# TRIAL STATISTICAL ANALYSIS PLAN

## PERI-INTERVENTIONAL OUTCOME STUDY IN THE ELDERLY (POSE):

### EUROPEAN, MULTI-CENTRE, PROSPECTIVE OBSERVATIONAL

### COHORT STUDY

VERSION 1.2, 11.02.2020


| | |
|---|---|
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# SUMMARY

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACS | American College of Surgeons |
| AKI | Acute kidney injury |
| ASA | American Society of Anesthesiologists |
| BSCI | Brief Screen for Cognitive Impairment |
| CRF | Case Report Form |
| ICH | International Declaration of Helsinki |
| ICU | Intensive care unit |
| LOS | Length of stay |
| NSQIP | National Surgical Quality Improvement Program |
| RWTH | Rheinisch-Westfälische Technische Hochschule |
| USA | United States of America |
| WHO | World Health Organization |

# 1. INTRODUCTION

The Trial Statistical Analysis Plan (TSAP) is a detailed technical extension to the clinical study protocol focussing on data handling and statistical analysis, which follows the principles of the guidelines ICH E3, E6, E8, E9 and considers recommendations of the STROBE statement for cohort studies. It is related to:

| Document | Version | Relation |
|---|---|---|
| Study Protocol | Version 2.0, 14.06.2018 | Description of study design and objectives |

The study protocol can be accessed through https://pose-trial.org/study-documents/

This TSAP was written before analysing the data. It is limited to the description of the analysis of the primary outcome.

# 2. SOFTWARE UTILIZED

## 2.1 OPERATING SYSTEM

Current operating system is Windows 10 Professional. In the event of an update to a new version of the operating system, the new system is then used.

## 2.2 DATABASE

OpenClinica, Version 3.14.

## 2.3 STATISTICAL ANALYSIS

SAS (Version 9.4, SAS Institute Inc, Cary, NC, USA) and R Version 3.5.1 are used for statistical analyses. In the event of an update to a new version of SAS or R, the new version is then used.

# 3. STUDY DESIGN

The POSE-trial is a European multi-centre, prospective observational cohort study.

# 4. STUDY OBJECTIVES

An important goal of the POSE-trial is the description of the current health care of elderly patients. Therefore, many of the collected endpoints will be presented descriptively. The primary endpoint (time until all-cause mortality with maximum follow-up of 30 days) will additionally be analysed using inferential statistics.

# 5. TARGET VARIABLES

A detailed description of all variables can be found in the CRFs. The CRFs can be accessed through https://pose-trial.org/study-documents/

## 5.1 PRIMARY ENDPOINT

The primary endpoint is defined as the time after intervention until all-cause mortality (death from any cause). The maximum length of follow-up is set to 30 days.

Variables regarding the primary endpoint are given in Table 1. The exact definition of the primary endpoint (variables Surv_Time_30 and Surv_Status_30) is explained in section 6.4.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Surv_Time_30 | Survival time until all-cause mortality or censoring | Days | Continuous |
| Surv_Status_30 | Censoring status (1 = patient died) | | Dichotomous |

*Table 1: Primary endpoint.*

## 5.2 SECONDARY ENDPOINTS

On overview of all secondary endpoints is given in Table 2. A description of secondary endpoints classified by data type follows in subsections 5.2.1 to 5.2.4. The exact definition of some of the secondary endpoints is explained in section 6.5.

| Variable | Description | Data type |
|---|---|---|
| Discharge_Destination | Discharge destination category if patient was discharged before day 30 | Nominal |
| Hospital_Length_Stay | Hospital length of stay after intervention until follow-up | Continuous |
| ICU_Length_Stay | Total ICU length of stay after intervention | Continuous |
| Admission_ICU_FollowUp | Unplanned ICU admission at any time after intervention until day 30 | Dichotomous |
| Admission_Geriatric_FollowUp | Admission to a unit with "geriatric support" at any time-point until day 30 | Dichotomous |
| NSQIP_Outcome_Hospital | In hospital outcome according to the ACS NSQIP (None of the mentioned, Cardiac arrest, …) | Nominal |
| NSQIP_none | NSQIP: None of the mentioned | Dichotomous |
| NSQIP_Cardiac_Arrest | NSQIP: Cardiac arrest | Dichotomous |
| NSQIP_Myocard_Infarct | NSQIP: Myocardial infarction | Dichotomous |
| NSQIP_Pneumonia | NSQIP: Pneumonia | Dichotomous |
| NSQIP_Pulm_Embol | NSQIP: Pulmonary embolism | Dichotomous |
| NSQIP_Unplanned_Intub | NSQIP: Unplanned intubation | Dichotomous |
| NSQIP_Ventilator_48h | NSQIP: Ventilator > 48h | Dichotomous |
| NSQIP_Return_OP | NSQIP: Return to the operating room | Dichotomous |
| NSQIP_Stroke | NSQIP: Stroke | Dichotomous |
| NSQIP_AKI | NSQIP: Acute kidney injury | Dichotomous |
| NSQIP_DVT | NSQIP: DVT | Dichotomous |
| NSQIP_Venous_Thromb | NSQIP: Venous thromboembolism/ blood clot | Dichotomous |
| NSQIP_Super_SSI | NSQIP: Superficial incisional SSI | Dichotomous |
| NSQIP_Deep_SSI | NSQIP: Deep incisional SSI | Dichotomous |
| NSQIP_Organ_SSI | NSQIP: Organ space SSI | Dichotomous |
| NSQIP_Wound_Disruption | NSQIP: Wound disruption | Dichotomous |
| NSQIP_Systemic_Sepsis | NSQIP: Systemic sepsis | Dichotomous |
| NSQIP_Urinary_Infect | NSQIP: Urinary tract infection | Dichotomous |
| NSQIP_Discharge_PA_Care | NSQIP: Discharge to post-acute care (other hospital, nursing /rehab facility) | Dichotomous |
| Functional_Status_FollowUp | Actual functional status in hospital | Ordinal |
| BSCI_FollowUp | Brief screen for cognitive impairment at Hospital: Correct Number of recalled words | Continuous |
| FollowUp_Status | Patient status on day 30 (Alive, Dead, Follow-up not performed/not available) | Nominal |
| Complications_After_Discharge | Any of the following complications after hospital discharge requiring re-admission, renal replacement therapy or leading to death | Dichotomous |
| Cardiac_Complications | Cardiac complications after hospital discharge requiring re-admission or leading to death | Dichotomous |
| Pulmonary_Complications | Pulmonary complications after hospital discharge requiring re-admission or leading to death | Dichotomous |

