APNC
Statistics in Life Science

Statistical Analysis Plan

Reperfusion Treatment in Acute Pulmonary Embolism: A Multicenter Observational Study in the Nordic Countries (PE-NORDIC)

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Abbreviations

AUC-ROC	Area under the receiver operating characteristic curve
CDI	Catheter-directed interventions
CDT	Catheter-directed thrombolysis
COPD	Chronic obstructive pulmonary disease.
CT	Computed tomography
CTED	Chronic thromboembolic disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
ECMO	Extracorporeal membrane oxygenation
eCRF	electronic Case Registration Form
eGFR	estimated glomerular filtration rate
EQ-5D	Generic health-related quality of life assessment
FAS	Full analysis set
FT	FlowTriever®
GDPR	General data protection regulation
HDU	High dependency unit
ICU	Intensive care unit
IPTW	Inverse probability treatment weighting
MRC	Medical Research Council Dyspnoea Scale
MT	Mechanical thrombectomy
PE	Pulmonary embolism
PeMB-QoL	Disease-specific health-related quality of life
PVFS	Post venous thromboembolism functional status scale
RV/LV	Right ventricular/Left ventricular
ST	Systemic intravenous thrombolysis

1 Background

Current international guidelines recommend systemic intravenous thrombolysis (ST) for high-risk pulmonary embolism (PE). ST is an effective dissolvent of thromboembolic clots and has been shown to decrease the combined outcome of mortality and recurrent PE. However, ST carries a substantial bleeding risk including fatal or intracranial hemorrhage. The risk of bleeding is compounded by the fact that many risk factors for PE, such as recent surgery or cancer, also serve as contraindications for ST. According to guidelines catheter-directed interventions (CDI) is recommended in high-risk PE when ST is contraindicated or has failed. CDI is also recommended as an alternative in PE patients undergoing anticoagulation therapy in case of treatment failure, such as lack of improvement or haemodynamic deterioration.

Several methods of CDI are available, but no method is recommended over the other. In Sweden, the mechanical thrombectomy (MT) device FlowTriever® (FT) was introduced in 2021 and has since then been the predominant method. It combines large-bore aspiration with expanding mesh disks designed to trap and subsequently retract blood clots.

Studies evaluating FT are mainly industry-initiated, single-arm trials assessing short-term outcomes. Furthermore, these studies primarily include patients with less severe PE who do not meet guideline criteria for CDI treatment. PEERLESS, the first RCT to compare different CDI methods in PE, intermediate-risk PE patients were randomized to either FT or catheter-directed thrombolysis (CDT), however without including standard care as a comparator. In FLAME, an observational study, high-risk PE treated with FT was associated with a lower mortality and incidence of bleeding compared to a context arm. Investigator-initiated trials on MT mainly consist of single-arm studies with focus on intermediate-risk PE, with some small case-series on high-risk patients.

Treatment of acute PE using CDI is an evolving strategy as to techniques and availability. Follow-up of outcomes and safety is important when new techniques are employed. The PE-NORDIC (Reperfusion Treatment in Acute Pulmonary Embolism: A Multicenter Observational Study in the Nordic Countries) study will evaluate short- and long-term safety and effect outcomes in patients with PE treated with CDI and ST in Sweden and other Nordic countries.

2 Study Objectives and Hypotheses

2.1 Primary Objective and Hypothesis

The primary objective is to evaluate the composite of death from any cause or severe bleeding according to GUSTO (defined as intracranial bleeding or bleeding with substantial hemodynamic compromise requiring treatment) at day 30 after treatment between the patients with acute PE treated with CDI compared to ST.

We hypothesize that patients with acute PE treated with CDI, as compared to patients treated with ST, will have a lower composite incidence of severe bleeding and death, within 30 days.

2.2 Secondary Objectives

The secondary objectives are to evaluate:

- Short-term outcomes within 30 days in patients with acute PE treated with CDI compared to ST considering: all-cause mortality, cause of death, bleeding (according to GUSTO criteria), need for rescue treatment (including ST, CDI, extracorporeal membrane oxygenation (ECMO), surgical embolectomy), recurrent PE, hospital and intensive care unit (ICU) and/or high dependency unit (HDU)

free days and change in right ventricular to left ventricular (RV/LV) ratio before and within 72 h after treatment.

