Study protocol for data acquisition in the non-interventional observational study PE-NORDIC
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Reperfusion Treatment in Acute Pulmonary Embolism: A Multicenter Observational Study in the Nordic Countries (PE-NORDIC)

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Synopsis

Title:	**Reperfusion Treatment in Acute Pulmonary Embolism: A Multicenter Observational Study in the Nordic Countries (PE-NORDIC)**
Ethics:	Approved by the Swedish Ethical Review Authority Dnr 2019-00827, amendments: Dnr 2022-04256-02 Dnr 2023-04750-02 Dnr 2023-06931-02 Dnr 2024-00038-02 Dnr 2024-04908-02 2025-00546-02
Background:	International guidelines recommend immediate reperfusion with systemic thrombolysis (ST) as first-line treatment in high-risk pulmonary embolism (PE) [1]. The therapy improves haemodynamics and overall survival but is also associated with a significant risk of severe bleeding [2]. Catheter directed intervention (CDI) is recommended as an alternative reperfusion therapy in high-risk PE when ST is contraindicated or has failed, as well as in patients who deteriorate or fail to improve during anticoagulation (AC) treatment [1]. Despite lack of high-quality evidence and randomized studies between CDI and standard care, the use of CDI is spreading rapidly in high-risk PE and in less severe PE not fulfilling current treatment criteria [3]. Several CDI methods are available, including mechanical thrombectomy (MT) and catheter-directed thrombolysis (CDT), but no method is currently recommended over the other. In Sweden, the MT device FlowTriever® (FT) was introduced in 2021 and has since then been the predominant method. Industry sponsored trials have investigated FT in uncontrolled observational trials and primarily in intermediate-risk PE [3-4]. In the prospective non-randomized trial FLAME, high-risk PE treated with FT was associated with a lower mortality and incidence of bleeding compared to a context arm [5]. The recently published PEERLESS trial was the first randomized controlled trial (RCT) to compare different CDI methods, with patients with intermediate-risk PE being randomized to either MT with FT or CDT [6]. The investigator-initiated research on FT is limited to relatively small, descriptive, single-arm studies, or trials focusing on intermediate-risk PE [7-9]. There are several ongoing trials comparing different CDI methods to anticoagulation. However, in clinical practice, patients with acute PE may be subjected to different reperfusion strategies depending on severity and available resources. The PE-NORDIC observational study will compare the outcomes of different patient groups treated with current CDI methods used in the Nordic countries to patients treated with ST.
Objective:	To evaluate short- and long-term outcomes among patients treated with CDI and to compare it to patients treated with ST for acute PE.
Design:	Prospective multicenter observational cohort study.
Countries:	Sweden, Denmark
Timetable:	A three-year inclusion period, Q2 2025 – Q2 2028. 2028: Data analysis, concluding patient follow-up, publishing results.

Population:	Adult patients with acute PE treated with CDI or ST
Eligibility:	***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
Primary outcome:	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.
Secondary outcomes:	Within 30 days: 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. Within 1 year: Persisting dyspnea, RV dysfunction, ECG, cardiac biomarkers, 6-minute walk test (6MWT) 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.

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

Timeline

- Q2 2025 – Q2 2028: Participant inclusion, informed consent, prospective data collection
- 2025: Register the trial at ClinicalTrials.gov.
- 2025: Write and submit study protocol for peer-review in scientific journal
- 2028: Processing and analyzing data, summarizing and interpreting results, writing manuscript and submitting for peer-review in a scientific journal.

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 [1]. However, ST carries a substantial bleeding risk including fatal or intracranial hemorrhage [2]. 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 [1].

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 company-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 [3-6]. 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 [6]. 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 [5]. 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 [7-9].

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.

Aim and hypothesis

The aim is to evaluate short- and long-term outcomes of patients with acute PE treated with CDI and compare short- and long-term outcome to a group of patients treated with 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.

Study design

This is a prospective observational multicenter study in Sweden with short- and long-term follow-up. The Nordic countries (Denmark, Norway, Finland and Iceland) are currently engaged in discussions about potential participation. All 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 in Sweden who do not survive before informed consent can be obtained, a waiver of consent applies, and their data will be collected retrospectively.

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)

Follow-up
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. 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

Patient population

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, and their data will be collected retrospectively)

Exclusion criteria:

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

Included patients will be divided into two groups for comparison

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.

Primary outcome

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.

Secondary outcomes

Within 30 days: All-cause mortality, cause of death, bleeding (according to GUSTO criteria, severe/non-severe), 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) diameter ratio before and within 72 h after treatment.

Within 1 year: Persisting dyspnea, RV dysfunction, ECG, cardiac biomarkers, 6-minute walk test (6MWT) and sit-to-stand 60 test, 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.