| | | |
|---|---|---|
| Stroke_Complications | Stroke after hospital discharge requiring re-admission or leading to death | Dichotomous |
| AKI_Complications | Acute kidney injury requiring renal replacement therapy | Dichotomous |
| Functional_Status_TFU | Actual functional status in telephone interview | Ordinal |
| BSCI_TFU | Brief screen for cognitive impairment at telephone interview: Correct Number of recalled words | Continuous |

*Table 2: Secondary endpoints.*

### 5.2.1 Continuous secondary endpoints

Continuous secondary endpoints include:

- Duration of anaesthesia during intervention
- Hospital length of stay after intervention
- Total ICU length of stay after intervention
- The cognitive status measured by the brief screen for cognitive impairment (scale from 0-3) measured at follow-up

### 5.2.2 Dichotomous secondary endpoints

Dichotomous secondary endpoints include:

- Admission to ICU directly after intervention
- If admission to ICU directly after intervention, was the admission unplanned
- Admission to a unit with “geriatric” support directly after intervention
- Intraoperative transfusion of packed blood cells, fresh frozen plasma or platelets
- The occurrence of unplanned admission to ICU at any time after intervention until day 30
- The occurrence of admission to a unit with "geriatric support" at any time after intervention until day 30
- In hospital outcomes according to the ACS NSQIP (such as cardiac arrest, myocardial infarction, pneumonia, pulmonary embolism) after intervention until day 30
- The occurrence of unplanned re-intubation within the hospital stay or maximum 30 days post-interventional.
- The occurrence of peri-interventional major complications after hospital discharge that led to hospital re-admission (such as serious cardiac, pulmonary complications or stroke) or to renal replacement therapy (acute kidney injury)

### 5.2.3 Nominal secondary endpoints

Nominal secondary endpoints include:

- Hospital discharge destination (Other hospital, rehabilitation, nursing home, home, other)

### 5.2.4 Ordinal secondary endpoints

Ordinal secondary endpoints include:

- The functional status (independent < partially dependent < totally dependent) measured at follow-up

## 5.3 SENSITIVITY ANALYSES

We will perform the following sensitivity analyses:

- We will perform a sensitivity analysis of the primary endpoint (time until all-cause mortality) with the following two-way interaction effects:
    - Age and premedication before intervention
    - Frailty and premedication
    - Anaesthesia technique and severity of intervention

  The interaction effects were chosen based on clinical relevance. For the sensitivity analysis, the premedication before intervention and the anaesthesia technique are included as independent variables even if they are not selected as independent variables for the main analysis. All other independent variables are the same as in the main analysis.
- We will perform a sensitivity analysis of the primary endpoint (time until all-cause mortality), treating all missing data from covariates as missing, i.e., without using imputation techniques. The independent variables are the same as in the main analysis.

# 6. DATA HANDLING

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.

After closing of the OpenClinica database, the database will be exported in SAS format. Access to the study data can be requested from the Department of Anaesthesia (Medical Faculty, RWTH Aachen University). Requests will be handled on a case-by-case basis.

## 6.1 DATE AND TIME VARIABLES

Date Variables are transformed to a SAS defined numeric variable with SAS Format DATE9. Time variables are transformed to a SAS defined numeric variable with SAS Format TIME5.

## 6.2 PRECISION OF ESTIMATES

All summary statistics (e.g. mean, SD) will be rounded to one decimal place more than decimal places given in export from OpenClinica. Percentages will be rounded to two decimal places. Estimates and p-values will be rounded to four decimal places.

Because of possible rounding errors, the sum of percentages is not necessarily 100 %.

## 6.3 TRANSFORMATION OF HEAVILY SKEWED DATA

Heavily skewed continuous variables will be transformed for inferential statistic to improve model fit. The skewness of continuous variables will be investigated using histograms and boxplots by visual inspection.

## 6.4 DEFINITION OF THE PRIMARY ENDPOINT

The primary endpoint of time until death (all-cause mortality) is defined by a survival time and a status variable. The status variable is 1 if the patient experiences an event (dies) and 0 if the patient does not have an event (observation is censored). The survival time is the time until death or the time until last contact (censoring) with a maximum follow-up of 30 days.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Date_Intervention_End | Date of the end of anaesthesia (intervention) | DDMMYY | DATE |
| Date_FollowUp | Date the follow-up was performed | DDMMYY | DATE |
| Death_Hospital | Did patient die in hospital before day 30 | | Dichotomous |
| Date_Death_Hospital | Date of death in hospital | DDMMYY | DATE |

| | | | |
|---|---|---|---|
| Discharged | Was patient discharged before day 30 | | Dichotomous |
| Date_Discharge | Date of discharge | DDMMYY | DATE |
| FollowUp_Status | Patient status on day 30 (Alive, Dead, Follow-up not performed/not available) | | Nominal |
| Date_Death_Outside | Date of death outside | DDMMYY | DATE |
| Surv_Time | Time until event or censoring for maximum available follow-up | Days | Continuous |
| Surv_Status | Censoring status for maximum available follow-up | | Dichotomous |
| Surv_Time_30 | Time until event or censoring for maximum follow-up of 30 days | Days | Continuous |
| Surv_Status_30 | Censoring status for maximum follow-up of 30 days | | Dichotomous |