- Long-term outcomes within 1 year in patients with acute PE treated with CDI compared to ST considering: All-cause mortality, persisting dyspnea, RV dysfunction, ECG, cardiac biomarkers, 6-minute walk test (6MWT), sit-to-stand 60 test and health-related quality of life assessments. Potential cases of confirmed chronic thromboembolic pulmonary vascular disease (CTED) or chronic thromboembolic pulmonary hypertension (CTEPH) during the study period will be registered.
- Risk factors for complications and outcome in patients with CDI and ST, separately.

This study will be analysed and published in different reports, at least the following, but not limited to:

- A short 30-day follow-up, including the primary analysis as confirmatory and all other analyses exploratory.
- A long 1-year follow-up, all analyses will be considered exploratory

3 Study Design

This is a prospective observational multicenter study in Sweden and Denmark with short- and long-term follow-up. The other Nordic countries (Denmark, Norway, Finland and Iceland) are currently engaged in discussions about potential participation. Centers offering CDI for PE in the study countries will be invited to participate. Data will include patient characteristics, clinical examinations, physiological parameters, diagnostics, interventional procedures, laboratory analyses, as well as physical and psychological functional assessments.

All PE patients become eligible once they have been assigned to either CDI or ST (independent of dose) by a documented decision from the treating physician. Patients will be asked for consent when assessed capable of understanding the information and making an informed decision. Prospective data collection will begin as soon as consent is obtained. For patients who do not survive before informed consent can be obtained, a waiver of consent applies, and their data will be collected retrospectively.

Eligible patients will be identified at each participating center by the local research team (site investigators, study nurse etc.) with representatives at the intervention unit and or at the unit where ST is given respectively. Informed oral and written consent will be obtained before inclusion. Data from deceased individuals who were unable to provide consent are collected retrospectively from medical journals in accordance with ethical approval.

Data will be collected through medical records, and subsequently anonymized, organized and analyzed. Collection, handling, and storage of data will be done in accordance with the General Data Protection Regulation (GDPR).

The data set includes variables from the following stages of the individual patient trajectories (Table 1):

- Before treatment (within 24 hours)
- After treatment (within 72 hours)
- 30 days after treatment
- Follow-up visit 1 (within 3-6 months)

- Follow-up visit 2 (within 9-12 months)

An electronic Case Registration Form (eCRF), REDCap®, will be used for data collection. All study data will be noted and recorded in the eCRF.

3.1 Study Assessments

During each follow-up visit persisting dyspnea, right ventricular dysfunction, cardiac biomarkers, mortality, functional outcomes, as well as questionnaires regarding health-related quality of life will be collected. Potential cases of confirmed chronic thromboembolic pulmonary vascular disease (CTED) or chronic thromboembolic pulmonary hypertension (CTEPH) during the study period will be registered.

Table 1. Study activities

Activities	Before treatment	After treatment (within 72 hours)	Follow-up visit 1	Follow-up visit 2[1]
Informed consent	x	x	x	x
Echocardiogram	x	x	x[2]	x[2]
ECG	x	x	x	x
Lab tests	x[3]	x[3]	x[4]	x[4]
Vital parameters	x	x		
Patient surveys[5]			x	x
6MWT & STS60[6]			x	x

[1] A second follow-up visit will not be performed if findings from follow-up visit 1 are normal to the extent that no further follow-up is required according to standard clinical practice
[2] No echocardiogram will be performed if findings from previous echocardiogram are normal to the extent that it is not required according to standard clinical practice
[3] Troponin, NT-proBNP, creatinine, pH, lactate, PaO2, PaCO2
[4] Troponin, NT-proBNP, creatinine
[5] MRC, EQ-5D, PeMB-QoL, PVFS
[6] 6-minute walk test and sit-to-stand 60 test

3.2 Inclusion/Exclusion Criteria

Inclusion Criteria

- All adult patients (≥18 years), including pregnant women, with verified (CTPA, angiography or scintigraphy) acute PE who are planned for, or have received, treatment with CDI or ST
- Informed consent (for patients who do not survive before informed consent can be obtained, a waiver of consent applies)

Exclusion Criteria

- Ongoing enrolment in interventional CDI trial
- Surgical embolectomy as primary reperfusion treatment

3.3 Study Groups

- Intervention group: Patients treated with CDI.

- Comparison group: Patients treated with ST.
- Patients treated with ST before CDI will be described separately and excluded from all comparative analyses.

