European Registry of Cardiac Arrest - Study Three (EuReCa THREE)

An international, prospective, multi-centre, three-month survey of epidemiology, treatment and outcome of patients with out-of-hospital cardiac arrest in Europe

Study protocol

V1.6

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Deutsches Register Klinischer Studien (German Registry of Clinical Trials) Registration Number:
DRKS00028591 searchable via WHO meta registry (http://apps.who.int/trialsearch/)

Ethical clearence
EuReCa THREE was approved by the University of Kiel ethics committee with reference number D422/22 on 14.03.2022.

* Members of the Study Management Team and National Coordinators are supported in their work by their National Registries and National Resuscitation Committees.

CONTENTS

1. Introduction

The importance of establishing out-of-hospital cardiac arrest (OHCA) registries as a critical step in improving OHCA outcomes is recognised from clinical, academic and political perspectives [1-4]. The aim of the EuReCa project is to provide quality benchmarking for OHCA measurement in Europe by building and improving registries. OHCA registries must be based on Utstein style data collection so that variations in OHCA incidence, management and outcomes can be identified [5,6].

Improving data quality is an incremental need to enhance knowledge of OHCA. The EuReCa ONE project established a collaboration between 27 European countries. In October 2014, data on OHCA patients was collected, resulting in the most comprehensive estimate of European OHCA incidence and outcomes at the time [7]. As expected, the proportion of variation between data collection from individual countries was considerable. In the second EuReCa project, EuReCa TWO, it was shown that it is possible to collect data of high quality. EuReCa TWO collected information from 28 countries about all aspects of bystander resuscitation in addition to Utstein variables. (Reference EuReCa 2, Ventilate article by Jan)

To understand variations in OHCA incidence and outcomes internationally, data collected on each link of the Chain of Survival has to be comparable across participating countries. Ensuring this is one of the main aims of EuReCa. In EuReCa ONE and TWO, it was shown that collecting high-quality data on OHCA across a whole continent is possible. It is also possible to use the opportunity provided by a study of this magnitude to collect information on additional data points, as shown in EuReCa TWO, where information on bystander resuscitation was collected. (ref EuReCa2)

To enhance the key quality requirements of comprehensiveness and reliability, the aims of the EuReCa THREE project will be as follows:

- Expand the EuReCa network
- Improve the understanding of how response time and transport time influence return of spontaneous circulation (ROSC) and survival
- Overview of the longitudinal changes since EuReCA ONE
- Continue collecting data on established data-points/items to strengthen the robustness of European data collection

To achieve these aims, the following objectives will be fulfilled:

- Encourage participating countries to aim for national data collection and encourage additional countries to participate
- To provide robust estimates of incidence, management and outcome, the data collection period will be three months (1st September to 30th November 2022)
- Identify consistency and variation in the measurement of time points and time intervals in connection with response times
- Describe the time intervals of response time and transport time

EuReCa THREE is expected to create the largest-ever data collection of OHCA in Europe, providing the opportunity to generate more robust estimates of OHCA incidence and outcome also for particular subgroups.

2. Research Questions

To build on previous work and improve the robustness of estimates, the research questions in EuReCa THREE will closely mirror those of the previous EuReCa studies:

- What proportion of each country's national population is covered by data collection?
- What is the incidence of confirmed OHCA attended by emergency medical services (EMS) in different European countries/regions?
- **What is the EMS response interval for OHCA?**
- **How long is the EMS treatment interval for OHCA?**
- **How long is the transport interval from scene to hospital for OHCA?**
- **What is the influence of response interval and transport interval on survival?**
- What is the incidence of any CPR (cardiopulmonary resuscitation) attempted in OHCA throughout Europe?
- What is the incidence and the proportion of CPR by:
    - Bystander – on scene by chance
    - Person alerted to scene by ambulance dispatch
    - EMS
- **What is the response interval for persons alerted by dispatch and time from their arrival to EMS arrival on scene?**
- What is the initial cardiac arrest rhythm for OHCA patients?
- In patients where resuscitation was started or continued by EMS, what is the incidence and rate of any return of spontaneous circulation (ROSC) after OHCA?
- What is the incidence of patients never transported due to being declared dead on scene?
- What is the incidence of patients transported with ongoing CPR?
- What is the patient status at handover from EMS to an emergency department or hospital system with ongoing additional treatment in the next step of care (ROSC, ongoing CPR, dead)?
- What is the incidence of patients who are still alive at 30 days (whether in-hospital or discharged) after their cardiac arrest event / what is the incidence of patients who are discharged alive from hospital?
- In the Utstein comparator group (Collapse bystander-witnessed where the first rhythm is shockable):
    - What is the incidence of OHCA

  - What is the incidence of ROSC at hospital admission (at time of being handed over from EMS to an emergency department or hospital system with ongoing additional treatment, e.g. PCI)
  - What is the incidence of patients who are still alive at 30 days (whether in-hospital or discharged) after their cardiac arrest event / what is the incidence of patients who are discharged alive from hospital?
- What factors determine ROSC, admission and survival in patients with confirmed arrest and CPR started (as defined in questions above)?

