PERI-INTERVENTIONAL OUTCOME STUDY IN THE ELDERLY (POSE): EUROPEAN, MULTI-CENTRE, PROSPECTIVE OBSERVATIONAL COHORT STUDY

Clinical Trials.gov	NCT03152734
Chief Coordinating Investigator	Prof. Dr. med. Mark Coburn, MD Department of Anaesthesia RWTH Aachen University Hospital, Germany
Biostatistician	Prof. Dr. rer. nat. Ralf-Dieter Hilgers Department of Medical Statistics RWTH Aachen University Hospital, Germany
Central Organisation/ Project Management	Dr. med. Ana Stevanovic, MD Department of Anaesthesia RWTH Aachen University Hospital, Germany T +49 241 80 35766 F +49 241 80 33 35766
Status, Version, Date of Protocol	Final, V1.0, 11.05.17

I. General information and administrative Structure

Chief Coordinating Investigator

Prof. Dr. med. Mark Coburn
Department of Anaesthesia
University Hospital RWTH Aachen
Pauwelsstr. 30, D-52074 Aachen, Germany
T +49 241 80 88179
F +49 241 80 82593
E-Mail mcoburn@ukaachen.de

Investigator`s Representative and Study Coordinator

Dr. Ana Stevanovic
Department of Anaesthesiology
University Hospital RWTH Aachen
Pauwelsstr. 30, 52074 Aachen, Germany
T +49 241 80 35766
F +49 241 80 3335766
E-Mail astevanovic@ukaachen.de

Biostatistician

Prof. Dr. rer. nat. Ralf-Dieter Hilgers
Department of Medical Statistics
RWTH Aachen University Hospital, Germany
T +49 241 80 89358
F +49 241 80 82501
E-mail: rhilgers@ukaachen.de

Steering Committee (in alphabetic order):

Prof. Dr. Federico Bilotta
Department of Anaesthesiology and Intensive Care
University of Rome "La Sapienza"
Piazzale Aldo Moro 5, 00185 Rome, Italy

Prof. Dr. Cornelius Bollheimer
Department of Geriatric Medicine
University Hospital RWTH Aachen
Pauwelsstr. 30, 52074 Aachen, Germany

Prof. Dr. Wolfgang Buhre

Department of Anaesthesiology and Pain Medicine
Maastricht University Medical Center
P. Debyelaan 25, 6229 HX, Maastricht, Netherlands

PD Dr. Ulf Günther MHBA, DESA, EDIC
Department of Anaesthesiology and Intensive Care
University Hospital Oldenburg
Rahel-Straus-Str. 10, 26133 Oldenburg, Germany

Prof. Dr. Andreas Hoeft
Department of Anaesthesiology and Intensive Care
University Hospital Bonn
Sigmund-Freud-Str. 25, 53127 Bonn, Germany

Dr. Peter Lee MB BCh BAO FCARCSI MD
Department of Anesthesiology
Cork University Hospital, University College Cork
Wilton, Cork, Ireland

Prof. Dr. Idit Matot
Anaesthesia, Pain and Intensive Care Division
Tel Aviv Sourasky Medical Center
6 Weizmann Street, 64239 Tel Aviv, Israel

Prof. Dr. Steffen Rex
Department of Anaesthesiology
UZ/KU Leuven
Herestraat 49, 3000 Leuven, Belgium

Prof. Dr. Rolf Rossaint
Department of Anaesthesiology
University Hospital RWTH Aachen
Pauwelsstr. 30, 52074 Aachen, Germany

Prof. Dr. Jacob Steinmetz
Department of Anaesthesiology
Rigshospitalet
Blegdamsvej 9, 2100 Copenhagen, Denmark

Prof. Dr. Jos Tournoy
Division of Gerontology and Geriatrics
UZ/KU Leuven
Herestraat 49, 3000 Leuven, Belgium