*Table 3: Variables for the definition of the primary endpoint.*

```
/* Define primary endpoint (time until death)                */
DATA poseData; SET poseData;
  Surv_Time = . ; Surv_Status = .;
  * Patient still in hospital at day 30, alive;
  if Discharged = 2 and Death_Hospital = 2 then do;
    Surv_Status = 0;
    Surv_Time = DATDIF(Date_Intervention_End, Date_FollowUp,'ACT/ACT');
    end;
  * Patient died in hospital;
  if Death_Hospital = 1 then do;
    Surv_Status = 1;
    Surv_Time = DATDIF(Date_Intervention_End, Date_Death_Hospital,'ACT/ACT');
    end;
  * Patient discharged before day 30, died outside;
  if Discharged = 1 and FollowUp_Status = 2 then do;
    Surv_Status = 1;
    Surv_Time = DATDIF(Date_Intervention_End, Date_Death_Outside, 'ACT/ACT');
    end;
  * Patient discharged before day 30, still alive at telephone interview;
  if Discharged = 1 and FollowUp_Status = 1 then do;
    Surv_Status = 0;
    Surv_Time = DATDIF(Date_Intervention_End, Date_FollowUp, 'ACT/ACT');
    end;
  * Patient discharged before day 30, no follow-up;
  if Discharged = 1 and FollowUp_Status = 3 then do;
    Surv_Status = 0;
    Surv_Time = DATDIF(Date_Intervention_End, Date_Discharge, 'ACT/ACT');
    end;
  * Other scenarios should not be observed;
  else do;
    put 'Invalid category for' Surv_Stat;
    put 'Invalid category for' Surv_Time;
    end;
RUN;

/* Censor deaths due to the maximum follow-up of 30 days     */
DATA poseData; SET poseData;
  Surv_Time_30 = min(Surv_Time, 30);
  Surv_Status_30 = Surv_Status;
  if Surv_Time > 30 and Surv_Status = 1 then do;
    Surv_Time_30 = 30;
    Surv_Status_30 = 0;
  end;
RUN;
```

## 6.5 DEFINITION OF SECONDARY ENDPOINTS

The duration of anaesthesia (Duration_Anaesthesia) is defined as the difference in minutes between start and end of anaesthesia.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Date_Intervention_Start | Date of the start of anaesthesia (intervention) | DDMMYY | DATE |
| Anaesthesia_Start | Start of anaesthesia time | hh:mm | TIME |
| Date_Intervention_End | Date of the end of anaesthesia (intervention) | DDMMYY | DATE |
| Anaesthesia_End | End of anaesthesia time | hh:mm | TIME |
| Duration_Anaesthesia | Duration of anaesthesia | Minutes | Continuous |

*Table 4: Variables for the definition of the duration of anaesthesia endpoints.*

```
/* Define duration of anaesthesia                                    */
DATA poseData; SET poseData;
  Duration_Anaesthesia = INTCK('minute', Anaesthesia_Start, Anaesthesia_End) +
    1440*(Date_Intervention_End-Date_Intervention_Start);
RUN;
```

## 6.6 CATEGORIZATION OF INDEPENDENT VARIABLES

Some continuous variables are categorized for description (e.g. Kaplan-Meier curves). Continuous variables will, however not be categorized for inference on primary or secondary outcomes and treated as continuous covariates.

Some nominal variables are categorized to create variables with fewer categories. The newly created variables with fewer categories are used for inference.

### 6.6.1 Age categories

For description, the age of patients is categorized in categories from 80 to 84, 85 to 89 and 90 to 120.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Age | Age | years | Continuous |
| Age_Category | Age categorized in 3 groups | | Ordinal |

*Table 5: Variables for the categorization of age.*

```
/* Define age categories                                             */
DATA poseData; SET poseData;
  length Age_Category $12;
  if Age >=80 and Age<85 then Age_Category = "[80,85)";
  if Age >=85 and Age<90 then Age_Category = "[85,90)";
  if Age >=90 then Age_Category = "> 90";
RUN;
```

### 6.6.2 Intervention technique categories

The intervention technique was surveyed in 26 categories. For statistical inference, these 26 categories are grouped into 9 main categories:

1. Cardiovascular and Thoracic: Cardiac; Thoracic; Vascular major; Vascular minor
2. Gynaecologic and Urologic: Gynaecologic; Urologic major; Urologic minor
3. Abdominal: Gastrointestinal major; Gastrointestinal minor; Hepatic major; Hepatic minor
4. Orthopaedic, Trauma and Plastic: Athroplasty and spine; Multiple trauma related; Orthopaedic other; Orthopaedic trauma; Plastic
5. ENT and Eyes: Ear, nose and throat (ENT); Ophthalmologic
6. Interventional: Endoscopic digestive; Interv. Cardiology; Interv. Cardiorhythmology; Interv. neuroradiology
7. Neurosurgery: Neuro
8. Other surgery

9. Transplant: Transplant; Renal transplant

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Interventional_Category_26 | Different interventional techniques surveyed in 26 groups | | Nominal |
| Interventional_Category_9 | Different interventional techniques categorized in 9 groups | | Nominal |