All EuReCa THREE specific and new research questions are highlighted.

Secondary Research Questions

- What is the European incidence of and incidence of survival from OHCA with a traumatic aetiology?
- What is the European incidence of survival from OHCA in cases brought to a hospital with unsustained ROSC or ongoing CPR?
- What is the incidence of OHCA in children

3. Methods

Inclusion criteria

All patients who have an out of hospital cardiac arrest[†]* and are attended by the EMS at any stage during the event. This study will include all events that occur between 00:00 on 1st September 2022 and 23:59 on 30th November 2022. Patients will be included irrespective of their age, gender or personal factors. These inclusion criteria include all patients who receive resuscitation (chest compression, and/or defibrillation of any type)

- By the EMS
- Before the arrival of the EMS with continued resuscitation by the EMS
- Before the arrival of the EMS, that is immediately stopped (for any reason) when the EMS arrives
- Patients who achieve ROSC before the arrival of the EMS

It also includes patients found or declared dead (for any reason).

Some countries or registries may not be able to provide all necessary data to answer every research question. These registries will not be included in the analysis of the related research questions.

Participating registries/centres:

All registries throughout Europe, able to provide at least the core data required (see appendix 1), are invited to participate in this study. For every country there will be one national coordinator who is responsible for all requirements. Requirements are a written letter of intent to participate in this study, a written consent to follow this study protocol and a valid ethical approval (see below) if needed. Should there be more than one registry serving the same region and population, or if there is more than one registry within the country, the national coordinator is responsible for avoiding multiple submissions of patients' data and is responsible for combining data from different registries within the country. The national coordinator will be required to submit all the data for the whole country to the study management team.

Written approval of participation: All participating registries must guarantee the existence of written approval from the EMS organisations they serve, to use and submit data for the EuReCa THREE study. These approvals may follow local policy and do not need to have a specific format but must include

[†] A cardiac arrest that occurs in any location other than an acute hospital

terms clearly describing the permission to use and transmit defined data for research purposes on an international basis. The national coordinator is responsible for obtaining this approval.

Ethical approval: Ethical approval must be applied for by national coordinators (see above) if necessary. Ethical approval may not be required in every nation of the participating registries. Participants are not allowed to report data unless ethical approval or a documented waiver (stating there is no requirement for ethical approval) exists for their country. The ethical approval or the documented waiver must be sent to the Study Management Team. As only anonymised data will be reported and the data is recorded as part of routine care, a requirement for patient consent is not expected. It is however the role of the national coordinator to ensure that patient consent is not required in his/her jurisdiction.
EuReCa THREE was approved by the University of Kiel ethics committee with reference number D422/22 on 14.03.2022.

There are no interventions in this study other than the effort required by EMS personnel or systems to report to the study. There is no reported or estimated risk related to participation in this study, and since the treatment is not changed, there is no increased risk involved for the patient. The benefit to the patient is that countries get to benchmark their results and compare with best practice.

4. Data collection

To maximise the extent of population coverage, participating national, regional or local registries should encourage EMS centres to participate in existing registries to collect and provide data.

The participating registries will transfer anonymised data. Every single case requires a data sheet (DS). Data will be collected within the national, regional or local participating registries (either as a computer-based export from the national, regional or local registry or as a paper-based DS. After validation and anonymisation of data by the participating registries, all data will then be transferred by the national coordinator (computer-based in one single document meeting the requirements specified by the SMT) to the study management group.

National coordinators are responsible for quality control, i.e., the completeness, reliability and accuracy of the data, including timely submission of data to the study management group.
Every DS will be identified by a unique number, including the country and region of origin.

National Coordinators will be required to provide a description of the EMS system in their country or participating region.

Data (computer and paper-based) will be handled according to national laws concerning data security; the national coordinator is responsible for maintaining the necessary standards. Data will be protected by username and password.

5. Dataset

A consistent and uniform dataset is fundamental to the success of the EuReCa THREE study. The Utstein dataset has been developed and refined over decades, therefore core Utstein variables will provide the basis for the mandatory data variables to be transmitted to the study centre. Registries must ensure that their collected data variables are in exact concordance with the nomenclature and descriptions of the items (see appendix 1). Participating registries will be requested to extend their regular data collection to at least the items of this dataset for at least the length of the study period of EuReCa THREE. Participating EMS systems should be informed about the extension of the registry´s dataset and support the data collection.

For this study, the items are divided into core and optional. It is hoped that by using a simple and user-friendly dataset that the study group will encourage participation in the study while ensuring the data quality required is attained.

National coordinators and the study management team will ensure local monitoring of EMS data return and local manual check of all recorded cases. If any missing information is uncovered later, this will be reported retrospectively.

6. Statistical Analysis

The statistical analysis of the data collected will be provided in cooperation with the head statistician of the German TraumaRegister DGU, as in the previous EuReCa studies.

The calculation of incidence rates (for of out-of-hospital cardiac arrests and CPR) will be done per 100,000 inhabitants per year, based on the region covered by the registry.