Table of Contents

I. General information and administrative Structure 2

II. Synopsis 7

III. Abbreviations 10

1. Study Rationale and Clinical Relevance 11

1.1 Background 11

1.2 Rationale 11

2. Objectives 12

2.1 Primary endpoint 12

2.2 Secondary endpoints 12

2.3 Other secondary endpoints 13

3. Study Design, Setting and Duration 13

3.1 Study Design 13

3.2 Study Setting 13

3.3 Study Duration 14

4. Study Population 14

4.1 Number of Patients 14

4.2 Inclusion Criteria 14

4.3 Exclusion Criteria 14

4.4 Inclusion of vulnerable populations 15

4.5 Withdrawal Criteria 15

4.6 Subjects of Reproductive Potential 15

4.7 Risk-Benefit Assessment 15

5. Data collection 16

5.1 Outcomes 16

5.1.1 Primary outcome measure (at visit 3): 16

5.1.2 Secondary outcomes and baseline measures: 16

5.2 Study Flowchart 20

6. Study Termination 20

7. Statistics 21

7.1 Sample size 21

7.2 Statistical analysis 21

8. Ethical and Legal Aspects 21

8.1 Ethical approval 21

8.2 Protocol changes 22

8.3 Informed Consent 22

8.4 Subject privacy 22

8.5 Duties of the Principle Investigators 23

8.6 Duties of the National coordinator 23

8.7 Data Protection 23

9. Data Quality Assurance 23

9.1 Quality control 24

9.2 Data management 24

10. Data Handling and Record Keeping 25

10.1 Conclusion of Documentation 25

10.2 Record keeping 25

10.3 Archiving of Documents 25

11. Publication Policy 25

12. Funding and Insurance 26

12.1 Funding 26

12.2 Insurance 26

13. Statement of compliance 27

14. Signatures 28

15. References 29

16. List of Appendices 31

II. SYNOPSIS

Item	Description
Study Title	**P**eri-interventional **O**utcome **S**tudy in the Elderly: European, multi-centre, observational cohort study
Study Short Name	POSE
Protocol version	Final version V1.0, 11.05.2017
Registration with ClinicalTrials.gov	NCT03152734
Chief Investigator	Principal Coordinating Investigator Prof. Dr. med. Mark Coburn Department of Anaesthesia RWTH Aachen University Hospital Pauwelsstraße 30, 52074 Aachen, Germany Phone: +49 241 80 88179 Fax: +49 241 80 82593 E-Mail: mcoburn@ukaachen.de
Financing	This is an investigator-initiated trial. This trial will be supported by the Department of Anaesthesiology, University Hospital of RWTH Aachen, Germany
Insurance	A separate patient`s insurance will not be completed for this non-interventional observational trial.
Risk Benefit Assessment	POSE is a non-interventional observational study. Harms are not expected to any individual patient. Results from this study could help to improve health care systems with regard to the need of elderly patients (i.e. need for critical care units, more advanced monitoring devices, future health facilities and budget.)
Key Words	Elderly patients, mortality, postoperative outcome; post interventional outcome
Medical Study Rationale	The POSE study will predict critical stages and outcome in a large sample of all surgical and non-surgical interventional patients ≥80 years of age in Europe.
Study Objectives	POSE aims to be the first study to create evidence on peri-interventional mortality and outcome in the elderly population.
Evaluation Criteria	**Primary endpoint** is to determine the peri-interventional all-cause mortality rate on day 30 • **Secondary endpoints** are to assess an array of post-

Item	Description
	interventional major complications and functional and cognitive outcome until the post-interventional day 30. Furthermore, we aim to identify differences in the geriatric peri-interventional management across Europe
Study Design	European multi-centre, prospective observational cohort study.
Study Duration	Duration of subject participation: 30 days from anaesthesia Recruitment period for this study: 8 months Recruitment period per centre: 30 days within this 8 months Study duration in total: 16 months including evaluation and clinical study report.
Patients Number	7500 patients
Number of centres	Approximately 100-200 centres
Inclusion Criteria	1. Age ≥ 80 years 2. Written informed consent prior to study participation according to the national law requirements 3. All consecutive patients undergoing surgical and non-surgical interventions (e.g. radiological, neuroradiological, cardiological, gastroenterological) with anaesthesia care (performed by an anaesthetist) within the selected inclusion period of 30 days 4. Elective and emergency procedures 5. In-patient and out-patient procedures
Exclusion Criteria	1. People who are institutionalized by court or administrative order 2. Patients with re-intervention within the 30 days recruitment period, who were already enrolled in this study
Visits	**Visit 1 (Baseline visit pre-interventional)** • Patient demographics, functional and cognitive status, medical history, frailty and referring facility.

Item	Description
	Visit 2 (Intervention) • Intervention- and anaesthesia-related data and kind of post-interventional care **Visit 3 - Follow-up on day 30 (intervention day + 30 days)** **Medical record review:** • Mortality until day 30, hospital - and ICU length of stay, in-hospital outcome according to the ACS NSQIP and analysis of the new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury up to 30-days after intervention **After hospital discharge, events will only be defined as present if they lead to hospital re-admission or death.** • In-hospital cardiopulmonary resuscitation, unplanned ICU admission and /or intubation, discharge destination, admission to a unit with a geriatric care model, functional and cognitive status **Telephone interview in addition to the medical record review, if patient was discharged before day 30:** • Mortality and serious cardiac/ pulmonary complications, stroke and acute kidney injury after hospital discharge, if they led to hospital re-admission or in case of acute kidney injury to renal replacement therapy. • Patient`s functional and cognitive status
Sample size and Statistics	A total sample size of 7500 patients will provide reasonable and valid results for our study aims. The primary endpoint will be analysed by fitting a COX-Regression model to the data of the post-interventional mortality until day 30.