*Table 6: Variables for the categorization of interventional techniques.*

```
/* Define surgical categories                                    */
DATA poseData; SET poseData;
  length Interventional_Category_9 $30;
  Interventional_Category_9 = '';
  if Interventional_Category_26 in ('2', '20', '24', '25') then
    Interventional_Category_9 = 'Cardiovasc and thoracic';
  if Interventional_Category_26 in ('7', '22', '23') then
    Interventional_Category_9 = 'Gyn and uro';
  if Interventional_Category_26 in ('5', '6', '8', '9') then
    Interventional_Category_9 = 'Abdominal';
  if Interventional_Category_26 in ('1', '13', '16', '17', '18') then
    Interventional_Category_9 = 'Ortho, trauma and plastic';
  if Interventional_Category_26 in ('3', '15') then Interventional_Category_9 =
    'ENT and Eyes';
  if Interventional_Category_26 in ('4', '10', '11', '12') then
    Interventional_Category_9 = 'Interventional';
  if Interventional_Category_26 in ('14') then Interventional_Category_9 =
    'Neurosurgery';
  if Interventional_Category_26 in ('19', '21') then Interventional_Category_9 =
    'Transplant';
  if Interventional_Category_26 in ('26') then Interventional_Category_9 =
    'Other';
RUN;
```

### 6.6.3 Type of anaesthesia

The type of anaesthesia is categorized in 4 groups (general anaesthesia vs. regional anaesthesia vs. sedation anaesthesia vs. combined anaesthesia).

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Anaesthesia_Techniques | List of anaesthesia techniques used | | Nominal |
| Anaesthesia_Technique | Different anaesthesia techniques categorized in 4 groups of anaesthesia | | Nominal |

*Table 7: Variables for the categorization of anaesthesia techniques.*

```
/* Define anaesthesia categories                                 */
DATA poseData; SET poseData;
  Anaesthesia_Technique = "Combination";
  if Anaesthesia_Techniques = "1" then Anaesthesia_Technique = "General";
  if Anaesthesia_Techniques in ("2", "3", "4") then Anaesthesia_Technique =
    "Regional";
  if Anaesthesia_Techniques = "5" then Anaesthesia_Technique = "Sedation";
  if Anaesthesia_Techniques = "" then Anaesthesia_Technique = "";
RUN;
```

## 6.7 DEFINITION OF INDEPENDENT VARIABLES

### 6.7.1 Frailty

Frailty is defined similar to (Oresanya, Lyons and Finlayson 2014), which is based on the original publication by (Robinson, et al. 2009). A patient is classified as frail if at least 4 of the following 6 criteria are fulfilled:

- Mini-Cog score of ≤ 3 points
- Albumin level of ≤ 3.3 g/dl

- More than 1 fall in the last 6 months
- Haematocrit level of < 35%
- Preoperative functional status is partially dependent or totally dependent
- ≥3 comorbidities

By definition, if one criterion is missing, the criterion is interpreted as “not present”.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Mini_Cog_Total | Total point from the Mini Cog test at baseline | | Continuous |
| Albumin | Albumin level at baseline | g/dl | Continuous |
| History_Falls | History of falls during the last 6 months | | Ordinal |
| Haematocrit | Haematocrit level at baseline | % | Continuous |
| Functional_Status_BL | Functional status within 30 days before baseline | | Ordinal |
| Risk_Ischemic_Heart_Disease | Presence of Ischemic heart disease | | Dichotomous |
| Risk_Cardiac_Arrhythmia | Presence of cardiac arrhythmia or heart blocks | | Dichotomous |
| Risk_Chronic_Heart_Failure | Presence of chronic heart failure or cardiomyopathy | | Dichotomous |
| Risk_Peri_Vascular_Disease | Presence of peripheral vascular disease | | Dichotomous |
| Risk_Hemiplegia | Presence of hemiplegia | | Dichotomous |
| Risk_COPD | Presence of COPD | | Dichotomous |
| Risk_Chronic_Resp_Failure | Presence of chronic respiratory failure | | Dichotomous |
| Risk_Alcohol_Abuse | Chronic alcohol abuse | | Dichotomous |
| Risk_Cancer | Presence of cancer | | Dichotomous |
| Risk_Transpl_Organs | Presence of transplanted organ(s) | | Dichotomous |
| Risk_Dementia | Presence of dementia | | Dichotomous |
| Risk_Cerebrovascular_Disease | Presence of cerebrovascular disease | | Dichotomous |
| Risk_Mild_Cogn_Impair | Presence of mild cognitive impairment | | Dichotomous |
| Risk_Chron_Renal_Failure | Presence of chronic renal failure | | Dichotomous |
| Risk_Cogn_Complaints | Presence of other cognitive complaints | | Dichotomous |
| Diabetes | Presence of diabetes | | Dichotomous |
| Hypertension | Presence of hypertension requiring medication | | Dichotomous |
| Frailty | Frailty according to (Robinson, et al. 2009) | | Dichotomous |