4 Study Populations

4.1 Full Analysis Set

The full analysis set (FAS) will be defined according to the inclusion and exclusion criteria above.

5 Study Variables

5.1 Patient Characteristics Variables

Following patient characteristics will be collected and described:

- Age (years)
- Gender (Male, Female)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Marital status
- Occupation
- Highest level of education
- Ongoing pregnancy (Yes, No)
- PE within 12 weeks from post-partum (Yes, No)
- Comorbidities
    - Any comorbidity (Yes, No)
    - Hypertension (Yes, No)
    - Ischemic heart disease (Yes, No)
    - Chronic heart failure (Yes, No)
    - Diabetes (Yes, No)
    - Chronic obstructive pulmonary disease (Yes, No)
    - Previous stroke (Yes, No)
    - Chronic renal failure (Yes, No)
    - Active cancer (Yes, No)
    - Previous venous thromboembolism (Yes, No)
- Referral from another hospital (Yes, No)
- Clinical frailty scale (1-3, 4-6, 7-9)

5.2 Indication for Treatment

Following variables will be collected:

- Indication for reperfusion treatment
    - Circulatory instability (systolic blood pressure <90 mmHg) (Yes, No)

    - Persistent circulatory instability (drop in systolic blood pressure of 40 mmHg for at least 15 minutes) (Yes, No)
    - Circulatory instability (need for vasopressors or inotropes) (Yes, No)
    - Cardiac arrest (Yes, No)
    - Lack of improvement with anticoagulation treatment (Yes, No)
    - Clinical deterioration during anticoagulation treatment (Yes, No)
    - Other
        - Respiratory failure (Yes, No)
        - Syncope (Yes, No)
        - Severe right heart strain (Yes, No)
        - Thrombus burden (Yes, No)
        - Significant clinical concern (Yes, No)
- Indication for reperfusion treatment with CDI
    - Absolute contraindication to systemic thrombolysis (Yes, No)
        - History of haemorrhagic stroke to stroke of unknown origin
        - History of ischemic stroke in previous 6 months
        - Central nervous system neoplasm
        - Major trauma, major surgery, or head injury in previous 3 weeks
        - Active bleeding
        - Bleeding diathesis
    - Relative contraindication to systemic thrombolysis (Yes, No)
        - Transient ischaemic attack in previous 6 months
        - Oral anticoagulation
        - Pregnancy or first post-partum week
        - Non-compressible puncture sites
        - Traumatic resuscitation
        - Refractory hypertension (systolic blood pressure >180 mmHg)
        - Advanced liver disease
        - Infective endocarditis
        - Active peptic ulcer
        - Platelets < 100
        - Any other condition that increases the risk of treatment with systemic thrombolysis according to the treating physician
    - Insufficient treatment effect of systemic thrombolysis (Yes, No)
    - Other
        - Clinical concern for bleeding without contraindication for systemic thrombolysis (Yes, No)
        - Location of thrombolysis and/or extent of thrombosis (Yes, No)
        - Other

5.3 First Clinical Presentation of PE

The following variables for the first clinical presentation of PE will be collected:

- Invasive mechanical ventilation at start of reperfusion treatment (Yes, No)
- Syncope within 48 hours before start of reperfusion treatment (Yes, No)

- Cardiac arrest within 24 hours before start of reperfusion treatment (Yes, No)
    - Return of spontaneous circulation (ROSC) (Yes,No)
        - ROSC before start of reperfusion treatment/before completed treatment/after completed treatment
- Cardiac arrest during the reperfusion treatment (Yes, No)
    - ROSC (Yes, No)
        - ROSC before/after completed treatment
- Was the patient at any point treated with ECMO for PE (Yes, No)
    - ECMO initiated before/during/after reperfusion treatment)
    - ECMO terminated before/during/after reperfusion treatment)

5.4 Radiology and Imaging

Following radiology and imaging data will be collected:

- Pulmonary embolism diagnosed on (CTPA/Angiography/Scintigraphy)
- Distribution of PE (Unilateral/Bilateral/Saddle)
- Most proximally engaged lung segment (Central/Segmental/Subsegmental)
- Right ventricle/left ventricle (RV/LV) ratio before reperfusion treatment (computed tomography)
- Echocardiography before reperfusion treatment (Yes, No)
    - Left ventricular ejection fraction (LVEF) (%)
    - Right ventricular diameter (maximum) (mm)
    - Left ventricular diameter (maximum) (mm)
    - LV inner diameter in diastole (in PLAX-view) (mm)
    - Tricuspid annular plane systolic excursion (TAPSE) (mm)
    - Tricuspid regurgitation grade (0-5)
    - Maximum inferior vena cava (IVC) diameter (mm)
    - Minimum inferior vena cava (IVC) diameter (mm)
    - Maximum tricuspid regurgitation velocity (TRV-max) (m/s)Intracardiac thrombus (Yes, No)
    - McConnell sign (Yes, No)
    - D-sign (Yes, No)
    - Pulmonary artery acceleration time (PAAT) (ms)
    - Right ventricular outflow tract, velocity time integral (RVOT VTI) (cm)
    - RVOT mid systolic notch (Yes, No)
    - Left ventricular outflow tract, velocity time integral (LVOT LVI) (cm)
    - LVOT area (cm^2)
    - RV fractional area change (%)
    - RV lateral annular systolic velocity (cm/s)

5.5 Vital Signs Before Treatment

Following vital signs before treatment will be collected:

- Lowest systolic blood pressure (within previous 24 hours before treatment) (mmHg)
- Maximum heart rate at time of lowest systolic blood pressure (bpm)

- Maximum heart rate (within previous 24 hours before treatment) (bpm)
- Maximum respiratory rate (within previous 24 hours before treatment) (bpm)

5.6 Laboratory Tests Before Treatment

Following laboratory tests before treatment will be collected:

- Lactate (mmol/L)
- pH
- Creatinine (µmol/L)
- eGFR (mL/min/1.73m^2)
- aB-pO2 (kPa)
- aB-pCO2 (kPa)
- Troponin I (ng/L)
- Troponin T (ng/L)
- NT-proBNP (ng/L)

5.7 Reperfusion treatment with CDI

- Procedure duration (min)
- Main method of intervention (Mechanical thrombectomy, Catheter-directed thrombolysis)
- Catheter used (FlowTriever, Penumbra, EKOS, Other)
- Adjunct of catheter-directed thrombolysis (Yes, No)
- Dose of catheter-led tPa (mg)
- Autologous blood transfusion (Yes, No)
- Volume of blood transfusion (mL)
- Interventional complication (Yes, No)
- Type of complication (Bleeding, Perforation, Hemoptysis, Cardiac tamponade, Arrhythmia, Other)
- Systolic pulmonary artery pressure before treatment (mmHg)
- Diastolic pulmonary artery pressure before treatment (mmHg)
- Systolic pulmonary artery pressure after treatment (mmHg)
- Diastolic pulmonary artery pressure after treatment (mmHg)
- Successful catheterization to desirable position (Yes, No)
- At least partially succesful thrombus extraction or treatment (Yes, No)
- Clinical improvement after completed intervention (Yes, No)

5.8 Reperfusion Treatment Thrombolysis

- Procedure duration (min)
- Dose of tPa (mg)
- tPa agent (Actilyse [Alteplase], Metalyse [Tenecteplase])
- Premature discontinuation of thrombolysis (Yes, No)
- Reason for premature discontinuation of thrombolysis (*text to be categorized*)

5.9 Outcome Variables

5.9.1 Primary Outcome Variable

The primary outcome is a composite of death from any cause or severe bleeding according to GUSTO (defined as intracranial bleeding or bleeding with substantial hemodynamic compromise requiring treatment) at day 30 after treatment.

5.9.2 Secondary Outcome Variables

The secondary outcome variables, for the 30-days statistical report, in this study are:

- Outcome-related variables day 30, endpoints
  - All-cause mortality, incidence (Yes, No), time-to event, and cause of death
  - Incidence of severe bleeding (GUSTO criteria) (Yes, No)
    - Intracranial/extracranial
  - Incidence of non-severe bleeding (Yes, No)
    - Bleeding site
  - Need for rescue treatment (Yes, No) and type of rescue treatment (Systemic thrombolysis, Catheter-directed intervention, Surgical thrombectomy, ECMO)
  - Recurrent PE (Yes, No)
  - ICU/HDU length of stay (LOS) (h)
  - Hospital LOS (days), analysed as time to discharge from hospital
- Outcome-related variables after treatment 0-72 hours, descriptive
  - Cardiac arrhythmia requiring treatment (Yes, No)
    - Type of arrhythmia (atrial fibrillation or flutter, ventricular tachycardia, ventricular fibrillation, other)
    - Treatment received (cardioversion, pharmacological)
  - Echocardiogram (same variables as listed under Echocardiogram in 5.4 Radiology and Imaging)
    - Change in right ventricular to left ventricular (RV/LV) diameter ratio before and within 72h after treatment

