EUROBservational Research Programme

Atrial Fibrillation III (AF III) Registry

Protocol

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Protocol History

Changes in the protocol appendices will not be subject to protocol amendments, in particular the lists of the members of the registry committees, as these are subject to potential change. The functions represented in the committees will however not change.

Protocol Version	Protocol Version Date	Amended Pages	Changes

List of Abbreviations

Abbreviation	Definition
AF	Atrial Fibrillation
CHA2DS2-VASC	C=Congestive heart failure (1) H=Hypertension — high blood pressure (1) A=Age≥75 (1) D=Diabetes mellitus (1) S2=Stroke or TIA (transient ischemic attack, called a mini-stroke) (2) V=Vascular disease — coronary artery disease:CAD, myocardial infarction:heart attack, peripheral artery disease : PAD, or aortic plaque (1) A=Age 65-74 (1) Sc=Sex category — Female gender (1)
HAS-BLED	H=Hypertension A=Abnormal renal and liver function S=Stroke B=Bleeding L=Labile INRs E=Elderly (>65 years) D=Drugs or alcohol
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AFNET	German Atrial Fibrillation Competence NETwork
CRF/eCRF	Case Report Form/electronic Case Report Form
ECG	Electrocardiogram
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
EuroQoL, EQ-5D-5L	Quality of life assessment by the EuroQol Group
GARFIELD	Global Anticoagulant Registry in the FIELD
GLORIA™-AF	Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients With Atrial Fibrillation (Boehringer Ingelheim)
RACE-2	Rate Control Efficacy in Permanent Atrial Fibrillation
Record-AF	RECORD AF Registry
Calculation of the SAMe-TT2R2 score	S: Sex (female) 1 A: Age (<60 years) 1

	Me	Medical history*	1
	T	Treatment (interacting drugs, e.g., amiodarone)	1
	T	Tobacco use (within 2 years)	2
	R	Race (non-Caucasian)	2
	Max. points		8
	*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.		

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1. Background and Rationale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting approximately 2% of the general adult population. A systematic review of 184 worldwide population-based studies estimated that in 2010 the number of individuals with AF was 33.5 million[1], but the global prevalence of AF is probably underestimated due to limited data outside Europe and North America and 'subclinical' undiagnosed AF cases[1,2]. In Europe, over six million individuals suffer from AF, and its prevalence is estimated to at least double in the next 50 years as the population ages.

AF is associated with a significant morbidity and mortality, particularly from an increased risk of stroke and thromboembolism, heart failure and impaired quality of life, and represents a global health problem. The arrhythmia may have various clinical presentations, including a devastating stroke as the first clinical manifestation of otherwise asymptomatic AF[2,3]. Management strategies for thromboprophylaxis[2,4], rate or rhythm control[5,6] and the management of concomitant morbidity[7] in AF patients have been rapidly developing over the last 15 years[8-10]. In addition, an increasing body of evidence supports the importance of active screening for AF[11], in order to detect asymptomatic AF and initiate appropriate treatment, including oral anticoagulant (OAC) therapy for thromboprophylaxis in most AF patients[9,10].

Stroke prevention has greatly improved, with better management of vitamin K antagonist therapy (VKAs) and increasing uptake of non-vitamin K antagonist oral anticoagulants (NOACs) in clinical practice. The approach to rate control has also become more symptom-directed, given recent trials such as RACE-2[12], and whether patients with recent-onset AF would benefit from an early, aggressive rhythm control[13] including AF ablation[14] is currently being investigated. In previously completed large trials showing non-inferiority of rate vs. pharmacological rhythm control strategy, some benefits for symptomatic and functional improvement have been observed with rhythm control and one posthoc analysis from the AFFIRM trial reported a benefit of sinus rhythm and warfarin, but this was offset by an increased mortality with antiarrhythmic drugs and digoxin[15]. Management of cardiovascular risk factors, various comorbidities and underlying structural heart disease, as well as the counselling and support for appropriate lifestyle changes, are also important components of the holistic approach to AF management[10].