Study variables

Baseline characteristics

- Date of birth
- Gender
- Height
- Weight
- Ongoing pregnancy/post-partum period
- Comorbidities
    - Hypertension
    - Ischemic heart disease
    - Chronic heart failure
    - Diabetes
    - COPD
    - Previous stroke
    - Chronic renal failure
    - Active cancer
    - Previous venous thromboembolism
- Clinical frailty scale*
- Referral from other hospital
- Cardiac arrest (0-24 hours before treatment) and ROSC
- Syncope (0-48 hours before treatment)
- Invasive mechanical ventilation (0-24 hours before treatment)
- The highest amount of oxygen administered to achieve target saturation* (0-24 hours before treatment)
- Maximum heart rate (0-24 hours before treatment)

- Minimum systolic blood pressure (SBP) (0-24 hours before treatment)
- Shock index at the minimum SBP (0-24 hours before treatment)
- Maximum respiratory frequency (0-24 hours before treatment)
- ECG (0-24 hours before treatment)
- Maximum lactate level (0-24 hours before treatment)
- Lowest pH level (0-24 hours before treatment)
- Maximum cardiac troponin level (0-24 hours before treatment)
- Maximum NT-proBNP level (0-24 hours before treatment)
- Maximum creatinine level (0-24 hours before treatment)
- Estimated glomerular filtration rate (eGRF) at time of maximum creatinine measurement
- Lowest arterial pO2 (0-24 hours before treatment)
- Highest arterial or venous pCO2 (0-24 hours before treatment)
- Treatment with ECMO
- Diagnostic method of PE (CTPA/Angiography/Scintigraphy)
- Distribution of pulmonary embolism (i.e. unilateral or bilateral)
- Most proximally engaged lung segment (central or segmental or subsegmental)
- Right ventricular/left ventricular ratio (RV/LV ratio) on CT
- Echocardiogram (0-48 hours before treatment)
    - Left ventricular ejection fraction (LVEF, %)
    - Right ventricular diameter (maximum, mm)
    - Left ventricular diameter (maximum, mm)
    - Tricuspid annular plane systolic excursion (TAPSE, mm)
    - Tricuspid regurgitation grade (0-5)
    - Maximum/minimum inferior vena cava (IVC) diameter (mm)
    - Maximum tricuspid regurgitation velocity (TRV-max) (m/s)
    - Intracardiac thrombus (yes/no)
    - McConnell sign (yes/no)
    - Pulmonary artery acceleration time (ms)
    - RVOT VTI (cm)
    - RVOT mid systolic notch (yes/no)
    - RV fractional area change (%)
    - RV lateral annular systolic velocity (cm/s)
    - D-sign (yes/no)
    - LVOT VTI (cm)
    - LVOT area (cm^2)
    - LV inner diameter in diastole (PLAX, mm)

Details of reperfusion treatment variables

- Time from diagnostic radiology to start of treatment

- Indication for reperfusion treatment including:
    - Circulatory instability
        - Cardiac arrest
        - SBP < 90 mmHg
        - Drop in SBP of 40 mmHg for at least 15 minutes
        - Need for vasopressors to achieve a SBP >90 mmHg (despite an adequate filling status, in combination with end-organ hypoperfusion)
    - Lack of improvement from anticoagulant treatment
    - Deterioration during anticoagulant treatment
    - Other
        - Respiratory failure
        - Syncope
        - Severe right heart strain
        - Thrombus burden
        - Significant clinical concern

Details of treatment with CDI

- Indication for intervention including:
    - Absolute or relative contraindication to systemic thrombolysis
    - Insufficient treatment effect of systemic thrombolysis
    - Other
        - Clinical concern for bleeding without contraindication to systemic thrombolysis
        - Location of thrombosis and/or extent of thrombosis
- Methods/catheters used
- Dose and agent for patients treated with catheter-directed thrombolysis
- Procedure duration
- Use of autologous blood transfusion
- Volume of blood transfusion
- SPAP before and after treatment
- Successful catheterization
- Successful thrombus extraction/treatment
- Clinical improvement after completed intervention
- Procedural complications

Details of treatment with ST

- Dose, agent and duration of thrombolysis
- Premature discontinuation of thrombolysis (yes/no, cause)

Outcome-related variables within 72 hours after treatment

- Cardiac arrhythmia requiring treatment
    - Type of arrhythmia
    - Treatment received

- Echocardiogram**
- At the time of echocardiogram (variables closest in time):
    - Mechanical ventilation
    - Need for vasopressors/inotropes
    - FiO2
    - Lab tests: Troponin, NT-proBNP, creatinine, eGRF, pH, lactate, PaO2, PaCO2/PvCO2
    - Vital parameters: heart rate, respiratory rate, blood pressure
    - ECG

