

European Lead Extraction ConTRolled Registry ELECTRa Registry Protocol

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1 COMMITTEES and BOARDS

1.1 Executive Committee

The executive committee will provide scientific leadership for the conduct of the ELECTRa Registry, under the responsibility of SIC. It is composed of a 2 co-chairs, country centre investigators representatives, EORP and the SIC chair. The committee chair will oversee the conduct and execution of the ELECTRa Registry, and set the agenda for the executive committee.

Name Members	Country
1. Maria Grazia Bongiorno, chair	Italy
2. Charles Kennergren, co-chair	Sweden
3. Christian Butter	Germany
4. Jean Claude Deharo	France
5. Andrzej Kutarski	Poland
6. Aldo Rinaldi	UK
7. Aldo Maggioni , EORP	Italy
8. Carina Blomstrom-Lundqvist, Chair SIC	Sweden
9. Angelo Auricchio, EHRA President	Switzerland

1.2 Country Participation

All National Societies from the EHRA White Book and all other identified European Lead Extraction Centres have been invited to participate.

2 BACKGROUND AND RATIONALE

Background

The implant rate of Cardiovascular Implantable Electronic Devices (CIED) continues to rise in most countries. The number of leads per patient is increasing due to a higher proportion of dual versus single chamber devices and an increase of CRTP/D systems. Greater life expectancy, need for upgrade, multiple replacements of generators or pocket revisions for complications expose patients to infections.

Despite advances in technology and improvements in reliability, leads remain the weak point of the systems and in some cases may fail.

Transvenous Lead extraction is the gold standard in the treatment of CIED related infective complications and often required in the management of leads malfunction.

Initially NASPE and subsequently HRS and EHRA have published recommendations describing indications, settings, facilities, training and accreditation for transvenous lead extraction procedures.

Rationale

During the last 10 years transvenous lead extraction techniques have been improved, becoming more complete, sophisticated and efficient.

Recent advances in experience, tools, techniques and approaches in TLE have improved effectiveness and an increasing number of centers currently perform TLE procedures. Lead management requires a broad understanding of the pathophysiology of

mechanical and clinical issues associated with lead dysfunction, and a primary commitment to measuring outcomes and quality. A Survey able to characterize Centres performing TLE and to capture all the relevant clinical and procedural information of patients undergoing TLE may allow us to improve the knowledge of outcomes in real world clinical practice.

3 STUDY DESIGN AND METHODS

This is a prospective, multicentre, European Controlled Registry of consecutive patients undergoing TLE procedures in European Countries.

All consecutive patients will be enrolled per centre and followed up to 1 year.

Enrollment will start the day before the procedure.

Indications to perform procedures will be left completely to the decision of participating physicians.

No specific protocol or recommendations for the procedure, materials, techniques of lead extractions, or treatment after the procedure will be mandated during this observational study.

3.1 DURATION OF THE STUDY

It is anticipated that over 100 centres will participate in the registry. Each centre will register consecutive patients for a total of 3000 patients.

The study should commence recruitment of patients in October 2012 and finish in June 2013. In the event that less than 3000 patients are enrolled at that time the study can be continued until this number of enrollees is reached.

The number of centres involved in each country will be agreed upon in advance in consultation with the national coordinators who will have knowledge of clinical practices specific to each country. Follow up information will be collected for all patients after 12 months from the procedure. The “last patient last visit” should be conducted by the end of December 2013.

3.2 PRIMARY AND SECONDARY OBJECTIVES

3.2.1 Primary Objective

The primary objective is:

- to evaluate the acute and long-term safety of transvenous lead extraction.

Measures: major procedure-related complications (including deaths) in acute and long-term follow-up (see definitions in Chapt 3.6).

3.2.2 Secondary Objectives

The secondary objectives of the ELECTRa Registry are:

- To describe demographic, clinical, and biological characteristics of patients undergoing TLE procedure in a representative setting of European cardiology Centres.
- To describe the characteristics of leads undergoing extraction.
- To evaluate indications for TLE procedures.
- To describe the diagnostic and therapeutic approaches employed in the routine practice of physicians performing TLE procedures.
- To assess the acute and chronic outcomes (see definitions in Chapt 3.6) of TLE procedures.

The information collected in the Survey will permit a description of the European practice on TLE, a comparison of data among Centres and Countries, with possible evaluation of

- adherence to guideline recommendations,

- differences among small-medium-large volume Centres,
- experience-based outcomes,
- need of learning curve,
- timing and method of reimplantation after extraction.

- **3.2.3 Potential Value of the Registry**

Increased quality of care in the lead extraction process

Dissemination of knowledge

Verification and potential adjustment of standards for lead extraction procedures.

3.3 PARTICIPATING CENTRES

Centres will be enrolled on a voluntary basis from all the European Countries.