III. Abbreviations

ADL	Activities of daily living
ASA	American Society of Anesthesiologists
CRF	Case Report Form
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EU	European Union
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Act
ICH	International Declaration of Helsinki
ICU	Intensive care unit
IEC/IRB	Independent Ethics Committee/ Independent Review Board
ITT	Intention to treat
LOS	Length of stay
RWTH	Rheinische Westfälische Technische Hochschule

1. Study Rationale and Clinical Relevance

1.1 Background

In Europe, it is estimated that the elderly population (≥80 years) will increase from 5.3% of the total population in 2015 to 9% in 2040 [1]. The aforementioned demographic development suggests a dramatic growth in the number of elderly patients undergoing an increasing variety of surgical and non-surgical interventional procedures. Little is known about the peri-interventional 30-day mortality rates in the elderly population. The EUSOS study revealed an unexpectedly high in-hospital mortality rate of 4% in an unselected Pan-European non-cardiac surgery population [2]. However, the EUSOS study did not specifically address the elderly population. POSE will go far beyond the EUSOS study as POSE will assess specifically the elderly population, if in- or outpatient, elective or emergency surgery and it will also include cardiovascular surgery and non-surgical interventions. Compared with younger interventional patients, the elderly are at greater risk of mortality and morbidity after elective and especially emergency surgery [3]. The underlying mechanisms include age-related decline in physiological and cognitive reserve, and frequent comorbidities such as impaired hepatic and renal function, diabetes mellitus, dementia, delirium, coronary artery disease, heart failure, and patient poly-pharmacy. However data are mostly limited to specific higher risk populations, e.g. the elderly hip fracture patient. In these patients (≥65 years of age), the one-month mortality rate ranged from 8 to 10% [4]. The US National Surgical Quality Improvement Project revealed a dramatic thirty-day all-cause mortality rate of 8% from major non-cardiac surgery for patients older than 80 years [5]. Yet, these data are now more than ten years old and remain unique. In addition, data are lacking in the overall elderly surgical and non-surgical interventional population for: in-hospital and 30-day mortality, the need for planned and unplanned admission to the intensive care unit, the use of non-standard monitoring tools, rate of non-extubation at the end of intervention and re-intubation rate, the postinterventional outcome, as well as length of hospital stay and the discharge destination. Furthermore, risk scores like the NSQIP [6] and POSPOM [7] need to be further evaluated in the elderly surgical population to improve risk communication and clinical decision making. All these factors are of the utmost importance in planning both in and out of hospital health-care systems in Europe. All of the above underlines the urgent need to carry out this European multi-centre prospective observational cohort study.

1.2 Rationale

The ageing European population creates a pressing humanitarian and socioeconomic need to assess not only peri-interventional mortality, but also predict critical stages and outcome

during the patient´s hospitalisation period. Health care systems need to adapt to significant changes, such as the need for intensive care units (ICUs), specialized geriatric care models or more advanced monitoring devices, in order to plan future health facilities and budget. Professional medical organisations will have to foster and promote specific subspecialties at different levels (such as geriatricians in the surgical departments, geriatric anaesthesia fellowship programs, ICUs for the elderly), and advice for postoperative rehabilitation centres to promote recovery. Clinical research in elderly patients is particularly challenging due to patient heterogeneity, and has been further hampered by research that focuses on isolated interventions in frequently underpowered randomized controlled trials. Despite the increasing number of elderly patients, they are often excluded from randomized controlled trials due to frailty, cognitive impairment or other comorbidities. The downside of this approach is that the results of such trials are only valid for selected subpopulations and generalisation in the real world context is limited. To overcome the limitations of prospective randomised studies in the elderly, comparative effectiveness research using a “real life” observational study design is an appropriate and effective approach with favourable external validity. The POSE study will include a large sample of all surgical and non-surgical interventional patients ≥80 years across Europe.

2. Objectives

POSE aims to be the first study to create evidence on peri-interventional mortality and outcome in the elderly population undergoing surgery / non-surgical intervention where an anaesthetist was present.