Outcome-related variables day 30

- All-cause mortality
- Cause of death
- Incidence of severe bleeding (GUSTO criteria)
- Incidence of any bleeding
- Site of bleeding
- Rescue treatment including ST, CDI, surgical embolectomy and ECMO
- Recurrent PE
- ICU/HDU length of stay (LOS)
- Hospital LOS

Outcome-related variables at first follow-up, 3-6 months after treatment

- All-cause mortality and date of death
- Marital status
- Occupation
- Highest level of education
- Lab tests: Troponin, NT-proBNP, creatinine, estimated glomerular filtration rate (eGFR)
- Echocardiogram** (not performed in cases where findings from previous echocardiogram are normal to the extent that it is not required according to standard clinical practice)
- ECG
- Dyspnea at first follow-up in comparison to discharge
- Functional outcome (6-minute walking test and sit-to-stand 60 test)
- MRC (0-4)
- Generic health-related quality of life assessment (EQ-5D-5L)
- Disease-specific health-related quality of life (PeMB-QoL)
- Post venous thromboembolism functional status scale (PVFS)

- 6-minute walk test
- Sit-to-stand 60 test
- Respiratory movement measuring instrument (RMMI, Sahlgrenska only)
- Patient questionnaires regarding physical activity and symptoms when breathing (Sahlgrenska only)
- Confirmed CTED
- Confirmed CTEPH
- All-cause mortality
- Recurrent PE
- Bleeding requiring medical attention
- Time from treatment to first follow-up visit
- Anticoagulation
    - Agent
    - Dose
    - Compliance

Outcome-related variables at second follow-up, day 9-12 months after treatment

- All-cause mortality and date of death
- Lab tests: Troponin, NT-proBNP, creatinine, estimated glomerular filtration rate (eGFR)
- Echocardiogram** (not performed in cases where findings from previous echocardiogram are normal to the extent that it is not required according to standard clinical practice)
- ECG
- Dyspnea at second follow-up visit in comparison to first follow-up
- Functional outcome (6-minute walking test and sit-to-stand 60 test)
- MRC (0-4)
- Generic health-related quality of life assessment (EQ-5D)
- Disease-specific health-related quality of life (PeMB-QoL)
- Post venous thromboembolism functional status scale (PVFS)
- 6-minute walk test
- Sit-to-stand 60 test
- Respiratory movement measuring instrument (RMMI, Sahlgrenska only)
- Patient questionnaires regarding physical activity and symptoms when breathing (Sahlgrenska only)
- Confirmed CTED
- Confirmed CTEPH
- All-cause mortality
- Recurrent PE
- Bleeding requiring medical attention
- Time from treatment to second follow-up visit

- Anticoagulation
    - Agent
    - Dose
    - Compliance

End of study

- In case of study drop-out: date and reason

* defined according to support chart in eCRF
** same variables as listed under Echocardiogram in Baseline Characteristics

Table 2. Study outcome variables (overview)

Variables	Before treat-ment	After treatment (within 72 hours)	At 30 days	Follow-up visit 1	Follow-up visit 2[1]
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
Mortality			x	x	x
Bleeding			x		
LOS[7]			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
[7] Length of stay in ICU/HDU and hospital

Recording of data

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

General methodology

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).

Publishing and substudies

The main study results will be published in two separate articles. The first will report findings on short-term outcomes (up to and including 30 days), while the second will focus on long-term outcomes and follow-up visits. Both articles will be submitted to peer-reviewed scientific journals for publication. Planned substudies will be detailed in separate documents, which will outline the objectives, predefined outcomes, and statistical analysis plans for each substudy.

Statistical methods and sample size (will be updated in accordance with a finalized statistical analysis plan)

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.

The comparative analyses between the groups considering the continuous study outcomes will be performed using linear regression adjusted for known and statistically identified confounders. 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 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 the Poisson and negative binomial regression result in relative risks with 95% CI and p-value.

Additionally, sensitivity analyses will be conducted applying propensity score 1:1 matching using the patients' background data to estimate the propensity score, performed by using logistic regression. Matching will be made applying nearest neighbor matching with the optimal caliper width of 0.2 of the standard deviation of the logit of the propensity score, as recommended. The performance will be validated by comparing the patient characteristics between the matched groups, that are expected not to differ.

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).

Ethical approval
Dnr 2019-00827 (approved 2019-02-04), amendments: Dnr 2022-04256-02 (approved 2022-08-29), Dnr 2023-04750-02 (approved 2023-08-22) Dnr 2023-06931-02 (approved 2023-12-01) Dnr 2024-00038-02 (approved 2024-01-28) Dnr 2024-04908-02 (approved 2024-09-04), 2025-00546-02 (approved 2025-03-10)

ClinicalTrials.gov: TBA

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