Global end of study (EOS) is defined in Appendix II as the last Final Visit performed in a study patient. This date will be approved by the sponsor and announced by the CRO.

10.2 Duration of Study Participation for Individual Patients

Based on the sample size estimation, the expected mean follow-up time will be about 42 months per patient with a minimum follow-up time of 12 months and a maximum follow-up time of presumably 83 months until end of final visit after required number of endpoints has been reached. Every patient will be followed-up until global end of study. The exact duration of follow-up will be determined by the accrual of events (event-driven study).

11. Stopping and Discontinuation Criteria

When the study is terminated, the nature of termination will be documented (scheduled end/discontinuation with justification). Discontinuation of the study will be communicated in writing according to the legal requirement. The decision to stop the study will be reached jointly by the sponsor and the SC.

11.1 Discontinuation Criteria for the Study and Study Sites

Following a recommendation of the Data and Safety Monitoring Board (DSMB), the SC may decide discontinuation of the study due to efficacy criteria or adverse reactions in either study group. Discontinuation of the study can also be decided if patients cannot be recruited in sufficient numbers within a certain time period. Detailed criteria for a premature stopping of the entire trial based on safety concerns will be defined in the DSMB and SC charters.

Furthermore, the sponsor in collaboration with the international chief investigator has the right to close local study sites for enrolment of further patients if a major protocol violation occurs, if the site does not comply with the study protocol or decisions of the committees or the international chief investigator or if the site remains inactive for several months. Such decisions will always be taken on a case-by-case basis, but may be taken e.g. if the study procedures and study therapy is not delivered according to protocol and after reminders to adhere to the protocol from the study team.

11.2 Discontinuation Criteria for Patients

The investigator is not able to decide about the discontinuation of study participation of any patient. The investigator has only the option to discontinue study medication for compelling medical reasons. In this case, however, the patient will continue to be followed-up according to study protocol.

If a patient has been randomised but discontinued study participation prior to exposure to study medication, that patient will not be followed. Such patients will be replaced by enrolling other, additional patients.

Once a patient has been randomised and at least one dose of study medication was taken, but he/she discontinued study drug, the patient has to be followed according to study protocol (intention-to-treat) until global end of study.

The patients will be advised in the informed consent forms that they have the right to withdraw from study participation at any time without statement of reasons. However, the investigator should try to find out the reason for patient's withdrawal of consent and document these in the e-CRF.

In case, a protocol violation is noticed, the patient will remain in the intention-to-treat group and will be followed according to protocol.

Patients will be followed according to the study protocol irrespective of whether they experience any outcome event.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. The responsible investigator will take all acceptable measures to retrieve information on vital status of all patients enrolled in the trial.

12. Statistics

The main aim of the proposed study is to test the null hypothesis that the hazard rate, which is assumed to be constant during the study period, is identical in the two groups (usual care and NOAC).

Based on the stroke and death rates of published trials (MOST, ASSERT, Medtronic AT500 data set, SOS), an annualised rate of stroke, systemic embolism, or cardiovascular death of 5.3% in the control group is expected (details given in section 12.2).

12.1 Statistical Methods

The null hypothesis will be tested in a two-arm randomised trial in which patients are entered and then followed if either (a) a primary endpoint is observed or (b) the patient develops overt AF or (c) the observation period ends. Based on the sample size estimate, it is expected that patients will be accrued in a period of 71 months and followed up for the whole duration of study patient recruitment plus at least 12 months until the end of regular follow-up. The exact study duration will depend on the number of adjudicated primary outcome events.

12.1.1 Analysis of the primary outcome

The primary endpoint is the time from randomisation to the first occurrence of stroke, systemic embolism or cardiovascular death. Patients who develop overt AF during the trial period will be censored at that point in time but followed according to protocol until the global end of the trial. All other patients who will not reach the primary endpoint by the global end of the study will be censored at that time point. All randomised patients will be included in the analysis on a modified intention-to-treat-basis.

Cumulative incidence curves and corresponding p-values from competing risk analysis as well as tables with estimated (cause-specific) hazard ratios, confidence intervals, and corresponding p-values will be provided. The Cox-proportional hazards model will be used to estimate the (cause-specific) hazard ratio of edoxaban versus usual care.

12.1.2 Analysis of the secondary outcome

The following secondary endpoints will be analysed in the same way as the primary endpoint: time to components of primary outcome, time to major adverse cardiac events (MACEs), time to stroke or arterial embolism, time to major bleeding events.

Time to all-cause death will be analysed using Kaplan-Meier curves and corresponding p-values from the log-rank test as well as tables with estimated hazard ratios, confidence intervals, and corresponding p-values from a Cox-proportional hazards model.

12.1.3 Continuous secondary endpoints will be analysed as change from baseline using the baseline adjusted analysis of covariance (ANCOVA). Safety analysis

Safety data include adverse events as defined in section 8.1, primary safety endpoints, and data for other safety evaluations. Safety data will be collected on all enrolled patients (i.e. all patients that signed informed consent) in this study.

