EUROBservational Research Programme

European Infective Endocarditis Registry

EURO-ENDO
EACVI / VHD Working Group Registry

an ESC EURObservational Research Programme

Protocol

22 January 2016
Version 1.0

Study Sponsored by the European Society of Cardiology

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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 changes. The functions represented in the committees will however not change.

Protocol version Number	Protocol Version date	Amended pages	Changes
1.0	22 Jan 2016	Not Applicable	Not Applicable (first Version)

List of abbreviations

Abbreviation	Definition
CRF, eCRF	Case Report Form, Electronic Case Report Form
EORP	EUR*Observational* Research Programme
ESC	European Society of Cardiology
EACVI	Cardiovascular Imaging Association
EURO-ENDO	European Endocarditis
IE	Infective Endocarditis
VHD	Valvular Heart Disease
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
PET-CT	Nuclear Imaging: Positron Emission Tomography - Computed Tomography
TTE	Transthoracic Echocardiogram
TOE	Transesophageal Echocardiogram

Table of content

1. Background and rationale

Infective endocarditis (IE) is a severe disease, associated with high morbidity and in-hospital mortality (1-7). Despite improvements in diagnostic and therapeutic strategies, both the incidence and severity of the disease seem to be unchanged. Reasons for this persistent poor prognosis are numerous and include older patients with more severe disease, changes in the epidemiologic profiles and more patients with prosthetic or device related IE (8-10).

The motivations for creating a European Endocarditis Registry are the following:

- The epidemiologic profile of IE has changed during the past years, with important differences between countries and increasing numbers of staphylococcal and nosocomial endocarditis cases (1, 8). The European Society of Cardiology (ESC) Euro Heart Survey programme dedicated to valvular heart disease performed in 2001 already provided some useful information regarding the management of IE across Europe at that time (11). Hitherto, no attempt has been made to update and implement the results of the Euro Heart Survey in the contemporary era. There is, thus, a need for a comprehensive and dedicated IE survey.
- New diagnostic and therapeutic strategies have been developed in order to improve the diagnosis and the prognosis of the disease. The Guidelines on the prevention, diagnosis, and treatment of IE of the ESC were published in 2009 and gave new insight into both the diagnostic and therapeutic management of these patients (12). These recommendations were revised in 2015 (28) However, how these recommendations are implemented in real world clinical practice has never been studied.
- Although echocardiography is the first and recommended diagnostic method in IE (13), other non-invasive imaging techniques have received increasing attention, including multislice computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging (PET-CT) (14-19). However, their availability and use in different countries are unknown.
- Finally, although early surgery is recommended in patients with complicated IE, its impact on prognosis is still debated (20-26). With the present IE registry, it will be possible to assess if both the implementation of guidelines and the use of early surgery are associated with a reduction in in-hospital and 1-year mortality.

Therefore, this registry will give us the unique opportunity to assess the characteristics of IE in Europe, the current use of imaging techniques, as well as the correct implementation of the ESC guidelines and its consequence in terms of prognosis. All this will help improve the diagnosis and management of IE in Europe.

2. Objectives and end-points of the study:

2.1. Primary objective:

The main goal of the European Endocarditis Registry (EURO-ENDO) is to evaluate the outcome of patients diagnosed with Infective Endocarditis.

2.2. Secondary objectives:

- The secondary objectives are:
    - To assess the current clinical, epidemiological, microbiological, therapeutic, and prognostic characteristics of IE in Europe.

- To assess the current practices of imaging in IE in Europe and in affiliated countries
- To assess the degree of implementation of the ESC guidelines in practice.
- To compare these current data with those obtained in the Euro Heart Survey.

2.3. End-points

- The primary end-point is to evaluate the in-hospital mortality and the 1-year mortality
- The Secondary end-points will be evaluated by the following endpoints:
  1. 1-year morbidity (hospitalisations, need for surgery, relapses)
  2. Long-Term mortality
  3. The clinical, epidemiological, microbiological, and therapeutic characteristics.
  4. The number and timing of non invasive imaging techniques performed.
  5. The implementation of the ESC guidelines, concerning:
     - The practical use of echocardiography
     - The type and duration of antibiotic therapy
     - The indications and timing of surgical therapy

3. Study design and methods

The EURO-ENDO registry is a prospective multicentre observational study of patients presenting in the echocardiographic or imaging laboratories for definite IE and treated and followed by European centres and in ESC affiliated countries. Diagnostic methods, type of medical therapy, indications for surgery, and mode of follow-up will be obtained according to the usual practice of the participating centres.