2.1 Primary endpoint

To determine the peri-interventional (surgical and non-surgical interventional) all-cause mortality rate on day 30.

2.2 Secondary endpoints

- To assess all peri-interventional major complications (cardiac, pulmonary, acute stroke, acute kidney injury) at any time-point within 30-days.
- To assess postoperative in-hospital outcomes in compliance with the National Surgical Quality Improvement Program (NSQIP) for patients undergoing surgical interventions [6].
- To assess the proportion of not extubated patients at the end of surgery/ non-surgical intervention, or unplanned re-intubation within the hospital stay or maximum 30 days post-interventional.

- To assess the planned and unplanned admission rate to ICU within 30 days.
- To assess the post-interventional admission to a unit with a geriatric care model (e.g. geriatric units, geriatric co-management models, geriatric liaison services) or a surgical unit with no "geriatric" support.
- To assess hospital and ICU length of stay (LOS)
- To compare the postoperative in-hospital and 30-day outcome with preoperatively via NSQIP risk calculator and POSPOM predicted outcome for surgeries
- To assess current practice of intra-interventional monitoring for elderly patients
- To assess the intra-interventional anaesthesia-related data
- To assess the intra-interventional intervention-related data
- To assess the referring facility and discharge destination of the patients
- To determine the pre-interventional frailty of the patients
- To assess the peri-interventional functional and cognitive status up to 30 days after surgery/ non-surgical intervention
- To identify differences in the geriatric peri-interventional management in health-care systems across Europe

2.3 Other secondary endpoints

- Subgroup-analyses of the mortality until day 30 with regard to age, pre-interventional morbidities and type of surgery or non-surgical intervention, gender, centre and country
- Analysis of factors, which determine planned or unplanned admission to ICU after intervention
- Incidence of cardiopulmonary resuscitation failure rate

3. Study Design, Setting and Duration

3.1 Study Design

This is a European multi-centre, prospective observational cohort study. Beside the follow up contact on post-interventional day 30, all data will be collected during the clinical routine and there will be no study-related interventions.

3.2 Study Setting

Centres in Europe are invited to participate in this study. We aim to recruit 100-200 centres. All centres will recruit as many as possible consecutive patients within the self-selected time frame of 30 days. We appreciate a minimum of 50 included and completely documented patients per centre, but all included and completely documented patients will be analysed.

Each centre will designate a local principle investigator, who will be supported by a national coordinating investigator for any questions regarding the study conduction or the specific regulatory requirements of the respective country.

3.3 Study Duration

Each centre will have to choose a consecutive 30 days period within the recruitment period of 8 months. The estimated start of the recruitment period will be 01 August 2017. Last patient "in" is anticipated for 31 March 2018. Data cleaning process is planned for 4 months. First results will be available in October 2018. The total study duration will be 15 months including evaluation and clinical study report.

4. Study Population

4.1 Number of Patients

It is planned to enrol 7500 patients throughout Europe.

4.2 Inclusion Criteria

Subjects, fulfilling the following inclusion criteria will be suitable for participation in the study:

- Age ≥ 80 years
- Written informed consent prior to study participation according to the national law requirements
- All consecutive patients undergoing surgical and non-surgical interventions (e.g. radiological, neuroradiological, cardiological, gastroenterological) with anaesthesia care (done by an anaesthetist) within the selected inclusion period of 30 days
- Elective and emergency procedures
- In-patient and out-patient procedures

4.3 Exclusion Criteria

Subjects, fulfilling one or more of the following exclusion criteria will not be included in the study:

- People who are institutionalized by court or administrative order

- Patients with re-intervention within the 30 days recruitment period, who were already enrolled in this study

4.4 Inclusion of vulnerable populations

To ensure the generalizability of our data for elderly patients, we aim to include also legally incompetent patients with legally authorised representative/ health care proxy. Furthermore, we aim to include the emergency population. We propose that it is important to include these patients to ensure that the study population is representative of the wider population of patients, and to avoid selection bias. These patients will be included according to the legal provisions of the respective country, if the patient lacks the capacity to consent at this time-point.

4.5 Withdrawal Criteria

Patients may withdraw from study at any time-point. In case of consent withdrawal, further data collection will be stopped. Already collected data of this patient will only be abolished if required by the regulatory authorities/ institutional review board of the respective centre. Withdrawn patients will not be replaced and not followed up.

4.6 Subjects of Reproductive Potential

Not applicable

4.7 Risk-Benefit Assessment

There is no risk for this non-interventional observational trial. Harms are not expected to any individual patient.