The primary safety outcome in this study is a composite of cardiovascular death, stroke, and systemic embolism which will be analysed using time-to-event methodology as described in section 12.1.1. Similar analyses and summary statistics will be provided for the components of this safety composite endpoint.

SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary in its actual version at the start of the study by Lowest Level Terms (LLT). Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). Comparisons between treatment groups will be made using Fisher's exact tests for the proportion of subjects with an AE (grouped under one preferred term). SAEs will be summarized by severity and relation to study treatment received.

12.1.4 Subgroup analysis

A list of subgroup criteria will be pre-specified in the statistical analysis plan.

12.2 Sample Size and Power Calculations

Estimation of stroke rates in the NOAH - AFNET 6 population. The table below gives the estimated annual event rates based on recently published trials. Taken together, this information forms the basis for the sample size estimation and for the risk assessment for individual patients enrolled into NOAH - AFNET 6.

	Stroke	Cardiovascular death	Sum
ASSERT (16), 261 pts, 2.5 yrs. FU	1.7	2.9	4.45
MOST (17), 160 pts, 2.25 yrs. FU	5	4.2	9.2
AT500 (28), 725 pts, 1.833 yrs. FU	3.6		
Botto et al (31), 223 pts., 1 yr. FU	3.2		
AVERROES ASA arm (3), 2791 pts, 1.1 yrs. FU	3.4	3.1	6.4
AVERROES and ACTIVE ASA arms pAF (37), 1576 pts, 1.1 yrs. FU	2.1	3.1	5.2
ROCKET-AF pAF patients (38), 2514 pts, 2.4 yrs. FU	1.7	3.5	4.9
SOS (32), 4287 pts, 2.17 yrs. FU	1.2		
Estimated event rate control (weighed by patient-years FU)	*1.9*	*3.3*	5.3

Table 3: Published annual stroke and cardiovascular death event rates in patients with documented AHRE. Event rates are split by stroke and cardiovascular death. The sum of these two components determines the estimate for the primary outcome. All events are rounded to one decimal after calculation.

Estimation of the safety of edoxaban in the NOAH - AFNET 6 population. The safety assessment for the NOAH - AFNET 6 trial participants is based on the favourable bleeding profile of a edoxaban 60 mg OD re-

gime compared to warfarin in the ENGAGE-TIMI 48 trial, combined with the observations made in BAFTA and AVERROES that acetylsalicylic acid does not cause more severe bleeding events or therapy discontinuation than warfarin (3, 6, 23). Thus, the risk for patients randomised to edoxaban seems very small. The safety assessment is in line with the observed small bleeding rates in the ENGAGE-TIMI 48 trial (Table 4).

Development of overt, diagnosed AF in patients with AHRE. Some patients with AHRE will develop overt, diagnosed AF during the follow-up time. As diagnosis of overt AF constitutes an indication for oral anticoagulation, these patients will be censored at the time of developing overt AF. In addition to expected event rates and the potential for event reduction, the sample size estimate recognises that these patients will be censored at this moment. Most of these patients will be additional to the expected attrition rate in this double blind randomised trial. Based on data published in the ASSERT study and in a small portion of the MOST trial population, 13-16% of patients with AHRE will develop overt AF over a follow up time of 2.5 years (16, 17). Based on the increased use of clinical ECG monitoring, e.g. by Holter ECGs, it is expected that this rate will be higher in the NOAH - AFNET 6 population.