Data on morbidity and mortality will be recorded at 1 month (e.g. in-hospital), 12 months, and 2, 3, and 4 years after the enrolment in the registry. This information will be collected either by phone call or during an outpatient scheduled visit in each centre.

Standard management of patients will be performed as per routine clinical practice.

Drug prescriptions and indications to perform diagnostic/therapeutic procedures will be completely left to participating cardiologists' decision.

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

4. Selection of population

All patients hospitalized with a diagnosis of Infective Endocarditis.

No data will be collected before detailed information is given to the patient and a signed informed consent is obtained.

5. Selection of Countries

Due to the substantial geographic variations in the epidemiology of Infective Endocarditis among the European countries, this registry is aimed at generating data on international variability in disease presentation and management. All the ESC countries will be informed about the launching of the registry and they will have the possibility to propose centres. This strategy should ensure representativeness of the data collected in Europe and possibly beyond.

6. Selection of Centres

The investigator centres are accepted on a voluntary basis and any centre of any volume of activity can participate. A specific analysis on the patients' outcomes will be done splitting the centers in two subgroups: high and low volume as defined below. Centres will be appointed by the Executive Committee in collaboration with the National Imaging Community. The centres will be selected by the National coordinator of each country, although the NS presidents and the executive committee members will also have the possibility to propose additional centres.

The completeness of recruitment of patients will be obtained by selection of patients either from the echocardiographic laboratories, since all patients with IE beneficiate echo examination, whatever the referring centre, or from hospital centres treating patients with IE.

The aim is to select 5 to 15 centres (depending of the size of the country and the number of inhabitants) in each participating country and from approximately 30 countries which are expected to be at least 20 inside and 5 outside of Europe.

The selected centres are approved by the EACVI association as high level IE centres: high volume of treated patients (≥ 20 patients per year), and experts in IE treatment: diagnosis management, imaging and surgical therapy. Low volume centres (< 20 patients per year) and without surgical capabilities may also participate in the registry.

7. Inclusion and Exclusion Criteria

7.1. Inclusion Criteria

- Patients aged more than 18 years.
- Patients having signed an informed Consent.
- All patients with definite infective endocarditis, based on ESC 2015 diagnostic criteria, or
- Patients with only possible IE, but considered and treated as IE

Table 1 - ESC 2015 diagnostic criteria (28)

Major criteria

1. Blood cultures positive for IE
   a. Typical microorganisms consistent with IE from 2 separate blood cultures:
      - Viridans streptococci, *Streptococcus gallolyticus (S bovis),* HACEK group, *S. aureus*; or
      - Community-acquired enterococci, in the absence of a primary focus; or
   b. Microorganisms consistent with IE from persistently positive blood cultures:
      - ≥2 positive blood cultures of blood samples drawn >12 h apart; or
      - All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or
   c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800
2. Imaging positive for IE
   a. Echocardiogram positive for IE:
      - Vegetation;
      - Abscess, pseudoaneurysm, intracardiac fistula;
      - Valvular perforation or aneurysm
      - New partial dehiscence of prosthetic valve
   b. Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT
   c . Definite paravalvular lesions by cardiac CT

Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use
2. Fever defined as temperature >38°C
3. Vascular phenomena (including those detected only by imaging):: major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

Table 2 - Definition of IE according to the modified Duke criteria (adapted from Li (27))

Definite IE

Pathological criteria

- Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria

- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible IE

- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected IE

- Firm alternate diagnosis or
- Resolution of IE syndrome with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

7.2. Exclusion Criteria

- Patients already included in an interventional clinical study which would interfere with the patient's usual care.

  Note: participation in observational studies is not considered as an exclusion criteria.

8. Patient visits

Data will be collected in the main part in all patients at the time of diagnosis during the hospital stay and at 1, 2, 3 and 4 years after enrolment either by phone call or during an outpatient scheduled visit in each centre.

9. Variables Collected

No data will be collected before detailed information on the study is given to the patient and a signed informed consent is obtained. After informed consent, the following data will be collected at inclusion and during hospitalisation.