All variables collected for the project will be uniformly checked prior to analysis. These checks will include range checks, cross checks, and plausibility checks. Time stamps will be checked for logical sequence. In cases where the integrity of data is questionable, queries will be sent to the respective registry

Statistical analysis will be based on the research questions listed above. For each research question, the appropriate population will be defined first (for example, patients with confirmed arrest for whom CPR was started). Results will be presented for the whole group as well as for each participating registry (or country) separately, if possible. Descriptive analysis will be performed with adequate measures of statistical precision: for both, categorical and continuous variables, 95% confidence intervals (CI95) will be calculated.

For certain endpoints like ROSC, hospital admission or survival, multivariate logistic regression analysis will be performed in the whole dataset. Independent predictor variables were selected from the Utstein Core Dataset for this study if their relevance was proven by published data. The source of data (participating country, or registry) will be included in these analyses in order to adjust for local variations. Country-specific effects (like bystander CPR) may be evaluated for interactions. Countries could be excluded from those models in case of serious deviation from completeness (for example, insufficient data about final hospital outcome), or if selected items of interest were missing or rather incomplete (like mode of bystander CPR, or time variables).

7. Organisation

The "European Registry of Cardiac Arrest - Study three (EuReCa THREE)" will be conducted by the EuReCa THREE study group on behalf of the European Resuscitation Council (ERC).

The members of the Steering Committee are appointed by the European Resuscitation Council. The steering committee will be chaired by the Principle Investigator. The steering committee is responsible for the scientific conduct.

The Study Management Team is appointed by the Steering Committee. This team is responsible for the administration of all project tasks.

National Coordinators. National coordinators are appointed by each country, and there can only be one coordinator in each country. National coordinators will be responsible for: Ensuring that mandatory approvals (i.e., ethical approval) exist; communication with the participating registry or registries; measures to generate good data quality; supervision of data collection and complete transmission of the data of their country.

8. Data Management and Ownership

The University Hospital Schleswig-Holstein, Institute for Emergency Medicine / The University of Kiel, faculty of medicine, will act as custodian of the data. Data will be handled according to national laws concerning data security.

The local, regional or national registries will keep the ownership of their data. They will provide the data (by submission) to the study management group for the evaluation of the research questions listed previously. Submitted data cannot be revoked. Submitted data may not be published elsewhere before acceptance of the EuReCa THREE paper. Inclusion of the data in national yearly reports is permitted. Members of the EuReCa THREE study group will have the right to access the data for scientific and other purposes. The use of the data for additional analysis can be applied for by the national coordinators. A written application must be sent to the steering committee, who will decide if the objective falls within the aim of this study.

All participants (registries, national coordinators, steering group, SMT, writing group) have committed to dealing in a confidential manner with data and unpublished results. Breach of confidentiality will result in exclusion of the country from all analyses and publications, including authorship.

9. Publication plan

Publications will be organised by the writing group. The writing group comprises the Principle Investigator, a statistician, the Steering committee and the study management team. The Principle investigator is the first author followed by the steering committee, the statistician, the study management group and the national coordinators. All other contributors and all other representatives of all other countries will appear in the appendix and “medline”.

All publications should be in accordance to the STROBE-Statement [8].

10. Timeline

August 31, 2022	Latest time point to submit signed MoU
September 1, 2022	Begin study period, first patient in
November 30, 2022	Last patient, end of study period
January 31, 2023	Last patient in for 30-day-survival
April 30, 2023	Last data submitted (incl. for 30-day-survival) by national coordinator
August 2023	Analysis and first draft
October 2023	ERC meeting present preliminary results to participants
Early 2024	Publication of EuReCa THREE

11. References

1. European Parliament. Declaration of the European Parliament of 14 June 2012 on establishing a European cardiac arrest awareness week. In: Parliament E, editor. P7_TA(2012)0266; 2012.
2. Chamberlain D. A prize worth the effort: a common European registry of out-of-hospital cardiac arrest. *Resuscitation* 2011; **82**(8): 965-6.
3. Global Resuscitation Alliance. Improving Survival from Out-of-Hospital Cardiac Arrest: A Call to Establish a Global Resuscitation Alliance. Utstein Abbey, Stavangar, Norway, 2015.
4. Grasner JT, Masterson S. EuReCa and international resuscitation registries. *Current opinion in critical care* 2015; **21**(3): 215-9.
5. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Resuscitation* 2015; **96**: 328-40.
6. Gräsner JT, Herlitz J, Koster RW, Rosell-Ortiz F, Stamatakis L, Bossaert L. Quality management in resuscitation--towards a European cardiac arrest registry (EuReCa). *Resuscitation* 2011; **82**(8): 989-94.
7. Gräsner J-T, Lefering R, Koster RW, et al. EuReCa ONE - 27 Nations, ONE Europe, ONE Registry. A prospective one month analysis of out-of-hospital cardiac arrest outcomes in 27 countries in Europe. *Resuscitation* 2016; **105**: 188-95.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of clinical epidemiology* 2008; **61**(4): 344-9.

Appendix 1 – Dataset