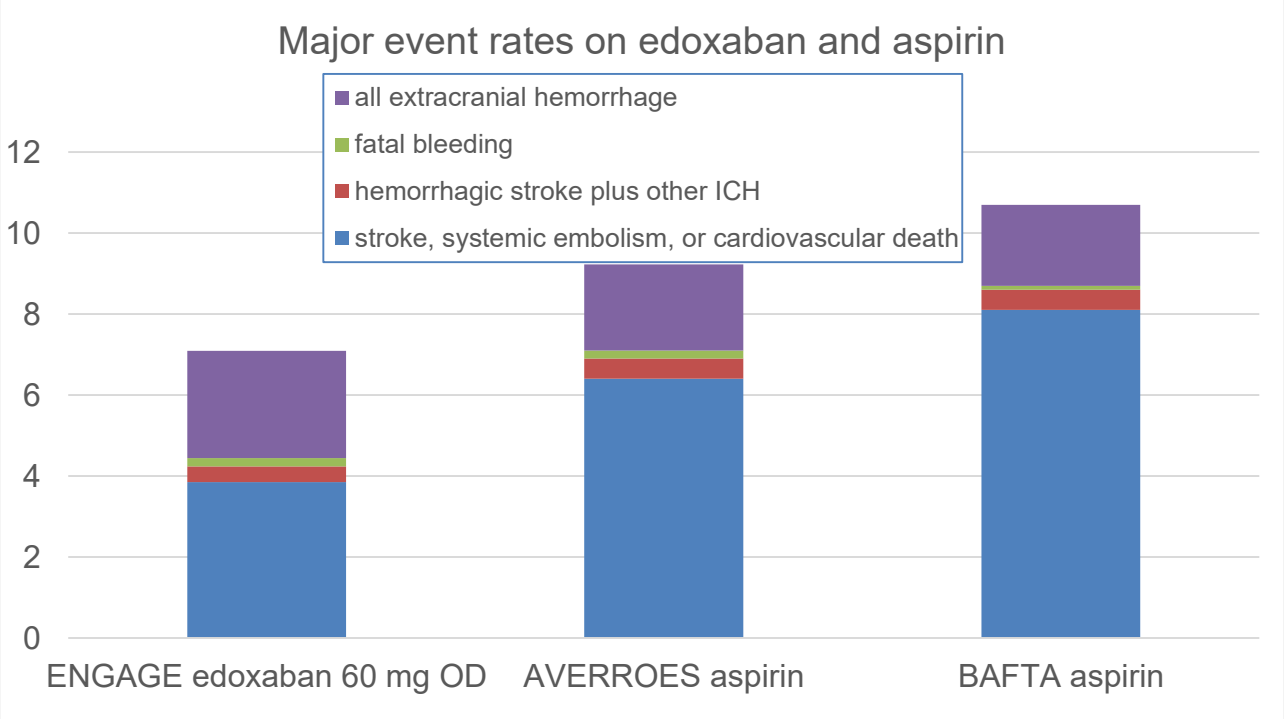

Figure 4

	stroke, systemic embolism, or cardiovascular death	fatal bleeding	hemorrhagic stroke plus other ICH	Major extracranial hemorrhage
ENGAGE edoxaban 60 mg OD dosing regime	3.85	0.20	0.39	2.65
AVERROES aspirin	6.40	0.20	0.50	*1.2**
BAFTA aspirin	8.10	0.10	0.50	2.00

Table 4

Figure 4 and corresponding Table 4
Major efficacy and safety annual event rates for patients randomised to edoxaban 60 mg OD in the ENGAGE-TIMI 48 trial compared to event rates reported in patients randomised to acetylsalicylic acid in the AVERROES and BAFTA trials (3, 6, 23). All events are given as annualised rates in percent.
*For the AVERROES acetylsalicylic acid group, only the AVERROES major bleeds are reported, although some of the “clinically relevant non-major bleeds” in AVERROES would have been classified as “major” in BAFTA and ENGAGE.

Estimation of the benefit of edoxaban in the NOAH - AFNET 6 population. Patients randomised to edoxaban will have a reduction in stroke or TIA rates by 2/3 (67%), (3, 39), and a 10% reduction in cardiovascular death. The effect estimate for stroke prevention is based on the effect size observed for stroke prevention with VKAs vs. acetylsalicylic acid, assuming that edoxaban is at least as effective as dose-adjusted warfarin in preventing strokes in AHRE patients (1, 33). This assumption discounts the fact that NOAH - AFNET 6 will compare the potentially more effective agent edoxaban to a control therapy that will consist of acetylsalicylic acid or placebo. The effect size for reduction in cardiovascular death is the point estimate of reduction in cardiovascular deaths observed in the four NOAC trials compared to warfarin. This conservative estimate is thus based on the assumption that the mortality benefit of edoxaban vs. usual care in NOAH - AFNET 6 is not bigger than the mortality benefit of edoxaban compared to dose-adjusted warfarin observed in ENGAGE-TIMI 48 and in the other three NOAC trials (34). These assumptions result in an estimated event rate of 0.64% per year for stroke and a 3% event rate for cardiovascular death. The event rate in the edoxaban group in NOAH - AFNET 6 (3.64% per year) is very similar to the observed event rate in patients enrolled in ENGAGE and randomised to edoxaban that match the NOAH - AFNET 6 inclusion criteria (3.45% per year, unpublished data provided by Daiichi Sankyo based on analysis of the ENGAGE data base).

Sample size. Based on these assumptions, computation of sample size is based on a hazard ratio of 0.68, accrual period of 71 months and minimal follow-up of 12 months. Specifically, it assumes annual hazard rates of 5.3% for the standard treatment group versus 3.64% for the NOAC group. This is equivalent to median event-free survival of 13 years for the standard treatment group versus 19 years for the NOAC group. This effect size is considered realistic, in the sense that an effect of this order of magnitude can be reasonably anticipated in this field of research.