*Table 8: Variables for the definition of frailty.*

```
/* Define frailty                                                */
DATA poseData; SET poseData;
  Frailty_Points = 0;
  Frailty = 0;
  if Mini_Cog_Total ne . and Mini_Cog_Total <= 3 then Frailty_Points =
    Frailty_Points + 1;
  if Albumin ne . and Albumin <= 3.3 then Frailty_Points = Frailty_Points + 1;
  if History_Falls = '3' then Frailty_Points = Frailty_Points + 1;
  if Haematocrit ne . and Haematocrit < 0.35 then Frailty_Points = Frailty_Points
    + 1;
  if Functional_Status_BL ne '1' then Frailty_Points = Frailty_Points + 1;
  if sum(Risk_Ischemic_Heart_Disease, Risk_Cardiac_Arrhythmia,
    Risk_Chronic_Heart_Failure, Risk_Peri_Vascular_Disease, Risk_Hemiplegia,
    Risk_COPD, Risk_Chronic_Resp_Failure, Risk_Alcohol_Abuse, Risk_Cancer,
    Risk_Transpl_Organs, Risk_Dementia, Risk_Cerebrovascular_Disease,
    Risk_Mild_Cogn_Impair, Risk_Chron_Renal_Failure, Risk_Cogn_Complaints,
    Hypertension = 1, Diabetes = 1) >= 3 then
    Frailty_Points = Frailty_Points + 1;
  if Frailty_Points >=4 then Frailty = 1;
RUN;
```

### 6.7.2 Multimorbidity

Following the definition by the (World Health Organization 2015), multimorbidity is defined as the presence of at least two chronic conditions. We consider the following comorbidities:

- Diabetes
- Chronic renal failure

- Ischemic heart disease
- Chronic heart failure or cardiomyopathy
- Hemiplegia
- Chronic respiratory failure
- Cancer
- Dementia
- Mild cognitive impairment
- Hypertension requiring medication
- Cardiac arrhythmia or heart blocks
- Peripheral vascular disease
- COPD
- Chronic alcohol abuse
- Transplanted organ(s)
- Cerebrovascular disease
- Other cognitive complaints

If there is no information on the presence of a comorbidity, it is interpreted as “not present”.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Risk_Ischemic_Heart_Disease | Presence of Ischemic heart disease | | Dichotomous |
| Risk_Cardiac_Arrhythmia | Presence of cardiac arrhythmia or heart blocks | | Dichotomous |
| Risk_Chronic_Heart_Failure | Presence of chronic heart failure or cardiomyopathy | | Dichotomous |
| Risk_Peri_Vascular_Disease | Presence of peripheral vascular disease | | Dichotomous |
| Risk_Hemiplegia | Presence of hemiplegia | | Dichotomous |
| Risk_COPD | Presence of COPD | | Dichotomous |
| Risk_Chronic_Resp_Failure | Presence of chronic respiratory failure | | Dichotomous |
| Risk_Alcohol_Abuse | Chronic alcohol abuse | | Dichotomous |
| Risk_Cancer | Presence of cancer | | Dichotomous |
| Risk_Transpl_Organs | Presence of transplanted organ(s) | | Dichotomous |
| Risk_Dementia | Presence of dementia | | Dichotomous |
| Risk_Cerebrovascular_Disease | Presence of cerebrovascular disease | | Dichotomous |
| Risk_Mild_Cogn_Impair | Presence of mild cognitive impairment | | Dichotomous |
| Risk_Chron_Renal_Failure | Presence of chronic renal failure | | Dichotomous |
| Risk_Cogn_Complaints | Presence of other cognitive complaints | | Dichotomous |
| Hypertension | Presence of hypertension requiring medication | | Dichotomous |
| Diabetes | Presence of diabetes | | Dichotomous |
| Multimorbidity | The presence of at least two or more chronic conditions. Definition according to (World Health Organization 2015). | | Dichotomous |

*Table 9: Variables for the definition of multimorbidity.*

```
/* Define multimorbidity                                    */
DATA poseData; SET poseData;
  Multimorbidity = 0;
  if sum(Risk_Ischemic_Heart_Disease, Risk_Cardiac_Arrhythmia,
    Risk_Chronic_Heart_Failure, Risk_Peri_Vascular_Disease, Risk_Hemiplegia,
    Risk_COPD, Risk_Chronic_Resp_Failure, Risk_Alcohol_Abuse, Risk_Cancer,
    Risk_Transpl_Organs, Risk_Dementia, Risk_Cerebrovascular_Disease,
    Risk_Mild_Cogn_Impair, Risk_Chron_Renal_Failure, Risk_Cogn_Complaints,
    Hypertension = 1, Diabetes = 1) >= 2 then Multimorbidity = 1;
RUN;
```

### 6.7.3 Timed up and go test result

The mobility assessment from the timed up and go test is derived as in (Bischoff, et al. 2003). The test result is evaluated as normal mobility if the patient was able to perform the timed up and go test in 12 seconds or less. If the patient was not able to perform the timed up and go test or took more than 12 seconds to perform the test, the test result is evaluated as limited mobility.

| Variable | Description | Unit | Data type |
|---|---|---|---|
| Timed_Test_Able | Was the patient able to perform the timed up and go test | | Nominal |
| Timed_Test_Time | Result from the timed up and go test | seconds | Continuous |
| Timed_Up_Go | Evaluation of normal or limited mobility. Definition according to (Bischoff, et al. 2003). | | Dichotomous |

*Table 10: Variables for the definition of mobility according to the timed up and go test result.*

```
/* Define mobility according to timed up and go test result */
DATA poseData; SET poseData;
  length Timed_Up_Go $17;
  if Timed_Test_Able = 1 and Timed_Test_Time <= 12 then Timed_Up_Go = "normal
    mobility";
  if Timed_Test_Able = 1 and Timed_Test_Time > 12 then Timed_Up_Go = "limited
    mobility";
  if Timed_Test_Able = 2 then Timed_Up_Go = "";
  if Timed_Test_Able = 3 then Timed_Up_Go = "limited mobility";
RUN;
```

## 6.8 MISSING DATA

There will be no missing data for the primary endpoint (as patients without any information on follow-up have a censored survival time at time 0).

Variables with a very high proportion of missing data (e.g. 70% missing values) will be excluded from all inferential analyses.