Certain ethnic differences in the risk for incident AF, patients' thromboembolic risk profile, safety of VKAs and availability of various AF treatments have been well described. Multiple community-based and other studies consistently show higher AF prevalence in Caucasians compared to other ethnicities16-18.

Available data suggest that Caucasians with AF might be less vulnerable to AF-associated cardiovascular morbidity and mortality compared with non-white ethnic groups19. However, the rates of AF-associated outcomes were similar among white, black and Hispanic AF patients in the ORBIT-AF registry, suggesting that AF treatment may attenuate ethnicity-related differences in outcomes20.

Recent data consistently show higher annual risk of ischemic stroke in Asian AF patients compared with non-Asians, both in non-anticoagulated21,22 and anticoagulated patients23-26. The use of VKAs in Asian patients is challenging, due to increased risk of bleeding and stroke compared with non-Asians, and the maintenance of therapeutic anticoagulation may be more difficult27,28. NOACs in standard doses were more effective and safer in Asians than in non-Asian AF patients, whilst low-dose NOACs had comparable effects in both populations29.

Compared to Caucasians, African-Americans are less likely to receive VKAs, require higher warfarin doses to maintain therapeutic anticoagulation30 and have greater risk of intracranial haemorrhage than Caucasians31. Data from landmark NOACs trials are limited with this regard, since <2% of participants

were African-Americans. The relevance of ethnicity has been encountered in the SAMe-TT2R2 score which is used to identify patients who would do well on VKAs32.

African-American and Hispanic patients are more often treated by rate control compared with Caucasians and are less likely to undergo AF catheter ablation33. In a subgroup analysis of the AFFIRM trial, 5-year survival of Hispanics and whites was higher in the rate-control arm, whilst blacks had similar survival in both rate- and rhythm control arm34. Data on ethnic differences in AF-related quality of life and cognitive impairment are lacking.

Management of AF may be challenging in clinical practice, requiring a multidisciplinary approach, referral to a specialized AF Heart Team and active patient involvement with informed, shared decision making. The latest European Society of Cardiology (ESC) Guidelines on AF management, issued in 2016, recommend such integrated AF care and provide evidence-based guidance on screening, risk assessment and treatment of AF patients[10].

The need for a new registry of AF clinical practice in Europe

Guideline-adherent therapy of AF has been shown to improve outcomes[35,36], but the management of patients with AF in clinical practice sometimes may differ from evidence-based recommendations. To assess the management of AF in clinical practice, the concept of systematic collection of contemporary data regarding the management and treatment of AF in the member ESC countries was conceived more than 15 years ago.

The first European registry of AF management was undertaken during 2003-2004, as part of the Euro Heart Survey (EHS) programme[37] . The EHS clearly showed great heterogeneity in the management of patients with AF, with major implications for outcomes, especially stroke prevention[37,38], and it was used to derive new stroke and bleeding risk assessment tools (the CHA2DS2-VASc and HAS-BLED scores, respectively) for use in the European guidelines, based on these important European data[39,40].

Many other analyses from the EHS on AF have been published, including data on healthcare costs of AF in Europe[41] , thus making important contributions to our knowledge and understanding of this common arrhythmia[42-44].

The EHS on AF was followed by a highly successful EORP-AF programme, with the Pilot and Long-Term General Registry – both with a cohort design. The EORP-AF Pilot General Registry provided additional contemporary insights into AF management in Europe[45-58] and showed how guideline adherent therapy based on the 2012 ESC guidelines was associated with a significant reduction in adverse outcomes[52]. The EORP-AF Long-Term General Registry has completed the patient enrolment phase, which started in 2014, and is now collecting the 1-year and 2-year follow-up data.