The criterion for significance (alpha) is set at two tailed 5% and for power (1-beta) at 80%. Thus, if the true population hazard ratio of control to treated patients is 0.68 then at least 220 events are expected to be observed. Assuming that the competing event of non-cardiac death has a hazard rate of 0.02 for both groups then at least 865 patients per group are needed to have a power of 80% to detect as significant that difference at the two-sided 5% level of significance. Patients who develop overt AF during the trial period will be censored at that time point. The hazard of developing overt AF or of dropping out of the trial for other reasons (e.g. withdrawal of consent) is assumed to be at 0.287 throughout the trial. This 0.287 hazard is equivalent to 25% first year development of overt AF or of dropping out of the trial for other reasons, and goes up to 57% by the end of the third year. Taking this into account, the number of patients per group becomes 1,269 (63, 64, 65). This estimate is based on the assumption that 5% patients per year will decide to stop the study during the follow-up. In addition, it is expected that 16% of the patients will develop overt AF, and thus require oral anticoagulation outside of the trial, over a follow-up period of 2.5 years (based on ASSERT, 41/261 patients over 2.5 year follow-up) (16, 17). Thus, 2,538 patients have to be randomised and treated.

12.3 Interim Analysis and reassessment of the Sample Size

The Steering Committee assessed pooled event rates after about 1,000 patient-years of observation in the entire study population (without knowledge of study group assignment or study treatment). The event rate was 4.61% (95%-confidence interval: 3.46%, 6.16 %). This event rate is not significantly different to the assumed event rate of 4.4% per year (p=0.748). In this respect, the number of required events does not change. However, since the recruitment rate was lower than expected, the required accrual period changes from 54 to 71 months.

12.4 Patient Selection for Analyses

Under the mITT principle, all randomised patients with a qualifying AHRE (refer to section 6.2.4) and intake of at least one dose of study drug will be included in the primary analysis and censoring mechanism will be applied to those patients without event at the end of the study follow-up. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up. Patients without an event and who are lost to follow-up will be censored on the day of last contact with the patient. In addition, a sensitivity

(robustness) analysis will be conducted using per-protocol population (i.e., among those without major protocol violations).

Patients who develop overt AF during the trial period will be censored at that time point. The hazard of developing overt AF is assumed to remain constant and it is estimated at 0.287.

Safety analysis will be performed on all enrolled patients (i.e. all patients that signed informed consent) in this study.

13. Access to Source Data / Documents

13.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

13.2 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study.

In case of data that are result of patient reporting and will not be documented in clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation on paper.

13.3 Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

The investigator agrees that representatives or the designees of the sponsor such as monitors and auditors, and appropriate Regulatory Agencies will be given direct access to the regular clinical files of the patient.

14. Quality Control and Quality Assurance

14.1 Quality Control

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Initiation Visit

At each site an initiation visit will be performed by a representative of the CRO before enrolment of the first patient at this site.

14.3 Study Monitoring

A Risk Based Study Monitoring Plan (RBSMP) will establish the guidelines for conducting quality management (e. g. on-site monitoring visits, off-site central monitoring, and other tasks of quality control). The RBSMP will identify the requirement to perform an ongoing review of any e-CRF item (automated, by means of statistics and by research professionals, e. g. manual queries), the amount of source data verification and review, the frequency of on-site monitoring visits and actions to be taken based on the result of central and on-site monitoring. Thus, frequency of on-site visits and amount of source data verification is dynamic and dependent on performance and quality of each study site. Authorised, qualified representatives of the designated CRO will accomplish the monitoring of the study sites during the trial.

It is important that the investigator and relevant personnel are available during the monitoring visits and that an appropriate location and sufficient amount of time is devoted to the process. During the monitoring visit a PC with internet connection should be available to the monitor for direct connection to the internet database of the study and to all the data of the patients if stored in the data system of the hospital or catheter lab.

The main duty of the monitor is to help the sponsor and the investigator to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial. At regular intervals during the study, the local site will be contacted through monitoring visits, letters/ emails or telephone calls by a monitor to review the progress of the study.

14.4 Close Out Visit

Independent close out visits will be performed, primarily to collect study drugs. The close out visit may be combined with the last monitoring visit.

14.5 Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

The investigator should permit auditing by or on behalf of the sponsor and inspection by applicable regulatory authorities. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.5.1 Inspections

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and/or clinical research organisation facilities or at any other establishments deemed appropriate by the regulatory authorities.

14.5.2 Audits

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated Standard Operating Procedure (SOP), Good Clinical Practice (GCP) and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study.

15. Ethical and Legal Consideration

This is an investigator initiated (IIT), phase IIIb trial which meets all relevant ethical and regulatory standards (ICH-GCP). The trial will be conducted in accordance with the principles laid down in the Declaration of Helsinki in its version of October 2013 (Fortaleza) (Appendix IX).

Before initiating the study in each country, approval of the corresponding regulatory authority and Institutional Review Board/ Independent Ethics Committee (IRB / IEC) will be obtained.