    At the time of echocardiogram (or closest in time to 48 hours after treatment, if echocardiogram is missing):
    - Need for vasopressors/inotropic drugs (Yes, No)
    - Mechanical ventilation (Yes, No)
    - Supplemental oxygen FiO2 at time of follow-up (%)
    - Lab tests: Creatinine, eGFR, Troponin I, Troponin T, NT-proBNP, Lactate, pH, PaO2, PaCO2
    - Vital parameters: SBP, DBP, heart rate, respiratory rate

The secondary outcome variables, for the 1-year statistical report, in this study are:

- Outcome-related variables at first follow-up, 3-6 and 9-12 months after treatment, endpoints
  - All-cause mortality during first year, incidence (Yes, No), time-to event, and cause of death
  - Distance in 6-minute walk test (m)
  - Sit-to-stand test 60 (s)
  - Level of dyspnea (better, unchanged, worse)
  - Echocardiogram (same variables as listed under Echocardiogram in 5.4 Radiology and Imaging)

- Medical research council dyspnoea scale (MRC) (0-4)
- Generic health-related quality of life assessment (EQ-5D)
  - Movement (1-5), 1 corresponds to high and 5 to low movement level (descriptive)
  - Care (1-5), 1 corresponds to high and 5 to low care level (descriptive)
  - Activity (1-5), 1 corresponds to high and 5 to low activity level (descriptive)
  - Pain (1-5), 1 corresponds to low and 5 to high pain level (descriptive)
  - Anxiety (1-5), 1 corresponds to low and 5 to high anxiety level (descriptive)
  - EQ-VAS (0-100), where 0 corresponds to worst health and 100 to best possible
- Disease-specific health-related quality of life (PeMB-QoL). The PEmb-QoL dimension scores will be calculated by taking the mean of the constituting items. Dimension scores will be then transformed to a scale from 0–100 to make them comparable across dimensions, with higher scores indicating worse outcome.
  - FC: Frequency of complaints (Question 1, 8 items, reverse scoring where lower scores correspond to better quality of life)
  - AD: Activities of daily living limitations (Question 4, 13 items, reverse scoring where lower scores correspond to better quality of life; Item 4a, will be considered as missing if answered “I do not work”)
  - WR: Work-related problems (Question 5, 4 items, reverse scoring where lower scores correspond to better quality of life)
  - SL: Social limitations (Question 6, 1 item)
  - IC: Intensity of complaints (Question 7 and 8, 1 item each)
  - EC: Emotional complaints (Question 9, 10 items, reverse scoring where lower scores correspond to better quality of life)
  - Question 2 and 3 do not require scoring, only descriptive.
- Post venous thromboembolism functional status scale (PVFS) (0-4), 0 corresponds to not affected of thromboembolism daily, 4 severely affected in daily life

- Outcome-related variables at first follow-up, 3-6 and 9-12 months after treatment, descriptive
  - Echocardiogram (same variables as listed under Echocardiogram in 5.4 Radiology and Imaging)
  - Lab tests: NT-proBNP, Troponin I, Troponin T, creatinine, eGFR

Exploratory analyses of changes between consecutive follow-up visits may also be conducted for selected parameters, as deemed relevant.

5.10 Confounders and Predictors

Due to the observational study design, following variables will be investigated, whether they are potential confounders and predictors that need to be taken into account in the analysis:

- Age
- Sex
- Mechanical ventilation
- Cardiac arrest 0-48h before treatment
- Chronic heart failure
- Active cancer
- Chronic obstructive pulmonary disease

- Circulatory instability
- Renal failure
- Previous venous thromboembolism
- Lactate before treatment

6 Statistical Methods

6.1 Sample Size

In the recent review of retrospective data from the Swedish sites, the incidence of the primary composite endpoint was 28% in the ST group compared to 10% in the CDI group (FlowTriever).