The POSE study will include a large sample of all surgical and non-surgical interventional patients above the age of 80 years across Europe. The results of this study may support health care systems to adapt to the patients´ needs (i.e. the need for critical care units for the elderly, more advanced monitoring devices, geriatricians in the surgical departments, or geriatric anaesthesia fellowship programs). Furthermore, the results may support future health facilities and budget planning.

5. Data collection

5.1 Outcomes

The primary aim of this study is to assess the all-cause mortality rate within 30 days after surgery or non-surgical intervention.

The secondary aims are to analyse the peri-interventional course, treatment measures and other outcomes of this specific population and the differences throughout Europe.

5.1.1 Primary outcome measure (at visit 3):

The primary efficacy outcome is defined as the ***all-cause mortality*** (death from any cause) from intervention until day 30.

5.1.2 Secondary outcomes and baseline measures:

Pre-study questionnaire

During the online registration for this study on the POSE website https://pose-trial.org, all centres will have to complete a questionnaire regarding their institution (see Appendix 1).

Visits

The following data, which will be collected during this study, are presented in detail in the case report form in the Appendix 2.

Visit 1 (Baseline visit pre-interventional)

- Patient demographics (age, gender, weight, height, smoking status, alcohol consumption, American Society of Anesthesiologists (ASA) physical status)
- Patient`s functional status of independency (within 30 days before the intervention), assessed by interview of the patient according to the NSQIP [6] (Independent, partially dependent, totally dependent).
- Chronic Medication (at least until 7 days before intervention)
    - Use of steroids, anticoagulants, antiplatelet therapy, ACE inhibitors, AT II-Receptor blocker, beta blockers, or psychotropics
- Medical history:

- Variables according to the NSQIP [6] (Ascites, systemic sepsis, ventilator dependence before intervention, disseminated cancer, diabetes, arterial hypertension requiring medication, previous cardiac event, congestive heart failure, history of severe COPD, dialysis, acute renal failure)

- Comorbidity variables according to the POSPOM [7] criteria

- Most recent pre-interventional routine laboratory values (only if done in the clinical routine): haemoglobin and haematocrit level; serum creatinine and serum albumin
- Referring facility and distinction between inpatient and outpatient procedures
- Frailty assessment according to the frailty associated criteria [8] This includes in addition to the medical history and laboratory values, history of falls, weight loss, the Mini-Cog™ [9] (Appendix 3) and timed "Up & Go" test [10] (Appendix 4).

Visit 2 (Intervention)

- Intervention related data (date, kind of intervention, urgency of intervention, wound class (clean, clean-contaminated, contaminated, dirty) [11], surgical procedure category, WHO safe surgery checklist)
- Anaesthesia related data (premedication, anaesthetic technique, anaesthesia duration, intra-interventional monitoring, mean anaesthesia drugs during general anaesthesia, intra-interventional transfusion of packed red blood cells, fresh frozen plasmas and platelets)
- Extubation at the end of intervention
- Planned or unplanned ICU admission at the end of intervention
- Post-interventional admission to a specialized unit with "geriatric support" see also 2.2.

Visit 3 - Follow-up on day 30 (intervention day + 30 days)

Medical record review:

- Mortality from intervention until day 30
- Hospital - and ICU LOS (including day of intervention, excluding discharge day)
- In-hospital outcome according to the ACS NSQIP [6] (e.g. pneumonia, cardiovascular complication, surgical site infection, urinary tract infection, venous thromboembolism, acute or progressive renal failure and re-surgery)

- Analysis of the new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury from intervention up to 30-days after intervention (according to the following definition:)

1. ***Serious cardiac complication*** (Cardiac arrest: The absence of cardiac rhythm or presence of a chaotic cardiac rhythm requiring the initiation of CPR, which includes chest compressions. Myocardial infarction defined according to the American Heart Association [12]:

a) Acute rise and/or fall of cardiac troponin, with at least **one value** above the 99th percentile upper reference limit (unless clearly explained by non-ischemic aetiology e.g. pulmonary embolism, sepsis, renal failure, severe acute neurological disease)

AND at least **one** of the following:

b) - Symptoms of ischaemia, **OR**

-New/presumed new significant ST-segment-T wave changes or new left bundle branch block, **OR**

- Development of pathological Q-waves in the electrocardiography (ECG), **OR**

- Imaging evidence (e.g. new loss of viable myocardium/ wall motion abnormality), **OR**

- Identification by angiography or autopsy

For patients, who underwent Coronary artery bypass grafting:

a) Acute rise of cardiac troponin >10 x 99th percentile upper reference limit

AND

b) - New pathological Q-waves or new left bundle branch block in the ECG, **OR**

- Imaging evidence (e.g. new loss of viable myocardium/ wall motion abnormality), **OR**

- Identification by angiography or autopsy

2. ***Serious pulmonary complication*** (Pneumonia: Clinical or radiological diagnosis. Pulmonary embolism: Radiological diagnosis. Signs of pneumonia or pulmonary embolism in the autopsy)
3. ***Acute Stroke*** (Defined as a new focal or generalised neurological deficit of >24h duration in motor, sensory, or coordination functions with compatible brain imaging

and confirmed by a neurologist. Transient ischemic attack is not considered as acute stroke. Signs of stroke in the autopsy.)