Following the experience of the ESC-AF Pilot, conducted in 9 ESC countries, enrolling more than 3000 patients, the ESC-AF Long-Term Registry, a prospective, multicentre, observational study of patients presenting to Cardiology Centres in European and Mediterranean countries, will prospectively collect data from a sample of hospitals of different levels of complexity from which patients were recruited. It focused on capturing a broad spectrum of cardiology and AF speciality units regularly following outpatients with AF and admitting patients with acute, pre-existing or new onset AF thus building-up a network of centres representative of European real world clinical practice.

In 2016, the ESC published new guidelines on the management of AF[10]. A new 1-year survey under the EORP programme would enable a timely assessment of the uptake and implementation of these new ESC guidelines in clinical practice, and would inform us about outcomes related to contemporary guideline-

adherent management of AF. The assessment of adherence to guidelines will allow for targeted education programmes in order to improve practices ("virtuous circle"). The design and protocol would be broadly similar with the previous protocol for the EHS-AF and EORP-AF Long-Term General AF Registry and compatible with other EORP programmes, in order to allow comparability of datasets, as well as additional modelling information on time trends, modelling of prevalence/incidence, cost and health economics, etc. This dataset could also be compared to published data from other recent AF surveys or registries (some funded by industry, some still ongoing) in Europe, such as AFNET, Record-AF, GARFIELD, GLORIA™-AF and others.

2. Objectives

2.1. The general objectives

The general objectives of the EORP Registry on AF guidelines implementation in clinical practice are summarized as follows:

- Identification of contemporary patterns in AF management in practice, assessment of their compliance with the ESC AF Guidelines 2016 and identification of major gaps in the Guidelines implementation in clinical practice in order to facilitate their implementation in daily management of AF patients.
- Characterisation of the clinical practice settings associated with good versus poor AF Guidelines implementation.
- Assessment and comparison of the outcome of guideline-adherent versus guideline non-adherent management strategies.

2.2. The specific objectives

The specific objectives of the EORP-AF guideline implementation registry are to:

- Assess whether (and how often) active screening (opportunistic or systematic) is used to detect AF in daily practice.
- Assess the modalities of AF documentation triggering AF treatment in clinical practice (that is, whether only the guideline-recommended electrocardiographic documentation of AF lasting at least 30 seconds triggers AF treatment in clinical practice, or alternative methods such as the handheld devices, apps using pletismography, pulse palpation, etc. are also considered diagnostic of AF).
- Assess whether the diagnostic work-up of AF patients complies with current 2016 ESC guidelines on AF.
- Evaluate appropriateness of treatment in AF patients in relation to the current 2016 ESC guidelines on AF, as well as the most recent guidelines on other cardiovascular diseases and cardiovascular disease prevention.
- Evaluate the use of oral anticoagulation therapies (that is, the Vitamin K antagonists, oral direct thrombin inhibitors or oral Factor Xa inhibitors), or non-pharmacological therapies (that is, the left atrial appendage occlusion/exclusion) for the prevention of AF-related thromboembolic events and assess the factors driving a particular choice.
- Assess the use of various antiarrhythmic therapies, including catheter ablation and assess the factors driving a particular choice.
- Evaluate the use of an integrated approach to AF management in clinical practice, including patient education, support, involvement in shared decision making, the use of technology tools for information on AF, communication and clinical decision support tools, as well as the engagement of multidisciplinary teams and/or AF Heart Team in AF management in daily practice.
- Obtain contemporary information on the occurrence of major adverse cardiovascular and cerebrovascular events in AF patients.
- Evaluate mortality and other outcomes in relation to therapeutic decisions including adherence to guidelines in the registry cohort at 1 year.