15.1 Ethical Consideration

15.1.1 Institutional Review Board / Independent Ethics Committee

Provided this is not contradictory to national law, the local investigator is responsible for submitting an application to the appropriate IRB / IEC. Furthermore the local investigator is required to forward to the sponsor a copy of the written and dated approval or favourable opinion of the local IRB/ IEC signed by the chairman and including information on the composition of the IRB / IEC. The trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, investigator's CV, etc.) and the date of the review should be clearly stated on the written IRB/ IEC approval/ favourable opinion. The corresponding national coordinator together with the CRO will provide substantial support for any IRB / IEC submission. The sponsor is responsible to assure that approval of the local IRB / IEC in each country is obtained prior to study start in the respective study site or country in accordance with local requirements.

During the trial, any substantial modification to the clinical trial protocol will be submitted to the IRB / IEC. It will also be informed of any event likely to affect the safety of patients or the continued conduct of the trial, in particular of any change in safety.

If requested, a progress report is sent to the IRB / IEC annually and a summary of the trial's outcome at the end of the study.

15.1.2 Steering Committee

The trial Steering Committee (SC) will consist of a small group of expert cardiologists, a neurologist, and an expert biostatistician (refer to Appendix I). The functions of the SC are the following:

- Overall responsibility for the execution and scientific reporting of the trial.
- Advice on the scientific and clinical aspects of the study protocol and related documents.
- Responsibility for the conduct of the study according to the guidelines of good clinical practice (GCP) including the monitoring of patient recruitment.
- Reassessment of the sample size based on the blind review of the biostatistician.
- Reassessment of benefit/ risk ratio following the recommendations of the DSMB.
- Decisions on continuation or termination of the study based on the recommendations of the DSMB.

A SC charter providing operating procedures and responsibilities will be discussed and enacted at the latest during the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings. Minutes of each meeting will be provided.

15.1.3 Endpoint Review Committee

The Endpoint Review Committee (ERC) will consist of four experts in cardiology and stroke neurology. The committee will centrally adjudicate all primary outcome events as well as any hospitalisation for other reason and any other SAE. Adjudication will primarily be performed as a continuous online-process within the e-trial management system, depending on the number of documented and cleaned SAEs. If needed, additional

meetings may be performed, either face-to-face or conference calls. Minutes of each meeting will be provided.

An ERC charter providing operating procedures and responsibilities will be discussed and enacted latest at the kick-off meeting prior to start of adjudication.

15.1.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the SC and study investigators. It will consist of one statistician and two clinicians with expertise in clinical trials and in the management of patients in the scope of the study. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. They regularly monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the SAEs and further AEs selected to their discretion during the course of the trial. DSMB will perform unblinded interim analyses following a plan set out in the DSMB charter, and give recommendations to the SC to continue or stop the trial. The Haybittle-Peto boundary (40, 41) will be implemented as stopping rule guidance for the DSMB.

A DSMB charter providing operating procedures and responsibilities will be kept as a separate document and discussed and enacted latest at the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings and may have an open part with guests and a closed part. Minutes of each meeting will be provided. After each meeting, recommendations will be given to the SC in a written form.

15.1.5 National coordinators

National coordinators are selected experts that support submission to the competent authorities and IRB/IEC in their individual countries. The national coordinators provide their expertise regarding regulatory affairs in their countries. The national coordinators supervise and monitor the patient recruitment, and support recruitment measures on a national level. A national coordinator can also be a member of the SC.

15.2 Legal Consideration

The study will be notified to the competent authority of each participating country and approval obtained prior to study start in the respective country. Submission to relevant regulatory authorities in all participating countries lies within the sponsor’s responsibility (if not required otherwise according to country specific requirements). The corresponding national coordinator will provide substantial support for any submission process. The study will be performed in accordance with the respective national legislation in each country.

15.3 Modification of Protocol

Any substantial modification to the clinical trial protocol requires written approval/favourable opinion by the IRB / IEC prior to its implementation, unless there are overriding safety reasons that require immediate action. In some instances, a modification may require a change to the informed consent form. In this case, the investigator must receive an IRB /IEC approval/favourable opinion concerning the revised informed consent form prior to implementation of the change.

Substantial modifications will be notified to the competent authorities too.

15.4 Financing and Insurance

The costs necessary to perform the study will be agreed upon with each investigator and will be documented in a separate financial agreement which will be signed by the investigator and the CRO on behalf of the sponsor, prior to the study commencing.

A patient insurance has been effected by the sponsor of the trial. Country specific requirements will be taken into account.

The insurance certificate as well as the insurance conditions will be handed out to all investigators. On demand, the insurance conditions have to be provided to the patients.

15.5 Investigators' Information on IMP

Edoxaban as well as acetylsalicylic acid are authority approved and marketed in all European countries. The respective summary of product characteristics is publicly available in the internet.

15.6 Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO.

The investigating physicians shall take care that patient documents (e.g. copies of reports on special findings) transmitted to the CRO or the sponsor contain no names, but only the year of birth and a relevant patient number. The storage of data for statistical analysis shall likewise be performed only under the patient's random/study number.

15.7 Data Handling and Record Keeping

15.7.1 Completion of case report forms

All medical data in this trial are to be recorded directly in the e-CRFs. Documentation on paper will be restricted to exceptional circumstances only.