Centres will be anonymous and stratified on the basis of their volume of activity:

High volume Centres:	> 30 pts/y
Medium volume Centres	15>30 pts/y
Low volume Centres	< 15 pts/y

3.4 POPULATION ENROLLED IN THE REGISTRY

3.4.1 Inclusion criteria

Enrollment and Follow-up: All consecutive Patients with indications for TLE (following HRS guidelines) in the participating Centres during the enrollment period will be included

3.4.2 Time of inclusion: the day before the procedure.

3.4.3 Exclusion criteria

A. Patients unwilling or unable to give informed consent or unable to complete follow-up.

B. Psychological problems that might limit follow-up.

All patients (or legal guardians in case of patients unable to consent) are required to sign an informed consent form approved by the local ethical committee (according to national need)

3.4.5 Withdrawal from the study

Definitions of withdrawals from study:

Withdrawal of consent, Patient lost to follow-up before 12 months.

3.5 DATA COLLECTION

Data will be collected using a web based system.

The complete CRFs with the specifications and the definitions will follow in a dedicated addendum.

3.5.1 Pre Procedure Evaluation

To be filled out before the procedure, if lead extraction is planned

- Physical examination including height, weight, BMI, LVEF, NYHA Class, blood pressure.
- Concomitant cardiovascular disease including coronary artery disease, valvular heart disease, hypertrophic or dilated cardiomyopathy, congenital heart disease, previous sternotomy, chronic heart failure, electrical primary disease, other heart disease.
- Risk factors and concomitant diseases including hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease.

- Cardiac Implantable Electronic Device history (Re-intervention, Upgrading, Replacements)
 - 12-lead electrocardiogram.
 - PA and LL Chest-X ray.
 - Transthoracic (+ TEE if systemic infection) echocardiography.
 - Laboratory tests.
 - Pharmacological treatment (antibiotics, anticoagulation, antiplatelets, antihypertensive and heart failure treatment).
 - Indications for Lead Extraction.

3.5.2 Lead Extraction procedure

Personnel, tools, techniques, approaches, outcomes

- number of personnel
- cardiothoracic surgeon stand-by, presence of the surgeon at the procedure
- procedural room setting
- tools used
- techniques used
- approaches used
- type of anesthesia
- procedural time
- fluoroscopic exposure
- acute outcomes
- complications (major, minor, see definitions)

3.5.3 Post-procedure evaluation

Post-procedure and pre-discharge

- ECG and vital sign monitoring
- Echocardiographic evaluation
- Chest X-Ray
- Pharmacological and Antibiotic therapy
- In-hospital complications and mortality

3.5.4 Reimplantation and discharge

Need for reimplantation

- Type of CIED
- Acute Complications
- Investigations at discharge
- Therapy at discharge

3.5.5 Follow-up data

Twelve months follow-up is required to evaluate clinical failures of TLE procedures, endpoints and long-term complications.

3.5.5.1 Outcome even in case of failure or refusal

Follow-up is scheduled for all enrolled consecutive patients also in case of failure or refusal of the procedure.

3.6 DEFINITION OF SUCCESS, FAILURES, COMPLICATIONS AND MORTALITY

To compare the clinical efficacy of the treatment with regard to the complete extraction of lead we define:

- 1 - Radiological Success
- 2 – Clinical success based on achievement of clinical outcome according to “intention to treat”

3.6.1 Success

A - Radiological Success

Removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure related death

Total = complete

Partial = less than 4 cm remains in the cardiovascular system

B – Clinical success based on the achievement of clinical outcome according to intention to treat measured

Acutely

Long term (12 months)

3.6.2 Failures

Inability to achieve either complete radiological or clinical success, or the development of any permanently disabling complication or procedure related death.

Failures will be defined as radiological and clinical.

Major complications are considered clinical failures.

3.6.3 Complications

Extraction events are classified as major complications or minor complications according to their severity, as described below.

3.6.3.1 Major complication: Any of the outcomes related to the procedure which is life threatening or results in death. In addition, any unexpected event that causes persistent or significant disability, or any event that requires significant surgical intervention. They are:

1. Death
2. Cardiac avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube or surgical repair
3. Vascular avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube or surgical repair
4. Pulmonary embolism requiring surgical intervention
5. Respiratory arrest or anesthesia related complication leading to prolongation of hospitalization
6. Stroke
7. Pacing system related infection of a previously non-infected site

3.6.3.2 Minor complication: Any undesired event related to the procedure that requires medical intervention or minor procedural intervention to remedy, and does not limit persistently or significantly the patient’s function, nor threaten life or cause death. They are:

1. Pericardial effusion non requiring pericardiocentesis or surgical intervention

2. Hemothorax not requiring a chest tube
3. Hematoma at the surgical site requiring reoperation for drainage
4. Arm swelling or thrombosis of implant vein resulting in medical intervention
5. Vascular repair near the implant site or venous entry site
6. Hemodynamically significant air embolism
7. Migrated lead fragment without sequelae
8. Blood transfusion related to blood loss during surgery
9. Pneumothorax requiring a chest tube
10. Pulmonary embolism not requiring surgical intervention