4. ***Acute kidney injury*** (Defined according to the AKIN classification [13] as AKI stage ≥2. This means increase of creatinine >2-3x from baseline within the hospital stay. Or urine output less than 0.5 ml kg^{-1} per hour for more than 12 hours. Or signs of acute kidney injury in the autopsy.)

After hospital discharge, events will only be defined as present if they lead to hospital re-admission or death.

- Rate of in-hospital cardiopulmonary resuscitation within the post-interventional hospital stay until discharge or maximum day 30
- Unplanned ICU admission within the post-interventional hospital stay until discharge or maximum day 30
- Unplanned intubation after intervention within the post-interventional hospital stay until discharge or maximum day 30
- Hospital discharge destination
- Admission to a unit with a geriatric care model within the post-interventional hospital stay until discharge or maximum day 30
- Patient`s functional status of independency assessed by interview of the patient according to the NSQIP [6] (Independent, partially dependent, totally dependent).
- Brief screen for cognitive impairment by one Item of the BSCI [14] (the recall of three words -dog, apple, house- after 2 minutes)

Telephone interview in addition to the medical record review, if patient was discharged before post-interventional day 30:

- Assessment of mortality
- Assessment of serious cardiac/ pulmonary complications, stroke and acute kidney injury after hospital discharge, if they led to hospital re-admission or in case of acute kidney injury to renal replacement therapy.
- Patient`s functional status of independency assessed by interview of the patient according to the NSQIP [6] (Independent, partially dependent, totally dependent).
- Brief screen for cognitive impairment by one Item of the BSCI [14] (the recall of three words -dog, apple, house- after 2 minutes)

5.2 Study Flowchart

Appendix 5

6. Study Termination

There are no reasons for prematurely termination of the entire study or for an individual subject expected (except of patient withdrawal).

7. Statistics

7.1 Sample size

According to the aim of our European multicentre observational cohort study, a sample size or power calculation is explorative rather than rigorous. Taking two dichotomous effect modifiers into account, a reasonable total sample size to detect for example a 2% change from 10% to 8% could be detected by a log-rank test at the overall 5% significance level (Bonferroni Correction) with 80% power would be 3313 (balanced design, nQuery Advisor 7.0). Taking these arguments into consideration, we believe that a total sample size of 7500 patients will provide reasonable and valid results for our study aims.

7.2 Statistical analysis

All patients enrolled in this study will be analysed. Statistical analysis will be performed after database cleaning process and database lock. At that time the initially planned statistical analysis will be described in the trial statistical analysis plan. Dichotomization of the relevant effect modifying factors will be defined. The primary endpoint will be analysed by fitting a Cox-Regression model to the data of the postinterventional mortality until day 30. The analysis will use age and type of intervention as stratification variables allowing for in-cluster correlation. Since the number of factors to be investigated is high, variable selection techniques (e.g. CART regression tree, LASSO methods or bootstrapp methods) will be used. The importance of the independent factors will be investigated based on the parameter estimates and corresponding 95% confidence intervals. Similar methods will be used to evaluate secondary endpoints. We will use SASTM and/or R for statistical analysis.

8. Ethical and Legal Aspects

This study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

8.1 Ethical approval

This is a solely observational study, without any interventions. All patients will receive routine care.

Ethics approval may not be required in all participating nations. National coordinators will be responsible for clarifying the need for ethics approval in the respective country. They will support the national centres with the application for a permission to collect observational

clinical data. Centres will not be permitted to record data unless ethics approval or an equivalent waiver is in place. If applicable informed consent forms and any other written information, which will be provided to the subjects should be subject to the Independent Review Board (IRB)/ Independent Ethics Committee (IEC) review and given approval/ favourable opinion. If informed consent is not required by the local IRB, a waiver must be obtained from the IRB/ IEC.