The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

15.7.2 Archiving

The investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator has to retain the study documents (i.e. investigator site file) after the completion or discontinuation of the study for the time period as required by national legislation. This especially applies to patients' signed informed consent forms and the patient identification list.

The investigator must notify the sponsor prior to destroying any essential study documents within the specified period following completion or discontinuation of the trial.

15.8 Confidentiality

All information disclosed or provided by the sponsor (or any company / institution acting on his behalf), or produced during the trial, including, but not limited to, the clinical trial protocol, the e-CRFs and the results obtained during the course of the trial, is confidential. The investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor. The sub-investigators shall be bound by the same obligation as the investigator. The investigator shall inform the sub-investigators of the confidential nature of the trial. Both, the investigator and the sub-investigators shall use the information solely for the purposes of the trial, to the exclusion of any use for their own or for a third party's account.

15.9 Responsibilities

The sponsor of this trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the trial with regard to ethical aspects, clinical trial protocol compliance, integrity and validity of the data recording.

16. Final Report and Publication Policy, Property Rights

The sponsor will be responsible for preparing the final study report that is to be signed by the SC. The sponsor will communicate the results of the trial to the investigators, authorities and IRBs/ECs.

The SC will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study within a timely fashion after completion of the study. All analyses will be the responsibility of the SC. Manuscripts for publication will be drafted by members of the SC or other interested investigators. All manuscripts will be subject to coordinated submission and review prior to submission. Coordination will be done by SC.

NOAH - AFNET 6 is an investigator-driven trial. Interested investigators and academic initiatives will be encouraged and supported as appropriate if they propose additional issues that may be studied within the main trial. These materials must be submitted to the SC for review and comment prior to publication or public dissemination. All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met.

The publication rules are regulated separately and described in detail in a publication policy that is confirmed by the SC.

All information and documents provided by the sponsor or its representatives are and remain the sole property of the sponsor. The investigator shall not mention any information for any other intellectual property rights.

All results, data, documents and inventions, which arise directly or indirectly from the trial in any form, shall be the immediate and exclusive property of the sponsor.

17. Definitions and Classification

17.1 Protocol Violation

Protocol violations are any unapproved changes, deviations or departures from the study design or procedures of a research project that are under the investigator’s control and that have not been reviewed and approved by the SC.

17.2 Major Protocol Violation

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator’s control and not in accordance with the IRB- or EC-approved protocol that may affect the participant’s rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Patients with major protocol violations will be excluded from the per protocol analysis. Some major protocol violations may be reported to regulatory authorities within defined time periods as mandated. Study specific definitions of major protocol violations will be given by the SC.

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19. Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol, with the current EU regulation, with the principles of good clinical practice, and in accordance with the Declaration of Helsinki.

Date	**Signature**
_____	_____ Melanie Calvert
_____	_____ John Camm
_____	_____ Gregory Chlouverakis (study statistician)
_____	_____ Hans-Christoph Diener
_____	_____ Andreas Götte (sponsor representative)
_____	_____ Paulus Kirchhof (international chief investigator)
_____	_____ Gregory Lip
_____	_____ Emmanuel Simantirakis
_____	_____ Panos Vardas
_____	_____ Antonia Zapf (study statistician)
_____	_____ Signature principle investigator
	_____ (Name principle investigator; printed)

Appendix I: Members of the Steering Committee

(in alphabetical order)

Melanie Calvert
PROM and patient experience expert
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Appendix II: Time Schedule

FPI depends on release of study drugs; FPI estimated late in 1st quarter 2016.

	Tasks	**Date**
Draft study planning	Draft Protocol, review and finalisation by Steering Committee	December 2014
Availability of study drug	Market authorisation of edoxaban within the EU	25.06.2015
Final study planning	Final protocol	January 2015
Study preparation	Definition of study drug types and supply procedures	December 2015
	Set up of the e-trial management system, preparation of e-CRF; preparation of all other study relevant documentation	October 2015 - January 2016
	Site selection, site contacts, site evaluation	November 2015 - November 2020
	Initial EC and CA submission in each participating country	January 2016- July 2020
Study initiation	Site contracting	January 2016 - December 2020
	Supply of the sites with study materials, initiation visits	May 2016 - December 2020
	Recruitment period (FPI to LPI)	June 2016 - April 2022
Study duration*	Treatment and follow-up until all necessary primary endpoints have been reached	May 2022 – April 2023
	Treatment and follow-up until last patient last visit (global end of study)	May 2023 – July 2023
	Mean follow-up period of all patients, assuming a linear patient recruitment	42 months (minimum 12 months, maximum presumably 83 months)
Interim analysis	Assessment of pooled event rates after 1,000 patient-years of observation in the entire study population, alternatively 24 months after enrolment of the first patient	Q4 2019
Results	Primary EP Analysis acc. to SAP	Q4 2023
	Submission of primary result paper for publication	Q4 2023

*NOAH – AFNET 6 is an event driven trial. The total study duration may therefore be longer or shorter than the estimates given here.