3.6.4 Mortality

Total mortality will be classified into different groups, which will also be evaluated separately. All-cause death will be classified in the following groups:

1. Non-cardiovascular death, including unknown
 - a. non-sudden
 - b. sudden (trauma, homicide)
2. Cardiovascular death
 - a. cardiac
 - i. sudden (including arrhythmic, myocardial infarction)
 - ii. non-sudden
 - b. vascular (e.g. embolic, SAB, stroke, other)
 - i. sudden
 - ii. non-sudden
 -

3.6.5 Timing of Complications and Mortality

- **3.6.5.1 Intra-procedural:** Any event related to the performance of a procedure that occurs or becomes evident from the time the patient enters the operating room until the time the patient leaves the operating room. This includes complications related to the preparation of the patient, the delivery of anesthesia, and opening and closing the incision.
- **3.6.5.2 Post-procedural:** Any event related to the procedure that occurs or becomes evident **pre-discharge**.
- **3.6.5.3 Long-term: within 12 months**

3.6.6 Death and Complications Relationship

1. Indication related
2. TLE procedure-related
3. Treatment post-TLE related

4 STATISTICAL CONSIDERATIONS AND SAMPLE SIZE

All patients enrolled will be included in the analysis. Statistical tests may be carried out for exploratory purposes, as appropriate. Multivariable analysis may be used to explore relationship between baseline covariates and post-baseline endpoints, as appropriate.

About 3000 patients are estimated as needed either to make an experience solid enough to judge the quality of the study or to obtain a preliminary continental profile of patients undergoing a TLE procedure according to the collected information listed above. The major complication rates in larger centres are estimated to be around 2-3% and to be able to demonstrate a difference of 5 % in complication rate. To detect a difference of 3 % in major complication rates between patients treated at experienced versus less

experienced centres with a power of 90 % and a type I error of 5 %, a total sample size of approximately 1600 subjects is required.

5 STUDY MONITORING AND AUDITING

Monitoring of Centres will be executed according to the general rules of EORP

A monitor will review dataforms for completeness and for correctness; a quarterly report will be issued

5.1 Source data verification and on-site audits

A monitor (nurse from EHRA) will contact the site prior to the start of the registry to review with the site protocol, registry requirements and their responsibilities to satisfy registry requirements.

When reviewing data collection procedures the discussion will also include identification, agreement and documentation of data items for which the CRF, patient files (paper or database), tracings of investigations, and questionnaires, will serve as a source document. The investigator and the head of the medical institution agree to allow the monitor direct access to all relevant documents whenever needed and in the event of an audit.

The monitor will monitor the registry consistent with the demands of the registry to verify the following:

1. Data are authentic, accurate and complete.
2. Safety and rights of subjects are being protected.
3. Study conducted in accordance with the currently approved protocol .

To ensure compliance to the protocol the monitor may conduct a quality assurance audit. Such audits/inspections can occur at any time during or after completion of the study. If an auditor inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and relevant issues.

A sample of at least 10% of centres is suggested. All patients in a centre being audited must be checked.

6 ETHICAL ISSUES

The National Coordinator in conjunction with the local investigators will be responsible for obtaining the approval of the local and national review boards for this study, if necessary.

The TLEES Research Department of the ESC 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 study (if necessary, i.e. based on local standards).

6.1 Protection of Human Subject

This study does not dictate the manner in which patients are evaluated or treated with TLE procedure. Patients are not randomized in any way and the only risk to patients is that of confidentiality. Patient identifiable data will be stored on local computers (not in a central database) in order to allow subsequent follow-up of patients.

Patient data collected will be strictly anonymous. Only a code, gender, date of birth (month, year) will identify patients. No other patient identifiers will be collected. In order to

maintain strict security, 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.

7 PUBLICATION POLICY

Data will be published under the responsibility of the Steering Committee of the study. Requests for further analyses to support ancillary publications must be submitted to the Steering 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, Steering Committee members and personnel of the Scientific Secretariat and Data Management team. Authorship will be determined by mutual agreement. Contribution of the author to the study design, enrollment, data review, and manuscript preparation and review will be considered when determining the order of authorship.

8 PROPOSED TIME PLAN

Executive-Steering Committee Meeting	December	2011
Final protocol and CRF	February	2012
Official launch at EHRA summit	March	2012
Start ethical committee process	July	2012
Start recruitment of patients	October	2012
Complete recruitment	June	2013
Results on baseline characteristics, in-hospital		
Outcomes and safety complications.	August	2013
Trial announcement during EHRA Europace	June	2013-4
Complete follow-up.	June	2014