For clinical trials with medicinal product to be submitted in CTIS (CTR studies), please use the following template: https://english.ccmo.nl/investigators/publications/publications/2022/05/25/template-protocol

TEMPLATE RESEARCH PROTOCOL

(March 2024)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018
- April 2024: link to template protocol to be used for CTR studies added and additional explanation and comments in section 9 Safety reporting

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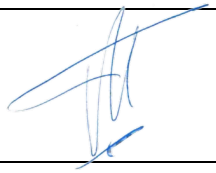
Coordinating Investigator *Prof. Dr. FA Klok*		16-12-2024

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
ACT	Activated Clotting Time
AE	Adverse Event
AR	Adverse Reaction
BARC	Bleeding Academic Research Consortium
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
CDT	Catheter-directed thrombectomy
DOOR	Desirability of Outcome Ranking
COPD	Chronic obstructive pulmonary disease
CTEPH	Chronic Thromboembolic Pulmonary hypertension
CTPA	Computed tomography pulmonary angiography
DSMB	Data Safety Monitoring Board
ECPR	Extracorporeal cardiopulmonary resuscitation
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IB	Investigator’s Brochure
IC	Informed Consent
ICH	Intracranial haemorrhage
ICU	Intensive care unit
IFU	Instructions for use
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention to treat
LMWH	Low molecular weight heparin
LOS	Length of stay

METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MCU	Medium Care Unit
NYHA	New York Heart Association
PE	Pulmonary embolism
PERT	Pulmonary Embolism Response Team
QoL	Quality of life
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
UFH	Unfractionated heparin
VA-ECMO	Venoarterial Extracorporeal Membrane Oxygenation
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Patients with high-risk pulmonary embolism (PE) require immediate reperfusion therapy on top of anticoagulation. The standard reperfusion treatment in these patients is full-dose systemic thrombolysis. This carries a significant risk of major bleeding (10-25%) and intracranial haemorrhage (ICH, 3%). Catheter-directed thrombectomy (CDT) is a promising alternative to systemic thrombolysis with a more direct effect on reducing pulmonary artery clot burden and very likely a better safety profile. Randomized trials evaluating the safety and efficacy of CDT in high-risk patients are currently unavailable. We hypothesize that in high-risk PE patients, CDT is superior to the current standard of systemic thrombolysis in terms of mortality and adverse events, i.e., is associated with a lower composite incidence of all-cause mortality, treatment failure, major bleeding and all-cause stroke. We also hypothesize that CDT will lead to a shorter length of stay (LOS) at the intensive care unit (ICU) and in-hospital, faster recovery, and better long-term quality of life (QoL).

Objective: To determine whether CDT in high-risk PE relative to systemic thrombolysis is:

- more effective and safer in terms of a reduction of the composite endpoint on all-cause mortality and adverse events defined as treatment failure, major bleeding and all-cause stroke at day 30 (primary outcome)
- leads to a better Desirability of Outcome Ranking (DOOR) at day 7
- associated with a lower level of oxygen supplementation at 48 hours
- associated with shorter length of stay (LOS) at the intensive care unit (ICU) and in the hospital
- associated with better functional recovery as well as better patient-reported outcomes such as QoL at one year
- cost-effective after a time horizon of one year

Study design: TORPEDO-NL will be an investigator-initiated, academically sponsored, multicentre, open-label, randomized controlled trial (RCT) designed to show superiority of CDT (2 systems; technical variant) on top of regular anticoagulation over systemic thrombolysis plus regular anticoagulation in patients with high-risk PE in the Netherlands. A 2:1 (thrombectomy: systemic thrombolysis) randomization will be applied. The randomization procedure will be web-based, using randomly sized blocks consisting of 3,6 or 9 patients. Randomization will occur after the verification that a thrombectomy procedure can be started (randomization-to-needle time) within 60 minutes. Randomization will be stratified by centre.

Study population: Patients with acute PE who are at a high-risk for mortality but do not have 'catastrophic PE' and do not have a strict contraindication to either systemic lysis or CDT, as defined according to the selection criteria, will be enrolled.