- Allow comparisons with the dataset from the previous EHS and EORP AF Long Term registries, to allow additional modelling information on time trends, modelling of prevalence/ incidence, costs, healthcare utilisation and health economics, in the European population.
- Assess progression of AF from paroxysmal (self-terminating) to persistent (non-self-terminating) AF and the impact of validated and less well-established risk factors for progression of AF, including duration of history of associated diseases, blood pressure, Body Mass Index (BMI), kidney function, Brain Natriuretic Peptide (BNP) levels and pulmonary disease.
- Evaluate changes in the quality of life at baseline and at the 12-month follow-up visit, using a QoL Questionnaire (EuroQoL EQ-5D-5L).
- Evaluate the epidemiology and risk profiles of patients, as well as the rates of outcome events in each of the main ethnic groups (if the size of the sub-population allows these analyses).
- Evaluate the influence of ethnicity on INR for patients on VKA for subsequent events.

2.3. Aims for immediate analysis:

1. Analysis of the frequency of a complete diagnostic work-up concerning:
    a. Screening for AF
    b. Documentation of AF
    c. Underlying heart disease
    d. Other possible associated conditions
    e. Clinical type of AF
    f. Individual patient risk profile assessment
    g. Consequences of AF
2. Analysis of the frequency of guideline-adherent use of:
    a. Anti-thrombotic treatment
    b. Rate control measures
    c. Drugs in pharmacological cardioversion
    d. Electrical cardioversion
    e. AF ablation
    f. Therapies for maintenance of sinus rhythm
    g. Comprehensiveness of management of associated cardiovascular disease (particularly focusing on hypertension and coronary artery disease and systolic heart failure).
3. Analysis of the relationship between the management of AF and morbidity/mortality at 1 year.

In addition, the registry will in itself contribute to the awareness of the new ESC guidelines by asking questions about the topics covered in the guidelines.

This registry is non-interventional and no additional examinations are requested from the investigators than those usually performed in standard practice.

3. Study Design and Methods

The ESC AF III registry is an international, prospective, longitudinal multicentre, observational study in European countries.

Recruitment will be performed in a consecutive manner. To facilitate consecutive enrolment, all consenting patients who meet the eligibility criteria will be admitted to the study during a period of 3-month recruitment in each centre, without any limit to the maximum number of patients included.

A follow-up survey at one year will allow evaluation of long-term morbidity/mortality (hospitalisations, therapy changes, etc.) and will also allow comparison between outcomes in European regions with different patterns of practice. Follow-up would be by patient visit and/or chart review and/or telephone follow-up via patient or their general practitioner (again, depending on the healthcare system).

During the course of the survey patients will be followed up according to the usual practice of the centres.

Standard management of patients currently performed in routine clinical practice will be followed. Drug prescriptions and indications to perform diagnostic/therapeutic procedures will be completely left to the participating cardiologists.

No specific protocols or recommendations for evaluation, management, and/or treatment will be put forth during this observational study.

4. Selection of Population

The registry will assess the implementation of 2016 ESC Guidelines on AF management in the contemporary diagnosis and management of patients with AF amongst cardiologists in Europe at the time of enrolment, also providing important information on events/management changes and major outcomes at 1 year.

The screened population will consist of patients presenting with atrial fibrillation, who are hospitalised in medical or surgical cardiology departments in the participating hospitals or who are seen in an outpatient setting (medical centre, e.g. private cardiology practice). All AF patients admitted for catheter ablation, initiation of drug therapy, or cardioversion (electrical or pharmacological) can be included. Also, patients visiting emergency or assessment units will be included, if they are under the care of a cardiologist.

The registry population will comprise consecutive in- and out-patients with AF presenting to cardiologists in participating ESC countries.

Consecutive patients will be screened at the time of their presentation to a study centre, and potential patients will be approached to obtain written informed consent. Patients with the primary or secondary diagnosis of AF will be included.

Only patients in whom a 1-year follow-up by the enrolling physician is deemed feasible should be recruited, either with a visit or by telephone.

Patients will be officially enrolled in the EORP-AF only if diagnosis of AF has been formally noted or confirmed in the patient's medical record. The qualifying visit or hospitalization for confirmed AF diagnosis should have occurred within the last year, and the patient need not be in AF at the time of enrolment.