For the main analysis, all independent variables without a high proportion of missing data will be handled in the inferential analyses using multiple imputation. The number of imputations is set in dependence of the percentage of incomplete cases with at least 10 and at most 25 imputations. Missing values are imputed using the fully conditional specification (FCS) method as described by (Brand 1999) and (Van Buuren, et al. 2006) (procedure PROC MI with fcs method in SAS). The number of burn-in iterations is set to 20. Heavily skewed continuous variables are transformed if necessary. We also include the primary outcome to impute missing values of independent variables (see (Moons, et al. 2006) and (Liu and De 2015)). The plausibility of imputed values is checked by considering descriptive statistics of the imputed and observed values.

If, for some reason, a variable cannot be handled using multiple imputation the variable will either be excluded from the analysis or included despite the missing values if the proportion of missing values is small (e.g. smaller than 5%).

In a sensitivity analysis of the primary endpoint, no missing data will be imputed and all patients with missing covariates will be excluded from the Cox regression model.

```
/* Multiple imputation of missing independent variables      */
PROC MI data = dataset_help nimpute = pctmissing(min=10 max=25) seed = 911023
    out = dataset_mi_help;
  class Sex Severity_Intervention Urgency_Intervention Frailty
    Interventional_Category_9 Referring_Facility Transfusion_Plasma
    Transfusion_Platelets Transfusion_Red_Blood_Cells Anaesthesia_Technique
    Multimorbidity Premedication_Intervention Timed_Up_Go;
  * If applicable: impute continuous variables;
  fcs nbiter=20 reg(Age /* example */);
  * If applicable: transform heavily skewed data;
  transform log(Age /* example */);
  * If applicable: imputed dichotomous and nominal variables;
  fcs nbiter=20 discrim(Sex Frailty /* example *// classeffects = include);
  * If applicable: impute ordinal variables;
  fcs nbiter=20 logistic(Severity_Intervention /* example *// order =
    internal);
  * Missing variables and other variables to estimate missing values. The
      order of variables states in which order missing variables are imputed.;
  var Surv_Time_30 Surv_Status_30 Age Sex Severity_Intervention
    Urgency_Intervention Frailty /* example */;
RUN;
```

# 7. DESCRIPTIVE STATISTICS

## 7.1 BASELINE CHARACTERISTICS

Descriptive statistics of all continuous baseline characteristics include the number of available observations (N), mean and standard deviation (SD) or median, as well as lower (Q1) and upper quartile (Q3) in the case of heavily skewed data.

Descriptive statistics of all dichotomous or nominal baseline characteristics include the number of available observations (N), frequency (n) and percentage (%).

Descriptive statistics of all ordinal baseline characteristics include the number of available observations (N), frequency (n) and percentage (%). If the ordinal characteristic is associated with established numerical values, mean values and standard deviations (SD) are given or median, as well as lower (Q1) and upper quartile (Q3).

A possible tabular summary of baseline characteristics is shown in Table 11.

| Characteristic | N | Statistical measure |
|---|---|---|
| Age | $N_{age}$ | Mean (±SD) or Median (Q1-Q3) |
| Sex (female) | $N_{sex}$ | n (%) |
| Referring facility | $N_{fac}$ | |
| Home/ Lives independent | | n (%) |
| Other hospital | | … |
| … | | |
| ASA Score | $N_{ASA}$ | Mean (±SD) or Median (Q1-Q3) |
| Class I | | n (%) |
| Class II | | … |
| Class III | | … |
| … | … | … |
| … | | |

*Table 11: Descriptive statistics of different types of baseline characteristics*

## 7.2 PRIMARY ENDPOINT

Descriptive statistics of the primary endpoint include the overall number of events until day 30 and a Kaplan-Meier curve of the survival rate within the entire collective. The plot of the Kaplan-Meier curve includes information on the number of patients at risk and the cumulative number of events. If considered useful, a 95%-confidence interval will be added to the plot (using the log-log method). If applicable, the median survival time is estimated using the Kaplan-Meier method. The estimated survival rate for 30 days will be reported.

In addition, the all-cause mortality until day 30 is shown in dependence of the defined age categories.

```
##############################################
## All-cause mortality in entire cohort      ##
##############################################
km <- survival::survfit(survival::Surv(Surv_Time_30, Surv_Status_30) ~ 1,
      data = poseData, conf.type = "log-log")
## Estimated survival rate after 30 days
summary(km, times = c(0, 30))
## Kaplan-Meier curve
pp <- survminer::ggsurvplot(fit = km,
                            xlab = "Time in days",
                            ylab = "Overall survival",
```

```
                            legend = "none",              # No legend
                            legend.labs = "",             # Add legend labs
                            conf.int = TRUE,              # Add confidence interval
                            risk.table = TRUE,            # Add number at risk
                            cumevents = TRUE)             # Add cum. no. of events

##############################################
## All-cause mortality by age category       ##
##############################################
km <- survival::survfit(survival::Surv(Surv_Time_30, Surv_Status_30) ~
      Age_Category, data = poseData)
## Estimated survival rate after 30 days
summary(km, times = c(0, 30))
## Kaplan-Meier curve
pp<- survminer::ggsurvplot(fit = km,
                            xlab = "Time in days",
                            ylab = "Overall survival",
                            legend.title = "Age group", # Add legend title
                            legend.labs = c("[80, 85)", "[85, 90)", "> 90"),
                                                        # Add legend labs
                            conf.int = TRUE,            # Add confidence interval
                            risk.table = TRUE,          # Add number at risk
                            cumevents = TRUE)           # Add cum. no. of events
```

## 7.3 SECONDARY ENDPOINTS

### 7.3.1 Continuous secondary endpoints

Descriptive statistics of all continuous endpoints include the number of available observations (N), mean and standard deviation (SD) or median, as well as lower (Q1) and upper quartile (Q3) in the case of heavily skewed data. The skewness of continuous endpoints is investigated using histograms and boxplots.