Inclusion criteria

1. Adult patients with confirmed acute PE, i.e. contrast filling defect in a lobar or more proximal pulmonary artery on computed tomography pulmonary angiography (CTPA), and/or obstructive shock with echocardiographic confirmed dilatation of the right ventricle and a congested vena cava inferior, both with/without echocardiographic signs of clot in transit or deep vein thrombosis of the leg.
2. High risk for mortality, i.e.
    a. post cardiac arrest (after temporary need for cardiopulmonary resuscitation), OR
    b. obstructive shock (systolic blood pressure <90 mmHg and signs of end-organ hypoperfusion (e.g. elevated lactate levels >2 mmol/l) or the need for vasopressors (adrenalin or noradrenalin) to maintain an adequate blood pressure), OR
    c. persistent hypotension (systolic blood pressure <90 mmHg or systolic blood pressure drop ≥40 mmHg for at least 15 minutes) not caused by new onset arrhythmia, hypovolemia, or sepsis, OR
    d. abnormal RV function on transthoracic echocardiography or CTPA AND elevated cardiac troponin levels AND respiratory failure defined as hypoxemia (SaO2 <90%) refractory to O2 supplementation by nasal cannula or Venturi mask, requiring full face mask O2 supplementation (100% FiO2), high-flow nasal O2, or (non-)invasive mechanical ventilation.
3. CDT available and technically feasible so as to allow for a randomization-to-needle time of 60 minutes or less.

Exclusion criteria

1. "Catastrophic PE", i.e. ongoing cardiac arrest and/or need for extracorporeal cardiopulmonary resuscitation (ECPR) and/or immediate indication for venoarterial extracorporeal membrane oxygenation (VA-ECMO) as judged by the responsible physician(s)
2. Glascow Coma Scale <8 following resuscitation for cardiac arrest
3. Alternative diagnosis than acute PE contributing largely to the acute hemodynamic and/or respiratory failure, e.g. sepsis, COPD GOLD 3 or 4, or known heart failure with NYHA Functional Classification of 4, as judged by the treating physician.
4. A known "do not admit to the ICU" or "do not resuscitate" directive
5. An absolute contraindication to systemic thrombolysis, i.e.
    ✓ History of hemorrhagic stroke

- ✓ Ischemic stroke in past 6 months
- ✓ Central nervous system neoplasm
- ✓ Major trauma, major surgery or major head injury in past 3 weeks (note: mild external laceration of the head after, e.g. syncope, does not count as major head injury, especially when a CT scan of the head shows no hematoma)
- ✓ Active bleeding, life-threatening or into a critically organ/area; OR known severe bleeding diathesis with previous bleeding fulfilling these criteria

6. Reperfusion therapy (systemic thrombolysis, surgical thrombectomy or CDT/other catheter directed therapy), or placement of a non-retrieved inferior vena cava filter for acute pulmonary embolism in the past 3 months
7. Thrombus in transit through a patent foramen ovale.
8. Known chronic thromboembolic pulmonary hypertension (CTEPH), or strong suspicion of CTEPH based on pre-existing clinical findings and combinations of signs of PE chronicity on echocardiography and/or CTPA.
9. Known hypersensitivity to systemic thrombolysis, heparin, or to any of the excipients
10. If, in the Investigator's opinion, or after consultation with the local PERT-team or EC-members, the patient is not appropriate for thrombectomy
11. Chronic use of full-dose oral or parenteral anticoagulation before presentation.
12. Pregnancy
13. Current participation in another study that would interfere with participation in this study
14. Previous enrolment in this study
15. Refusal of deferred consent by the next of kin or by the patient himself to use the data. Deferred consent will not be asked to relatives of patients who die in scene, but are included in the study.