4.1. Inclusion Criteria

- Patients diagnosed with AF will be enrolled in the study only if AF has been electrocardiographically documented or diagnosis of AF has been formally noted in the patient's medical record within the last 12 months or at baseline.
- The qualifying visit or hospitalisation for AF should have occurred within one year before the date of baseline, or at baseline.
- AF is the primary or secondary diagnosis, i.e. the current admission / visit may be due to other reasons.
- Patients need not be in AF at the time of enrolment.
- Signed Patient Informed Consent is mandatory.

4.2. Exclusion Criteria

- Only atrial flutter recorded.
- The qualifying episode of AF occurred more than one year before the date of baseline.
- Age <18 years.
- Participation in a randomized clinical trial.

Please note that patients can participate concomitantly in other registries.

5. Choice of Centres

All 56 member countries of the ESC will be invited to participate in this survey, in order to provide information on the characteristics of AF in various countries of Europe and on current pharmacological and non-pharmacological management of this arrhythmia. Other ESC affiliate countries and other countries worldwide will be allowed to participate upon their request.

The centres will be accepted on a voluntary basis through appointment by the national coordinators, according to the criteria reported below.

The national coordinator will supply a list of potential medical centres in his/her country that would be technically suitable to set up such a survey.

Sites of different types will also be included to reinforce representativeness.

The National Coordinator will be requested to outline the profile of the medical/surgical centre and to indicate whether the proposed medical centre is:

- University/public/private centre with or without on-site cardiac surgery and/or interventional cardiology.
- With/without admission of cardiac patients to internal medicine wards.
- The presence of a dedicated arrhythmia clinic.
- The availability of a Heart Team.

The site characteristics will be recorded on a specific site Case Report Form (CRF).

Participating centres in the same geographical area will be grouped into clusters. The number of clusters will be defined according to the size of the country population. The choice of clusters will allow the representation of each type of hospital in proportion to the distribution of medical centres in the individual country. Each cluster will generally comprise 4 to 6 centres.

For example, 1 university hospital, 1 large public non-university hospital with surgery and electrophysiology facilities, 1 smaller public centre without electrophysiology facilities, 1 large private centre (if appropriate).

It will be necessary to avoid double counting of patients referred to different centres in the same cluster.

5.1. Patient Visits

The survey will include all consenting patients and collect data at the following timepoints:

- One inclusion visit at the hospital (during hospitalisation or outpatient visit).
- One 12-month follow-up.

5.2. Follow-Up Data

Patient survival status will first be established by contacting physicians or community registration.

Where patients are deceased, the mode of death will be determined using the following classification: cardiovascular (sudden and non-sudden), non-cardiovascular or unknown.

Concomitant drug therapies will also be collected for deceased patients.

Where patients are alive, follow-up data concerning morbidity (that is, complications including embolic events, congestive heart failure or other major events) and some drug therapies (e.g., persistence with antithrombotic drugs) will be collected either through telephonic interview or by sending a questionnaire and by checking hospital records and/or other medical information systems.

5.2.1 Baseline Data

The variables associated with the objectives as described below will be collected in the electronic CRF.

The following information will be captured for each enrolled patient:

- Patient demographics (partial date of birth, gender, ethnic origin, height/weight)
- The enrolment setting, mode of AF diagnosis (including screening for AF, device memory interrogation, etc.), AF characteristics
- Cardiovascular risk factors, concomitant cardiovascular diseases and other diseases/conditions,
- Data on the AF-related diagnostic assessment, including electrocardiographic assessment, blood biochemistry, echocardiography and other diagnostic procedures,
- Data on the patient risk-stratification, including risk scores for stroke (e.g., CHA_2DS_2-VASc), bleeding (e.g., HAS-BLED), VKA decision-making (SAMe-TT_2R_2), etc.,
- Current use of treatments (pharmacological and interventional),
- Data on integrated AF management, including patient involvement, multidisciplinary approach, engagement of AF Heart Team,
- Major AF outcomes at discharge from enrolment visit/hospitalization,
- EuroQoL EQ-5D-5L (if these are available)

5.2.2 Follow-Up Data

Follow-up data 12 months +/- 2 months will be collected for all patients.