8.2 Protocol changes

Any change in the study protocol and/or informed consent form will have to be presented to the IRB/ IEC and approved before implementation (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

8.3 Informed Consent

An informed consent has to be obtained from patients prior study-participation, if required by the respective IRB/ IEC approval of the centre. The patients will voluntarily confirm their willingness to participate in the study, after comprehensive written and/ or verbally information by an investigator. The patients will sign an informed consent form for study participation as well as disclosure of individual data. The patients will receive a copy of the consent from.

By including the emergency interventional population some patients may lack the capacity to consent to participate in this study (e.g. due to delirium or dementia), especially at the earliest time-point. Therefore, either legal representatives or relatives will receive detailed verbal and written information and will be asked to give verbal and written informed consent/ assent. If patients recover the capacity to provide consent, they will be asked to give oral and written informed consent, as soon as possible. Country specific laws will be respected and applied to the informed consent procedure, especially for emergency cases, with absence of a legally authorised representative/ health care proxy at the intervention time-point.

8.4 Subject privacy

Patients will be informed about data protection. Data will be pseudonymised (coded by a 9 digits number) and handed out to third party anonymised. Access to encoded data or source documents will only be given to authorised bodies or persons (authorised staff, auditors, competent authorities or ethics commission) for validation of data. Confidentiality of the collected data will be warranted also in case of publication.

8.5 Duties of the Principle Investigators

Principle investigators of each centre will have to:

- Ensure that all relevant regulatory approvals have been obtained
- Ensure, that all sub-investigators and the assisting study personnel will be adequately qualified and informed about the study protocol, any amendments, and their study related responsibilities and functions.
- Be responsible for accurate data collection and timely documentation into the electronic case report form (eCRF)
- Be in close contact with the national coordinator

8.6 Duties of the National coordinator

The national coordinators will be appointed by the steering committee to lead the project within the respective country. They will support this study by:

- Recruitment of centres
- Translation of relevant study documents, needed for the application at the IRB/ IEC within the respective country
- Ensuring that the necessary regulatory approvals are in place prior to the start date of each participating centre in his/ her country
- Ensuring good communication with the participating centres in his/ her country

8.7 Data Protection

A unique 9 digits number will identify all subjects. Each principle investigator will safely keep a list, which will allow the identification of the coded (pseudonymised) patients.

9. Data Quality Assurance

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator has to inform the national coordinator/ chief coordinating investigator immediately about any inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or regulatory authorities, and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

9.1 Quality control

Standardisation procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardisation among sites (e.g., web-based-training, newsletters, centralised evaluations, and validation methods).

9.2 Data management

The principle investigator will maintain an Investigator Site File, which includes the protocol, IEC/ IRB approval/ judgment, local translation of informed consent form (if applicable), the signed patient informed consents (if applicable), a study staff log etc. Furthermore, each site will maintain a confidential pseudonymisation patient log (subject identification code list). All handling of personal data will comply with the GCP – guidelines.

All participating centres will be provided with data acquisition sheets (case report form - CRF) that enable standardised data collection after enrolment of the patient (see Appendix 2). These paper CRFs will include the patient`s name, birth date and 9 digits pseudonymisation number. The first 3 digits will consist of a country-specific number, the second 3 digits will be a centre-specific number and the last 3 digits, will correspond to the individual patient. All collected data have to be entered in the paper CRF and to be considered as source data.

The patients` source data and the pseudonymisation patient log will be stored in a locked cabinet/ room with restricted access on behalf of the principle investigator of each centre.

Investigators will enter the information required by the protocol anonymised into an Internet based electronic data collection system (eCRF). The eCRF (OpenClinica) will be developed by the Department of Anaesthesiology, University Hospital RWTH Aachen. Detailed information on the eCRF completion will be provided on the study website https://pose-trial.org. The access to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data collection system; answers to queries or changes of the data will directly be documented in the system. Plausibility checks will be performed to ensure correctness and completeness of these data. The database will be closed, after all data are entered and all queries are solved. It will not be possible to connect an anonymised eCRF entry to a specific patient.
The investigators will also have to maintain a screening log during the selected study recruitment period of 30 days. All potentially eligible patients will have to be listed in this screening log.

10. Data Handling and Record Keeping

10.1 Conclusion of Documentation

By signing the CRF (eCRF/ eSignature), the investigator confirms that all investigations have been completed and conducted in compliance with the clinical study protocol, and that reliable and complete data have been entered into the eCRF.

10.2 Record keeping

Data will be handled confidentially and all data will be stored for the length of the study and for 10 years afterwards.

10.3 Archiving of Documents

The investigator will keep the subject's files and original data as long as possible and according to the local methods and facilities. The investigator should maintain the trial documents as specified in the ICH-GCP-Guideline for at least 10 years. The investigator/ institution should take measures to prevent accidental or premature destruction of these documents.