### 7.3.2 Dichotomous secondary endpoints

Descriptive statistics of all dichotomous endpoints include the number of available observations (N), frequencies (n) and percentages (%).

### 7.3.3 Nominal secondary endpoints

Descriptive statistics of all nominal endpoints include the number of available observations (N), frequencies (n) and percentages (%).

### 7.3.4 Ordinal secondary endpoints

Descriptive statistics of all ordinal endpoints include the number of available observations (N), frequencies (n) and percentages (%). If the ordinal endpoint is associated with established numerical values, mean values and standard deviations (SD) are given or median, as well as lower (Q1) and upper quartile (Q3).

## 7.4 SENSITVITY ANALYSES

For the sensitivity analysis of the primary endpoint with maximum duration of follow-up available we use the same descriptive techniques as described in Section 7.2. Descriptive statistics of the primary endpoint include the overall number of events and a Kaplan-Meier curve for the entire cohort with information on the numbers at risk. If applicable, the median survival time is estimated using the Kaplan-Meier method.

# 8. INFERENTIAL STATISTICS

## 8.1 PRIMARY ENDPOINT

The primary endpoint is analysed using a multivariable Cox regression model with frailty term (PROC PHREG, PROC MI and PROC MIANALYZE). The multivariable Cox regression model includes the following fixed effects:

- age,
- sex,
- severity of intervention (3 categories),
- urgency of the intervention (3 categories),
- frailty as defined in section 6.7.1.

Other candidate variables are included only as independent variables in the multivariable Cox model if the p-value from the unviariable Cox regression model is at most 0.25. In the case of missing data, the pooled (or median) p-value from the univariable Cox regression models based on the multiply imputed data sets is taken. For continuous and dichotomous candidate variables the pooled p-value using Rubin's rule is considered for model inclusion. For nominal and ordinal candidate variables with more than two categories, the median type 3 test p-value is considered for model inclusion. The following candidate variables are considered for potential inclusion as fixed effects in the multivariable Cox regression model.

- type of intervention as defined in section 6.6.2 (9 categories),
- referring facility (5 categories),
- transfusion of plasma during intervention,
- transfusion of platelets during intervention,
- transfusion of red blood cells during intervention,
- anaesthesia technique as defined in section 6.6.3 (4 categories),
- multimorbidity as defined in section 6.7.2,
- premedication before intervention (3 categories),
- mobility assessments from the timed up and go test as defined in section 6.7.3.

The univariable and multivariable Cox models include a random center effect to account for the correlation between patients from the same center (frailty model with lognormal frailty distribution).

The proportional hazards assumption of all independent (candidate) variables is examined graphically using Schoenfeld residuals. The Schoenfeld residuals are taken from univariable Cox models without frailty term (resulting from the multiply imputed data sets in the case of missing data). If the proportional hazards assumption of an independent variable seems greatly violated (in a majority of imputed data sets), an interaction effect between the independent variable and time is included in the multivariable Cox regression model with frailty term.