The following information will be captured by phone, questionnaire or during a visit to the centre for each enrolled patient:

- Change in the patient's risk profile, including new co-morbidities,
- Data on the stroke and bleeding risk re-assessment,
- Medications, procedures, integrated care,
- Survival status,
- Other major outcomes including stroke, bleeding, hospitalizations, AF progression,
- Adherence to NOACs therapy,
- EuroQoL EQ-5D-5L (if these are available)

5.3. Data Management

5.3.1 Central Database

A central database is used to collect data from all EORP registries and surveys at the European Heart House, 2035 route des Colles, Les Templiers, BP 179, 06903 Sophia Antipolis Cedex, France. A registry-specific central database will be set up to contain the data for this study, from which data analysis will be performed. The database has limited access,

protected by individual encrypted and coded passwords. Backups are encrypted and stored off site.

5.3.2 Data Collection

Data Collection Officers/Investigators of the participating centres will have access to the eCRF, through login on the EORP website, for on-line data entry.

Usernames will be distributed by the EORP team to the participating centres. The login password must be created by the user. A paper version of the Case Report Form (CRF) can be downloaded from the webpage to provide the opportunity to collect data on paper before entering data in the eCRF. Edit checks will be implemented in the European Heart House. The hospital/national patient identifier will not be transferred to the central database at the Heart House.

The Case Report Form (CRF) will only be completed for patients with a confirmed diagnosis of AF, according to the predefined inclusion criteria. Follow-up Data will be collected on a separate follow-up form, at 1 year after the enrolment visit/hospitalization.

The paper version of the CRF will be available for download from the EORP webpage to provide the opportunity to collect data on paper before entry using the eCRF.

Edit checks will be implemented by the EORP data management team at the ESC.

The CRF will have a common section for all patients, with medical history, demographic data, and clinical and echocardiographic examination. Additional sub-sections of the CRF will be designed according to each specific question evaluated. The questionnaire will allow a descriptive report of current clinical practice in the community.

The uniqueness of the current survey, as reflected in the form, is the desire to address several crucial questions about the reasons for the physician's decision to treat a patient. These questions will be incorporated into the CRF, and will allow for a descriptive report of current clinical practice in the ESC community, as well as an analysis of the approach of physicians to therapy and the implementation of the ESC AF Guidelines.

An attempt should be made to gather all data regarding the course of events after hospital transfer including contact with physicians by telephone.

The database will be collected and analysed at the Heart House EORP department. For publications, please refer to the EORP publication policy. Ancillary analyses can be proposed under the sanction of the Executive Steering Committee, with appropriate access to the database.

5.3.3 Progress Status Reports

Database status and registry progress reports will be published on a protected and dedicated website by the EORP team, with different levels of access. This will enable all interested parties to have instant information on the survey status. Regular newsletters and recruitment rates will be provided.

5.3.4 Data Validation & Quality Control

The Database will be designed, managed, controlled and validated according to the ESC-EORP standards. The procedures related to this activity are available in the Data Management Plan. Data will be controlled and validate regularly during the enrolment phase, to enable database lock and data analysis shortly after the completion of enrolment.

5.4. Statistical Analysis

Based on the objectives of the EORP, data analysis will be mainly descriptive and report the cohesion of the management and guidelines. In addition, comparisons can be made between hospital types and countries. Additional reports will evaluate the results of interventions, using immediate results and one-year follow-up data.

All the patients enrolled will be included in the analysis. Since this is an observational study, descriptive summaries will be presented for all the patients, as well as for subgroups of patients. Statistical tests may be carried out for exploratory purposes, as appropriate.