11. Publication Policy

The study results will be published in appropriate international scientific journals. The study will be registered and study results will be disclosed by the coordinating principal investigator in one or more public clinical study registry(ies), according to national/ international use. The registration will include a list of the investigational sites. The steering committee and the national coordinators will be listed as co-authors in the publications. Top enrolling sites with >200 enrolled and completely documented patients, will also be able to designate one co-author.

Each participating centre including at least one patient can designate a collaborator that will be mentioned in the publications. For each further 25 included and completely documented patients one more collaborator can be designated. These collaborators will be mentioned in the POSE-study group and will be trackable via PubMed. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The steering committee will consider proposals for secondary analyses on the basis of the scientific quality of the proposal. Proposals will need to be revised and approved by the steering committee prior to submission.

12. Funding and Insurance

12.1 Funding

This clinical trial is an investigator-initiated trial. There is no external funding for this observational trial. Data management is supported by the Department of Anaesthesiology, University Hospital of RWTH Aachen, Germany

12.2 Insurance

Not applicable for this observational trial without any study-specific treatment.

13. Statement of compliance

Investigational Site(s)

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the case report form, ICH-GCP principles (EU Directive 2001/20/EG), the Declaration of Helsinki, and regulatory authority requirements of my country.

I agree to:

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate IEC/IRB before enrolling any patient in this study.
- Obtain informed consent for all patients prior to any study-related action performed, if applicable in my country.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files

Furthermore, I understand that:

- Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of RWTH University Aachen and – as applicable – of the appropriate IEC/IRB and regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to RWTH University Aachen
- Any deviation from the clinical study protocol may lead to early termination of the study site.
- With my signature below, I also acknowledge receipt of the study protocol.

14. Signatures

The study protocol is accepted by

Coordinating Investigator

Prof. Dr. med. Mark Coburn Department of Anaesthesia RWTH Aachen University Hospital	Aachen, 12.05.2017

The Coordinating Investigator`s Representative

Dr. Ana Stevanovic Department of Anaesthesia RWTH Aachen University Hospital	Aachen, 11.05.2017

The Biostatistician

Prof. Dr. Ralf-Dieter Hilgers Department of Medical Statistics University Hospital RWTH Aachen	Aachen, 22.5.2017

Principle Investigator

XX	XX,

15. References

1 Population structure and ageing - Statistics Explained. Population structure and ageing - Statistics Explained. Retrieved from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing#Population_structure.

2. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet. 2012;380: 1059-1065.

3. Griffiths R, Beech F, Brown A, Dhesi J, Foo I, Goodall J, et al. Peri-operative care of the elderly 2014: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2014;69 Suppl 1: 81-98.

4. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009;302: 1573-1579.

5. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005;53: 424-429.

6. Bilimoria KY, Liu Y, Paruch JL, Zhou L, Kmiecik TE, Ko CY, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217: 833-42.e1-3.

7. Le Manach Y, Collins G, Rodseth R, Le Bihan-Benjamin C, Biccard B, Riou B, et al. Preoperative Score to Predict Postoperative Mortality (POSPOM): Derivation and Validation. Anesthesiology. 2016;124: 570-579.

8. Oresanya LB, Lyons WL, Finlayson E. Preoperative assessment of the older patient: a narrative review. JAMA. 2014;311: 2110-2120.

9. Alagiakrishnan K, Marrie T, Rolfson D, Coke W, Camicioli R, Duggan D, Launhardt B, Fisher B, Gordon D, Hervas-Malo M, and Magee B. Simple cognitive testing (Mini-Cog) predicts in-hospital delirium in the elderly. J Am Geriatr Soc. 2007;55:314-316.

10. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39: 142-148.

11. Garner JS CDC guideline for prevention of surgical wound infections, 1985. Supersedes guideline for prevention of surgical wound infections published in 1982. (Originally published in November 1985). Revised. Infect Control. 1986;7: 193-200.

12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation. 2012;126: 2020-2035.

13. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, and Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11: 31.

14. Hill J, McVay JM, Walter-Ginzburg A, Mills CS, Lewis J, Lewis BE, et al. Validation of a brief screen for cognitive impairment (BSCI) administered by telephone for use in the medicare population. Dis Manag. 2005;8: 223-234.

16. LIST OF APPENDICES

Appendix 1	Pre-study questionnaire
Appendix 2	Case Report Form (CRF)
Appendix 3	Mini-Cog™
Appendix 4	Timed Up & Go test
Appendix 5	Study flow chart