Intervention: The intervention consists of immediate thrombectomy (FlowTriever, Inari Medical or Indigo, Penumbra Inc.) without systemic/locally administered thrombolysis. Thrombectomy is performed via jugular or femoral venous access by an interventional cardiologist, interventional radiologist or vascular surgeon according to the instructions for use (IFU) for the particular device. The catheter is advanced over a preplaced guidewire across the right heart into the pulmonary arteries to the location of proximal thrombus. Procedural therapeutic anticoagulation with heparin is administered. After removal of the dilator, the thrombus is extracted by controlled volume aspiration through an aspiration catheter using a syringe or dedicated aspiration system, with multiple aspirations performed as needed. Procedural objectives will be clearly stated prior to the intervention and patient's clinical and hemodynamic status and residual thrombus will guide the investigators to determine when to terminate the procedure. Treatment success is defined as clear evidence of right ventricular

recompensation. The procedure must be discontinued in case of treatment failure, i.e. lack of improvement or hemodynamic deterioration, and major CDT complications such as cardiac arrest or severe haemoptysis. Complications will be solved directly, with a procedure/treatment best suitable according to the treating physician, to minimalize the risk of damage and promote patient recovery.

Main study parameters/endpoints: The primary outcome is the 30-day composite incidence of the binary endpoints of

1) all-cause mortality
2) treatment failure
3) major bleeding
4) and all-cause stroke

Treatment failure in the first six hours after randomization is defined as life-threatening hemodynamic or respiratory deterioration. This deterioration is the clinical scenario if, following randomisation, the patient develops overt cardiorespiratory instability over at least 15 minutes necessitating CPR, escalation of respiratory support, or ECMO. After these first six hours, treatment failure will also be defined by increasing dosages of cardiorespiratory support (e.g. oxygen, catecholamines), and lack of improvement. Lack of improvement is defined by the presence of at least one of the following criteria: i) an equal or rising SCAI SHOCK stage (**Table 1**), ii) an equal or rising Fraction of Inspired Oxygen (FiO_2) level to maintain adequate oxygen saturation (i.e. ≥ 92%), or iii) an equal or decreasing P/F ratio. Treatment failure will be determined every 6 hours starting at the moment of randomisation, until the patient is considered stable and transferable to the ward.

Secondary endpoints include the individual components of the primary outcome as well as DOOR at 7 days as the first secondary outcome; this is defined as (i) survival with no new severe functional limitation, no treatment failure and no adverse event; (ii) survival with new-onset severe functional limitation, but no adverse events and no treatment failure; (iii) survival with BARC3b bleeding; (iv) survival with BARC3c bleeding or ischemic stroke; (v) survival with treatment failure; and (vi) death. Further ranking will be performed by the number of days that a patient needs organ support. Organ support is defined as respiratory organ support with high-flow nasal cannula or (non-)invasive mechanical ventilation, or cardiovascular organ support with a vasopressor or inotropic agent. Other secondary outcomes include amount and mode of O_2 delivered (to be assessed at 48 hrs), ICU and hospital LOS, QoL, symptom burden, functional recovery and 1-year cost-effectiveness.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Thrombectomy requires a procedure but may in part prevent the bleeding risks associated with systemic thrombolysis. Further, patients will be followed for 1 year and asked to complete a set of patient reported outcome measures several times. Benefit for patients involves a potentially lower mortality and incidence of treatment failure and/or adverse events, lower short-term oxygen requirement, a faster and better relief of functional limitations, a shorter LOS, at the ICU and in-hospital, and better long-term outcomes of care.

1. INTRODUCTION AND RATIONALE

Patients with acute pulmonary embolism (PE) usually have good outcomes.[1] However, their prognosis may vary dramatically according to whether the patient is hemodynamically stable. High-risk PE (5-7% of hospitalized patients with PE) is defined by hemodynamic instability and encompasses the clinical presentations of cardiac arrest, obstructive shock, or persistent hypotension.[2] These high risk patients have 30-day mortality rates ranging from 15% to as high as 77%. However, PE patients with respiratory failure that do not fulfill shock criteria, therefore currently not considered as high risk in the ESC guideline, also show a >30% risk of death and further respiratory failure.[3-6] High-risk PE patients require immediate reperfusion therapy on top of anticoagulation. The standard reperfusion treatment in these patients is thrombolytic therapy (class 1-B, 2019 European Society of Cardiology (ESC) guidelines), administered at last in part at the Intensive Care Unit (ICU), with the idea of accelerated fragmentation of the thrombus by lytic medication given systemically.[2] This carries a significant risk of major bleeding (10-25%) and intracranial hemorrhage (ICH, 3%).[2] This risk has been shown to be a major barrier for administering lifesaving systemic thrombolysis in daily practice conditions, which has been suggested to contribute to the high mortality of these patients.[7] The need to minimize the risk of serious bleeding or to offer alternatives to systemic thrombolysis in patients with a high bleeding risk has driven the development of alternative strategies for pulmonary reperfusion. Catheter-directed therapy (CDT), which includes catheter thrombectomy ("thrombectomy") may be associated with lower morbidity and mortality as it offers patients a fast and relatively safe relief of thrombus load and associated signs and symptoms, and may thus represent a better and safer option than systemic thrombolysis.