Multivariable analyses may be used to explore the relationship between baseline covariates and post-baseline endpoints, as appropriate.

The study being fully observational, a formal sample size has not been calculated.

However, a sample of 10,000 enrolled patients has been estimated as a minimum number to achieve the level of quality necessary to assess the profile of patients with AF at continental level, according to the collected information listed above. Specifically, the inclusion in the registry of such a number of patients should allow us to have sufficient information on a few subgroups of patients for whom a specific focus has been planned.

6. Registry Organisation

The following is a description of the logistic and scientific framework. For full details please refer to the general EORP rules.

6.1. The Oversight Committee

For the list of Oversight Committee members, please see Appendix A.

6.2. Executive Committee of the AF Guidelines Implementation in Practice Registry

The Executive Committee will be responsible for the formulation of the study protocol and to oversee its implementation. This committee will report to the EORP Oversight Committee of the ESC, who will be responsible for the final approval of the protocol and will oversee the implementation of the protocol.

For the list of Executive Committee members, please see Appendix A.

6.3. Steering Committee (National Coordinators)

This will be composed of the Chairperson, and one delegate per participating country selected by the national cardiology societies.

The prime responsibility is to provide input to the protocol and electronic Case Report Form (eCRF), responsibility for the performance of national centres, participation in the publication plan, etc.

Thus, members will be responsible for contact with the EORP investigators at national level and for the implementation of the protocol in their country. They will help translate the patient consent form and any relevant documents for the ethics committees and the relevant national authorities in order to get approval for the registry. They will also assist in the selection for the registry and in updating the ESC and the investigators with the ethical and legal requirements with regard to the registry in their country; they will provide support to centres for the Ethics submission (translation of documents in national languages, centralise IRB submission if applicable, etc.) and will ensure quality control of national data.

6.4. ESC Coordinating Centre

The database will be designed and set up by the EORP team based in the European Heart House in Sophia Antipolis, France, according to the requirements defined by the appointed Executive Committee. The database validation plan will be validated by the Scientific Expert Committee through its chairman.

The EORP team is in charge of operational management, site relationship co-ordination and central database expertise, assuring the constant quality control and continuity necessary to ensure that the projects are completed on time and within budget.

6.5. Duration of the Registry

The patient enrolment phase will last 3 months per centre, and follow-up will last 12 months from enrolment.

To qualify for the participation, each centre must recruit a minimum of 20 consecutive patients (no set maximum number of patients per centre).

Since this period will vary between centres, data collection in each separate centre continues for the required 3-month enrolment period. The registry will commence in 2018 (see Appendix B, for timeline), with individual centres commencing at different times to facilitate data collection.

The number of patients per centre, and number of centres involved in each country will be agreed upon in advance, in consultation with the national co-ordinators (who will have the knowledge of the clinical practice specific to each country), according to EORP proposals.

Follow-up will be performed by the local investigator at 12 months after enrolment.

6.6. Ethical Issues

The National Coordinator will be responsible for obtaining the approval of the local and national review boards for this registry, if necessary.

The EORP team will distribute the relevant documents in English to the National Coordinator, who will be responsible thereafter for its translation and adaptation to local standards. All patients will be approached by the local centre investigator and will be asked for their written informed consent to participate in the EORP registry on AF.

6.7. Protection of Human Subjects

The Atrial Fibrillation registry is an observational study that does not dictate the manner in which patients are evaluated or treated for Atrial Fibrillation disorder. Physicians may decide to evaluate and manage outpatients and inpatients with Atrial Fibrillation disorder in the most appropriate way, according to the local standard of care. There is no selection of patients and it is necessary to obtain patients' consent.

In case of refusal, the patient will not be enrolled in the registry and their data will not be collected.

In order to facilitate subsequent follow-up of patients, direct identifiable data will only be stored on local centre computers or as a paper copy in the appropriate registry dossier (and not in the EORP central database).

Collected patient data will be anonymous. Only a code will identify patients in the database.