Definition of terms

- **Patient's Start Of Participation (PSOP)**
  - Date informed consent signed
- **Patient's Start Of Study (PSOS)**
  - Date and time of randomisation.
- **Patient's Start Of Treatment (PSOT)**
  - Date and time of intake of first dose of study medication.
- **Primary Endpoint Database Lock (PEDBL), global end of regular follow-up**
  - First date when the number of needed valid primary first endpoints has been verified. This date will be approved by sponsor. An endpoint is verified as valid primary endpoint after ERC assessment, only. The verification of a valid primary endpoint as first primary endpoint in a patient is performed by means of statistics.
- **Last Visit, termination of study medication in each patient before global end of study**
  - Final Visit of each study patient after end of regular follow-up to be performed in all patients still in follow-up at the time of PEDBL.
- **Extended Reporting Period (ERP)**
  - Period after each individual Final Visit until global EOS for reporting of AEs after termination of study medication.
- **Last Patient Last Visit (LPLV), global End Of Study (EOS)**
  - LPLV is the last Final Visit performed in a study patient, equivalent to global End Of Study (EOS). This date will be approved by sponsor.
- **Final Database Lock (FDBL)**
  - After EOS, final data cleaning and last ERC assessment. This date will be approved by sponsor.
- **Notification of EOS to regulatory bodies**
  - Within 90 days after EOS this event has to be notified to all involved regulatory bodies. This date will be approved by sponsor.
- **Study Closure**
  - Date of all contracts closed and all administrative procedures finished.
- **Final Report**
  - Within one year after EOS a final report according to applicable international standards has to be provided to all involved regulatory bodies.

Appendix III: Definition of primary outcome events

Stroke comprises ischemic strokes as defined by the FDA (any stroke associated with a 4 point or greater increase in the NIHSS score at the time of the stroke compared to baseline) and includes ischemic infarction with (transient) clinical symptoms that resolve completely within 24 hours, but have a matching lesion on brain imaging as well as ischemic infarction interrupted by death within 24 hours. In contrast to the FDA definition, subarachnoid haemorrhage and haemorrhagic stroke are not counted as stroke in this trial but as major bleeding event.

Systemic embolism will be defined as an acute vascular occlusion of an extremity or organ not occurring in the central nervous system, documented by means of imaging, surgery, or autopsy.

Cardiovascular death will be defined according to the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials developed by the Standardized Data Collection for Cardiovascular Trials Initiative (35):

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular procedures, death due to cardiovascular haemorrhage, and death due to other cardiovascular causes.

- Death due to acute MI refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the MI, it will be considered a death due to MI.
- Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (24) or by autopsy findings showing recent MI or recent coronary thrombosis.
- Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.
- Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a cardiovascular investigation/ procedure/ operation should be considered as a death due to a cardiovascular procedure.
- Sudden cardiac death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
  - Death witnessed and occurring without new or worsening symptoms
  - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
  - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on review of recordings obtained by an implanted device (e.g. a defibrillator, pacemaker, or ECG recorder)
  - Death after unsuccessful resuscitation from cardiac arrest
  - Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac aetiology
  - Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available).
  - General considerations regarding sudden cardiac death
    Unless additional information suggests an alternate specific cause of death (e.g., death due to

other cardiovascular causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

- Death due to HF refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF aetiology. Deaths due to HF can have various aetiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
- Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
- Death due to cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure.
- Death due to cardiovascular haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.
- Death due to other cardiovascular causes refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Appendix IV: International Society on Thrombosis and Haemostasis (ISTH) Bleeding Definitions

Major Bleeding in Non-Surgical Patients (60)

1. Fatal bleeding.

and/or

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

and/or

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

Major Bleeding in Surgical Patients (61)

1. Fatal bleeding.

and/or

2. Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon.

and/or

3. Extrasurgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding.

and/or

4. Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalisation or a deep wound infection.

and/or

5. Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.
6. The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period (in case of unequal active treatment durations).
7. The population is those who have received at least one dose of the study drug.

Appendix V: Definition of overt AF

According to the definition as per ESC guidelines, AF is defined as a cardiac arrhythmia with the following characteristics:

1. The surface ECG shows ‘absolutely’ irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.
2. There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
3. The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).

An irregular pulse should always raise the suspicion of AF, but a surface ECG recording is necessary to diagnose AF. Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 s on a rhythm strip, should be considered as AF.

Within the context of NOAH - AFNET 6, an intracardiac ECG recording is not considered sufficient to prove occurrence of overt AF.