9.1. Baseline Data

The following information will be captured for each enrolled patient:

- **Clinical data**: age, sex, weight, height, cardiac and non cardiac history, comorbidity index (Charlson index (30)), date and timing of first signs and symptoms, underlying cardiac disease, at-risk situation or procedure, Roth's spots, temperature, Janeway,'s lesions, conjunctival haemorrhages, and Janeway's lesions (Charlson comorbidity index), cardiac murmur, heart failure signs, neurological complication, septic shock, AV block.
- **Biological and microbiological data**: sedimentation rate, C-reactive protein, creatininemia, haemoglobin, white blood cells, platelets count. Blood cultures and serologies will be performed as recommended.
- **Echocardiographic data**: vegetation, abscess, pseudo-aneurysm, valvular and perivalvular lesions, valve regurgitation or stenosis, as well as complete standard echocardiographic studies. Both TTE and TOE will be performed, unless contra-indications exist.
- **Other imaging techniques**: results of other imaging techniques performed at admission and during hospitalization will be reported, including CT scan, PET-CT, and cerebral or cardiac MRI.
- **Treatment before admission and during hospitalization**: including antibiotic therapy and all other treatments.

9.2. Follow-up Data

9.2.1. One-month follow-up: complications under therapy

The following occurring events during hospitalisation will be reported, including:

- Embolic event
- infectious complication
- Haemodynamic complications

- Need for surgery
- Overall mortality
- Cardiovascular death

9.2.2. Long-Term follow-up

The following occurring events at 1, 2, 3, or 4-year follow-up will be reported, including:

- Mortality and related causes
- Recurrence and relapse
- Hospitalisations and related causes
- Surgical valvular intervention

10. Data management

10.1. Case Report Form

Data Collecting Officers/Investigators of the participating centres will have access to the electronic case report form, through login on the EORP website, for on-line data entry. Individual Login names and passwords will be distributed by the EORP team to the participating centres.

The paper version of the CRF can be downloaded from the webpage to provide the opportunity to collect data on paper before entering it in the eCRF. Edit checks will be implemented in the European Heart House. Patient identification will not be transferred to the central database.

10.2. Central Database

A central database is used to collect data from all EORP registries at the European Heart House in 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 passwords; with the hardware being locked in a server room. Backups are encrypted and stored off site.

The database will be maintained at the European Heart House, according to the requirements defined by the appointed Executive Committee with the support of the EORP Team. The database will be located in the European Heart House, Les Templiers, 2035 route des Colles, CS 80179 BIOT – 06903 SOPHIA ANTIPOLIS Cedex.

10.3. Progress Status Reports

Database status and registry progress reports will be published on the website by the EORP Team. Users may have different levels of access to this data depending on their role. This way, all interested parties can obtain instant information on the survey status. Regular newsletters and recruitment rates will be provided to the centres.

11. Statistical considerations and sample size

All the patients enrolled will be included in the analyses. Since this is an observational study, descriptive summaries will be presented for all the patients, and for subgroups of patients. Univariate analysis will be applied to both continuous and categorical variables. Continuous variables will be reported as mean±SD or as median and Interquartile Range (IQR). Among-group comparisons will be made using a non-parametric test (Kruskal-Wallis test). Categorical variables will be reported as percentages. Among-group comparisons will be made using a chi-square test or Fisher's Exact test if any expected cell count is less than five.

Multivariable analyses may be used to explore relationship between baseline covariates and post-baseline endpoints, as appropriate. Considering the explorative and observational nature of the current study, no formal sample size calculation has been performed. However, the expectation is to enroll around 2000 patients (considering the participation of around 30 countries).

12. Study organisation

12.1. Oversight Committee

The entire EORP is managed and overseen by the EORP Oversight Committee whose main responsibility stands at a strategic level. The Chairperson is a past ESC President and the members are past/elect/current ESC Presidents, representative of the ESC Associations and/or Working Groups and are listed in appendix 1.

12.2. Executive Committee

The Executive Committee is composed of distinguished independent scientists and investigators of which some are representative of EACVI, VHD Working Group, and EORP. The Executive Committee is responsible for:

- Overall guidance of the Registry.
- The design and writing of the study protocol and CRF, and for overseeing its implementation.
- Monitoring the progress of the study, being in direct contact with the National Coordinators (responsible for the performance of the national network) and the EORP coordinating Department (responsible for the management of the study).

The members of the Executive Committee of the Infective Endocarditis registry are listed in appendix 2.

12.3. Steering Committee

The steering committee is composed of the national Coordinators who will be responsible for:

- Providing input to the protocol and Case Report Form
- Participating in the publication plan definition
- Participating at the registry meetings.
- Implementing the study in their country, in particular to:

- Assist in the selection of participating centres.
- Inform the EORP team and the investigators of the Ethical and legal requirements with regard to the registry in their country.
- Translate the master patient informed consent form and any relevant documents for review by the Ethics Committees and national authorities, if applicable.
- Provide support to the centres for any necessary Ethics Committee submission.
- Maintain continuous contacts with the investigators at national level.
- Assist in ensuring quality control of national data.