The p-values of all fixed effects from the multivariable Cox regression model are reported. Estimated hazard ratios and 95%-confidence intervals may also be reported if considered useful. For continuous and dichotomous variables pooled p-values and estimates from the multiply imputed datasets are derived using Rubin's rule (PROC MIANALYZE). For nominal and ordinal variables with more than 2 categories the median type 3 test p-value of all analyses is reported. If a categorical variable with more than two categories is found statistically significant according to this p-value, pairwise unadjusted comparisons are requested. These unadjusted comparisons are again pooled using Rubin's rule (PROC MIANALYZE) and the resulting pooled p-values are adjusted using the Hochberg method to counteract the problem of multiple comparisons (PROC MULTTEST).

```
/* Example: Examine proportional hazards assumption in simplified univariable
```

```
   Cox models */
ods graphics on;
PROC PHREG data = poseData_mi zph(transform=identity);
  by _Imputation_;
  model Surv_Time_30*Surv_Status_30(0) = Age / ties=efron;
RUN;
ods graphics off;
```

```
/* Variable selection for multivariable Cox model with missing data
   Example 1: combine p-values for continuous or dichotomous variable */
PROC PHREG data = poseData_mi;
  by _Imputation_;
  class Center_ID / param = glm order = internal;
  model Surv_Time_30*Surv_Status_30(0) = Age / ties=efron;
  random Center_ID / dist = lognormal;
  ods output ParameterEstimates=_es_uni;
RUN;
PROC MIANALYZE data=_es_uni;
  by Parameter;
  modeleffects Estimate;
  stderr stderr;
RUN;

/* Variable selection for multivariable Cox model with missing data
   Example 2: display median p-value for ordinal or nominal variable with more
   than 2 categories */
PROC PHREG data = poseData_mi;
  by _Imputation_;
  class Center_ID Severity_Intervention / param = glm order = internal;
  model Surv_Time_30*Surv_Status_30(0) = Severity_Intervention / ties=efron;
  random Center_ID / dist = lognormal;
  ods output ModelANOVA=_t3_uni;
RUN;
PROC MEANS data=_t3_uni median;
  var ProbChiSq;
RUN;
```

```
/* Multivariable Cox regression model                          */
PROC PHREG data = poseData_mi;
  by _Imputation_;
  class Center_ID Sex Severity_Intervention Urgency_Intervention Frailty
       /* if p-value < 0.25 in univariable Cox model selection */
       Interventional_Category_9 Referring_Facility Transfusion_Plasma
       Transfusion_Platelets Transfusion_Red_Blood_Cells Anaesthesia_Technique
       Multimorbidity Premedication_Intervention Timed_Up_Go
      / param = glm order = internal;
  model Surv_Time_30*Surv_Status_30(0) =
       Age Sex Severity_Intervention Urgency_Intervention Frailty
       /* if p-value < 0.25 in univariable Cox model selection */
       Interventional_Category_9 Referring_Facility Transfusion_Plasma
       Transfusion_Platelets Transfusion_Red_Blood_Cells Anaesthesia_Technique
       Multimorbidity Premedication_Intervention Timed_Up_Go
       / ties = efron;
  random Center_ID / solution dist = lognormal;
  lsmeans Severity_Intervention Urgency_Intervention
      /* if p-value < 0.25 in univariable Cox model selection */
      Interventional_Category_9 Referring_Facility Anaesthesia_Technique
      Premedication_Intervention / pdiff cl;
  * Save output to obtain pooled estimates;
  ods output ParameterEstimates=_es ModelANOVA=_t3 diffs=_diff;
RUN;

/* Example 1: Combine estimates from continuous and dichotomous variables and
   pool p-values */
PROC SORT data=_es;
  by Parameter CLassVal0 _Imputation_;
```

```
RUN;
PROC MIANALYZE data=_es;
  by Parameter ClassVal0;
  modeleffects Estimate;
  stderr stderr;
  ods output ParameterEstimates = es_mianal;
RUN;
* Exponentiate to obtain HRs and CIs;
DATA hr_mianal; SET _es_mianal;
  HR_comb = exp(Estimate);
  HR_LCL_comb = exp(LCLMean);
  HR_UCL_comb = exp(UCLMean);
  HR_pval_comb = Probt;
  keep Parameter ClassVal0 HR_comb HR_LCL_comb HR_UCL_comb HR_pval_comb;
RUN;
PROC PRINT data = hr_mianal;
RUN;

/* Example 2: Display median p-value for ordinal or nominal variables with more
   than 2 categories and combine estimates of pairwise differences */
* Display median p-value;
DATA _t3_sub; SET _t3;
  if Effect ne 'Urgency_Intervention' then delete; /* example */
RUN;
PROC MEANS data=_t3_sub median;
  var ProbChiSq ProbChiSq2;
RUN;
* Combine estimates of pairwise differences;
DATA _diff_sub; SET _diff;
  if Effect ne 'Urgency_Intervention' then delete; /* example */
  keep _Imputation_ StmtNo Effect Urgency_Intervention
       _Urgency_Intervention Estimate StdErr zValue Probz;
RUN;
PROC SORT data=_diff_sub;
  by Effect Urgency_Intervention _Urgency_Intervention _Imputation_;
RUN;
PROC MIANALYZE data=_diff_sub;
  by Urgency_Intervention _Urgency_Intervention;
  modeleffects Estimate;
  stderr StdErr;
  ods output ParameterEstimates = es_mianal_sub;
RUN;
* Adjust p-value to account for multiple comparisons;
DATA _es_mianal_sub; SET _es_mianal_sub;
  rename Probt = RAW_P;
RUN;
PROC MULTTEST inpvalues=_es_mianal_sub hochberg out=_es_mianal_sub2 noprint;
RUN;
* Exponentiate to obtain HRs and CIs;
DATA hr_mianal; SET _es_mianal_sub2;
  HR_comb = exp(Estimate);
  HR_LCL_comb = exp(LCLMean);
  HR_UCL_comb = exp(UCLMean);
  drop Parm StdErr LCLMean UCLMean DF Min Max Theta0 tValue RAW_P;
  rename hoc_p = adj_pVal;
RUN;
PROC PRINT data = hr_mianal;
RUN;
```

# 9. PREPARATION AND QUALITY CONTROL OF PROGRAM CODE

## 9.1 STORAGE OF LOG FILES

All SAS and R log files will be stored at the Department of Anaesthesia and can be obtained upon request.

## 9.2 CONTROL OF PROGRAM

Comments in the SAS or R-code are used to explain the code.

# 10.CHANGES FROM STUDY PROTOCOL

No changes are defined.

## 11.REFERENCES

Bischoff, H A, et al. "Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women." *Age and Ageing*, 2003: 315-320.

Brand, J P L. "Development, implementation and evaluation of multiple imputation strategies for the statistical analysis of incomplete data sets." *Erasmus University Rotterdam. Dissertation.* 1999.

Liu, Y, and A De. "Multiple Imputation by Fully Conditional Specification for Dealing with Missing Data in a Large Epidemiologic Study." *International Journal of Medical Research*, 2015.

Moons, K G, R A Donders, Stijnen T, and Harrell F E. "Using the outcome for imputation of missing predictor values was preferred." *Journal of Clinical Epidemiology*, 2006: 1092 - 1101.

Oresanya, L B, W L Lyons, and E Finlayson. "Preoperative assessment of the older patient: a narrative review." *Journal of the American Medical Association*, 2014: 2110-2120.

Robinson, T N, et al. "Redefining geriatric preoperative assessment using frailty, disability and co-morbidity." *Annals of Surgery*, 2009.

Van Buuren, S, J P L Brand, C G M Groothuis-Oudshoorn, and D B Rubin. "Fully conditional specification in multivariate imputation." *Journal of Statistical Computation and Simulation*, 2006.

Wood, A M, I R White, and Royston P. "How should variable selection be performed with multiply imputed data?" *Statistics in Medicine*, 2008: 3227-3246.

World Health Organization. *World report on ageing and health.* World Health Organization, 2015.