Appendix VI: Change management of anticoagulants at discontinuation of study drug

Hein Heidbuchel, Peter Verhamme, Marco Alings, Matthias Antz, Hans-Christoph Diener, Werner Hacke, Jonas Oldgren, Peter Sinnaeve, A. John Camm, and Paulus Kirchhof
Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace doi:10.1093/europace/euv309

(separate document)

Appendix VII: ESC guidelines 2010

(A. John Camm (Chairperson) (UK), Paulus Kirchhof (Germany), Gregory Y.H. Lip (UK), Ulrich Schotten (The Netherlands), Irene Savelieva (UK), Sabine Ernst (UK), Isabelle C. Van Gelder (The Netherlands), Nawwar Al-Attar (France), Gerhard Hindricks (Germany), Bernard Prendergast (UK), Hein Heidbuchel (Belgium), Ottavio Alfieri (Italy), Annalisa Angelini (Italy), Dan Atar (Norway), Paolo Colonna (Italy), Raffaele De Caterina (Italy), Johan De Sutter (Belgium), Andreas Goette (Germany), Bulent Gorenek (Turkey), Magnus Heldal (Norway), Stefan H. Hohloser (Germany), Philippe Kolh (Belgium), Jean-Yves Le Heuzey (France), Piotr Ponikowski (Poland), Frans H. Rutten (The Netherlands). Guidelines for the management of atrial fibrillation. European Heart Journal (2010)

(separate document)

Appendix VIII: Suggestions for optimal programming of devices for adequate detection of AHRE

The following section outlines adequate settings of devices for correct identification of AHRE episodes in patients who are potentially eligible for NOAH - AFNET 6:

- The intracardiac electrogram (IEGM) storage should be activated while the atrial tachycardia detection rate must be set to 170 bpm. Episodes at lower atrial rates are not qualifying episodes for NOAH - AFNET 6. Higher rate thresholds are acceptable, but may miss some episodes that would make patients eligible for NOAH - AFNET 6. Although false atrial tachyarrhythmia detection due to repetitive non-reentrant ventriculo-atrial synchrony is rare for episodes greater than 6 minutes in duration, this phenomenon can be diagnosed by checking the stored IEGMs and can be eliminated by avoiding very long programmed AV delays and/or by increasing the postventricular atrial refractory period.
- For pacemakers and implantable cardioverter-defibrillators (ICDs) with programmable atrial electrogram configuration, the later should be programmed Atip-Aring, in order to avoid noise detection and the use of short tip-to-ring spacing atrial leads (<10 mm) is strongly recommended.
- Finally the devices should be optimally programmed according to the individual patient and to the most recent practice guidelines (25, 26, 27), ensuring as far as possible optimum hemodynamic and avoiding unnecessary ventricular pacing.

Cardiac rhythm management (CRM) device manufacturers use different detection algorithms and settings for the most accurate device diagnostics and EGM recordings. In general two different technologies have been employed: 1. Mode switch based and 2. Rate and pattern based.

1. **Mode switch (MS) based AHRE detection** is very common in many pacemakers and defibrillators manufactured by different companies.
   a) **Medtronic** employs this technology for all CRM devices: In detail the nominal setting for mode switch is set at 185 bpm and IEGM recording is set nominally "on" for atrial high rate and ventricular high rate episodes. In the case the device is programmed with mode switch "off", the device can still detect and record AHRE by programming
   Data Collection Setup => AHRE => Detection Rate (Nominal 200 bpm) and Detection Duration (Nominal 5 sec) which can be programmed up to 60 sec.
   b) **Vitatron CRM** devices implanted after 2010 follow the same programming nominal values and recommendations as Medtronic (see above).
   c) **St Jude Medical** CRM devices also use mode switch triggered detection (nominally set at 180 bpm) and in the case that mode switch is turned "off" the device can use the high atrial rate setting for a consecutive number of cycles that the rate is exceeded. As they are both nominally "off", they should be activated. The IEGM recording is nominally "off" and must be programmed "on" (AT/AF detection trigger). St Jude Medical defibrillators follow the same AHRE detection method, however, they must have mode switch "on".
   d) **Boston Scientific** pacemakers and defibrillators use the same method (mode switch based) for detecting AHRE. Mode switch is nominally "on" and nominal values for trigger rate is nominally set at 170 bpm, mode switch duration at 8 cardiac cycles and entry and exit count at 8 cardiac cycles as well. IEGM recording is nominally "on".
   e) **Biotronik** uses both mode switch and rate based detection triggers of AHRE nominally set "on" with cut-off rates at 160 and 200 bpm, respectively. IEGM recording is nominally "on".
   f) **Sorin Group** CRM devices also use both mode switch and atrial burst-based detection triggers for AHRE detection and recording. IEGMs are always set to "on".
2. **Rate and pattern based detection** is mainly employed by Medtronic ICD devices and latest technology CRM devices: Both types of devices monitor the sequence of events in the atrial and ventricular channel and combine with exceeding a programmed threshold of atrial rate. This monitoring is nominally "on", the threshold is nominally set at 171 bpm and IEGM recording is always "on".

Appendix IX: Declaration of Helsinki (Version Fortaleza, October 2013)

http://www.wma.net/en/30publications/10policies/b3/