12.4. European Society of Cardiology coordinating centre (EORP Department)

The main coordinating centre is the EUR*Observational* Research Programme of the ESC (EORP).

The EORP Team's main role is to operationally coordinate the project, provide support to the Committees, National Coordinators and participating centres and guard the methodological concepts of the registry.

Specifically, the EORP Team has to assure the constant quality control and continuity, necessary to ensure that projects are completed on time and within budget.

The EORP coordinating centre is also responsible for the tasks related to the data management activities of the study (i.e. holder of the study database, cleaning of the data, database lock) as well as for the statistical analyses.

12.5. Investigator Centres

1 centre every 1 million of inhabitants (ranging from approximately 10 to 30 countries) are anticipated to participate in the study. Depending on the number of patients seen in each centre per year, it is anticipated that between 10 and 20 patients will be recruited by each centre. Centres will be appointed by the Executive Committee in collaboration with the National Imaging Community.

13. Duration of Registry

This registry is intended to start in 2016. It is anticipated that approximately 2000 patients will be enrolled yearly over a period of minimum 12 months.

There is no maximum number of patients per centre. The number of patients per centre, and number of centres involved in each country will be set up in advance in consultation with the National Coordinators who will have knowledge of clinical practices, specific to each country.

14. Ethical issues

The National Coordinators chosen by the chairs of the registry and in conjunction with local investigators/centres will be responsible for obtaining the approval of the local and/or national Ethics Committees for this registry, if applicable.

The EORP team will distribute the relevant documents in English to the National Coordinators, who will be responsible thereafter for their translation and adaptation to their local regulations. All patients will be approached by local centre investigators and will be asked for their written informed consent to participate in the registry, if applicable.

14.1. Protection of Human Subject

The EURO-ENDO EACVI/VHD Registry is an observational study that does not dictate the manner in which patients are evaluated or treated for IE. Physicians may decide to evaluate and manage outpatients and inpatients with IE 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' agreement.

In case of refusal, the patient will not be enrolled in the registry (if required by national laws or regulations) and their data will not be collected.

Patients' direct identifiable data will only be stored on local centre computers and not in the EORP central database in order to facilitate subsequent follow-up of patients.

Collected Patients data will be strictly anonymous. Only a code will identify patients in the database. Demographic data such as the age and gender will be collected. No other patient identifiers will be collected.

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

Patients having died before giving informed consent may also be included, unless the local IRB does not allow this procedure. Patients who cannot provide the informed consent at the time of admission in the cardiology ward due to very severe clinical conditions can give their consent some hours/days after admission, when more favourable clinical conditions allow them to receive the appropriate information.

15. Pharmacovigilance

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

16. Local monitoring

Periodically, the participating centres may be selected for auditing via on-site visits, which will be performed by ad-hoc clinical research assistants, trained by the EORP team, in order to assess consecutiveness of enrolment and the reliability of key, pre-defined clinical variables, via source documentation cross-checking.

The sites that will be monitored will be chosen on a risk-based strategy (e.g. number of patients enrolled, issues, high number of data management queries...).

17. 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. 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.

Participation of each centre will be acknowledged with their name reported on scientific publications according to the EORP publication policy.

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Appendix 1: **Oversight Committee members**

- Roberto Ferrari, Chairperson
- Fausto Pinto, President of the ESC
- Panos Vardas, Past-President of the ESC
- Jeroen Bax, President-Elect of the ESC
- Angeles Alonso, Expert
- Stephan Gielen, Representative EAPCR
- Patrizio Lancellotti, Representative EACVI
- Carina Blomström-Lundqvist, Representative EHRA
- Franz Weidinger, Representative EAPCI
- Frank Ruschitzka, Representative HFA
- Uwe Zeymer, Representative ACCA
- Nikolaos Maniadakis, Health Economics Expert
- Aldo P Maggioni, Scientific Coordinator for EORP
- Luigi Tavazzi, Past-Chairman of the OC

Appendix 2: **Executive Committee members**

- Gilbert Habib, Chair, EACVI
- Patrizio Lancellotti, Co-Chair, EACVI and ESC WG VHD
- Erwan Donal, Executive Committee, EACVI
- Bernard Cosyns, Executive Committee, EACVI
- Bogdan A. Popescu, Executive Committee, EACVI
- Bernard Iung, ESC WG VHD
- Raphael Rosenhek, ESC WG VHD
- Bernard Prendegast, ESC WG VHD
- Pilar Tornos, ESC WG VHD
- Paola Erba (Nuclear medicine, Pisa)
- Aldo P Maggioni, Scientific Coordinator EORP