Assuming 25% incidence of the primary composite endpoint in the ST group and 10% in the CDI group, assuming 80% power, equally large treatment groups, and using Fisher's exact test, 110 patients will need to be included per treatment arm.,. To maintain a statistical power of at least 80%, the number of enrolled patients will be increased to account for an anticipated 10% dropout rate, i.e. 244 patients in total in total, corresponding to 122 patients per treatment arm. Enrollment will be discontinued once 244 evaluable patients have completed the 30-day follow-up period, at which point the primary analysis will be conducted.

6.2 General Methodology

Descriptive statistics will be used for group characteristics and outcomes. Intergroup comparisons will be done using Fisher's exact test for dichotomous variables, Chi-square test for non-ordered categorical variables, and the Mann-Whitney U-test for continuous variables.

The comparative analyses between the groups considering the dichotomous study outcomes will be performed using logistic regression adjusted for known and statistically identified confounders (variables that are related both to the study group and the outcome). Odds-ratios with associated 95% CI, p-values and area under the receiver operating characteristic curve (AUC-ROC) will be presented. Hosmer-Lemeshow test will be performed as a goodness-of-fit test.

Comparative analyses between the groups considering the continuous study outcomes will be performed using linear regression or mixed models for repeated measures (MMRM) adjusted for known and statistically identified confounders, as well baseline value if available. Optimal covariance matrix (unstructured, compound symmetry or autoregressive) will be investigated by using Akaike's Information Criterion (AIC). Model assumptions will be checked by reviewing diagnostic plots, and if needed transformation (e.g. log) of the outcome variable will be performed. Least square means and difference of those with associated 95% CI, p-values and R^2 will be presented.

Outcome variables length of stay in ICU (hours) and length of hospital admission (days) will be handled as continuous variables in the case of no censored patients. In case of censored patients in the database, time to discharge will be studied using Cox proportional hazard model, resulting in hazard ratios with 95% CI and p-value. Proportional hazards assumptions will be checked graphically. Otherwise, the variables will be studied as continuous variables using either linear regression assuming normal distribution if applicable or Poisson or negative binomial regression depending on the distribution of the variables. Results from Poisson and negative binomial regression result in relative risks with 95% CI and p-value.

Additionally, a complementary analysis will be conducted applying inverse probability treatment weighting (IPTW) using propensity scores, estimated applying logistic regression. Confounders and predictors listed above in section 5.10 will be included in the estimation of propensity scores. The performance will be validated by comparing the patient characteristics between the weighted groups that are expected not to differ.

Risk factor analyses for binary outcomes will be investigated using univariable and multivariable logistic regression, and for time-to-event outcomes using Cox regression.

P-values < 0.05 will be considered significant. All analyses will be performed using SAS software version 9.4 or later (SAS Institute Inc., Cary, NC, USA).

6.3 Adjustment for Type I Error

The primary analysis of the 30-day statistical report will be the only confirmatory analysis in this study and will be evaluated at a significance level of 0.05. All other analyses will be exploratory in nature. However, to control the risk of type I error, the Bonferroni-Holm adjustment will be applied for these exploratory analyses.

6.4 Handling of Missing Data

Missing data might be expected. In case the primary analysis includes missing data for more than 5% of the patients, multiple imputation, using the baseline variables that are significantly related to the missingness and to the primary outcome itself, will be applied as a sensitivity analysis for the primary analysis. No other imputations will be made.

6.5 Primary Analyses

The primary analysis will be performed using logistic regression adjusted for known and statistically identified confounders and predictors. OR with associated 95% CI, p-values and AUC-ROC will be presented. Hosmer-Lemeshow test will be performed as a goodness-of-fit test.
A p-value <0.05 will denote statistical significance.

The sensitivity analysis of the primary variable will be performed by using the IPTW method described above in general methodology.

6.6 Secondary Analyses

The secondary analyses will apply methods described in the general methodology above. If the number of events allows adjustment will be made for known and statistically identified confounders and predictors.

6.7 Subgroup Analyses

The primary and selected secondary variables will be studied for following subgroups:

- Cardiac arrest before treatment (Yes, No)
- Type of PE risk (High, Intermediate-High)

6.8 Substudies

Separate research plans and statistical analysis plans will be written for following planned substudies:

- Health economy - substudy
- Echocardiography - substudy
- Clot burden and right ventricular dysfunction - substudy
- Site-specific QoL - substudy
- PeMB-QoL in relation to less severe PE population - substudy
- Physical activity and symptoms of dyspnea - substudy
- Anticoagulation and bleeding - substudy

7 Planned Tables and Figures

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