In order to maintain strict security and ensure data validity, each investigator/study personnel will have a unique login and password to enter patient information.

There will be no storage of clinical data outside of the data collection instrument, which will be a secure, web-based form. The main database will be secured according to current standards to ensure both ethical and integrity requirements of the data.

6.8. Pharmacovigilance

Investigators are reminded to report any adverse drug reaction to the Competent Authorities and/or to the Marketing Authorization Holder of the concerned product, as requested in routine clinical practice, according to the local routine pharmacovigilance rules.

6.9. Publication Policy

Data will be published under the responsibility of the Executive Committee of the study. Requests for further analyses to support ancillary publications must be submitted to the Executive Committee for review and approval.

Any publication of data collected as a result of this study will be considered a joint publication by the investigator, Executive Committee members and personnel of the Scientific Secretariat and Data

Management team. Authorship will be determined by mutual agreement. The contribution of the author to the study design, enrolment, data review, and manuscript preparation and review will be considered when determining the order of authorship. After the publication of the main paper, the database is available for further analyses to all participating Investigators. The Executive Committee must receive a copy of any presentation, manuscript, or abstract prior to dissemination, according to the terms outlined in the protocol.

To facilitate the success of the registry, best enrolling investigators will be offered co-authorship in one of the main papers (one paper per investigator). Also, the investigators who achieve a 100% follow-up (or the closest to 100%) will be offered co-authorship in the follow-up papers (again, one paper per investigator), in concordance with the EORP rules.

7. References

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Appendix A: The Registry Committees

The EORP Oversight Committee

Prof Alec Vahanian (France) - Chairperson

Prof Andrzej Budaj (Poland)

Dr Nikolaos Dagres (Germany)

Prof Nicolas Danchin (France)

Dr Victoria Delgado (Netherlands)

Assist Prof Jonathan Emberson (United Kingdom)

Assist Prof Christopher Peter Gale (United Kingdom)

Prof Guy Heyndrickx (Belgium)

Prof Bernard Iung (France)

Prof Stefan James (Sweden)

Prof Örjan Friberg (Sweden)

Prof Gianfranco Parati (Italy)

Dr Mikko Pietila (Finland)

Prof Eva Prescott (Denmark)

Prof Frank Ruschitzka (Switzerland)

Prof Frans Van De Werf

Prof Franz Weidinger (Austria)

Prof Uwe Zeymer (Germany)

Non-voting/ex-officio members:

Prof Aldo Maggioni (Italy)

Prof Nikolaos Maniadakis (Greece)

Dr Klaudia Vivien Nagy (Hungary)

Executive Committee of the AF III Registry

Tatjana S. Potpara (Serbia) - Chairperson

Harry Crijns (the Netherlands)

Gregory Y H Lip (United Kingdom)

Giuseppe Boriani (Italy)

Paulus Kirchhof (United Kingdom)

Nikolaos Dagres (Germany)

Elena Arbelo (Spain)

Radoslaw Lenarczyk (Poland)

Irina Savelieva (United Kingdom)

Christian Torp-Pedersen (Denmark)

Aldo Maggioni (Italy), Scientific Coordinator for EORP, non-voting

Appendix B: Registry timelines

- **AUGUST 2017 (until the ESC Congress) – EORP-wise preparations**

  EORP Oversight Committee approval, Registry first formal announcement - letter to the National Cardiology Societies

- **SEPTEMBER (to DECEMBER) 2017 – National Coordinator identification, submission for the ethical approval**

  Centre recruitment, Submission to local IRBs for ethical approval

- **JANUARY to SEPTEMBER 2018 - Centre setup and activation; patient enrolment**

  Individual centres may start enrolling anywhere between 15 March and 1 September 2018 (depending on the ethical approval date), making completion of the last 3-month enrolment period 30 November 2018.

- **12-MONTH FOLLOW-UP – the last date for follow-up completion is 30 NOVEMBER 2019.**