Multiple studies have shown that mortality in high-risk PE patients remains high and has not improved much compared to the ICOPER study 25 years ago.[8] In this study, 2.454 acute PE patients were studied, of which 4.4% had high-risk PE. Patients with high-risk PE who received systemic thrombolysis had a 90-day mortality of 46%. An analysis of German national data showed an in-hospital mortality of 77% in patients with high-risk PE, and a 1.5% risk of ICH.[7] Overall, high-risk PE patients who receive systemic thrombolysis are more prone to adverse bleeding events as compared to patients with arterial thrombi such as acute myocardial infarction (MI) and stroke.[9] In conclusion, mortality associated with high-risk PE is high, as is the incidence of systemic thrombolysis-induced major bleeding and other adverse events.

Although ultrasound-facilitated catheter-directed low-dose thrombolysis (EKOS, Boston Scientific) may be a safer alternative to systemic full-dose thrombolysis, it still carries a risk of bleeding, and reperfusion may not be complete or fast enough for the unstable, high-risk patients.[10] Currently, several companies offer catheter-directed mechanical (non-thrombolytic)

thrombectomy. The most used ones are Inari Medical (FlowTriever) and Penumbra Inc. (Indigo Aspiration/Lightning). Both systems are CE mark-approved for the treatment of (central) PE. The safety of both systems was assessed in prospective single-arm studies, albeit in intermediate-risk PE. In the FLARE study, 106 intermediate-risk patients with FlowTriever: a significant reduction in right ventricle/left ventricle (RV/LV) ratio at 48h post-procedure was observed, suggesting treatment success.[11] Major adverse events and death occurred in 3.8% and 1.0%, respectively. Major bleeding occurred in 1.0%. In the EXTRACT-PE study, 119 intermediate-risk PE patients were treated with the Indigo thromboaspiration device and a significant RV/LV ratio reduction at 48h post-procedure was reported.[12] Major adverse events and death occurred in 1.7 and 0.8%, respectively. Major bleeding occurred in 1.7%. One notable difference was the device-specific treatment time, which was faster in the EXTRACT-PE trial (median 37 min) than in the FLARE trial (approximate mean 57 min). The FlowTriever for Acute Massive pulmonary Embolism (FLAME) study was a prospective cohort observational study designed to evaluate treatment outcomes in patients with high-risk PE being treated with the FlowTriever catheter. The primary endpoint, evaluated through hospital discharge or 45 days (whichever came first), was a composite of all-cause mortality, clinical deterioration, bailout, and major bleeding. Secondary endpoints included individual elements of the primary composite, stroke, device-related complications, and access site injury.[13] A modest number of 53 patients was enrolled. The primary outcome occurred in 17% of patients with the following rates of the individual elements of the endpoint: death 1.9%; clinical deterioration 15.1%; bailout 3.8%; major bleeding 11.3%. Device-related complications occurred in 22.6%, with individual components of hemoglobin decrease (15.1%), vascular access hemorrhage (7.5%), and hypotension (1.9%). The mortality of this cohort of high-risk PE patients was remarkably low, however, the most severe (‘catastrophic’) PE cases were not enrolled and a proper comparison arm was not available.

Despite the accumulation of data from 3 studies, significant shortcomings in our understanding of mechanical thrombectomy remain, particularly in the measurement of outcomes with validated clinical impact and the likelihood for significant variability in the performance of thrombectomy procedures. Applicable guidelines do not make a difference between different thrombectomy devices and the CE approval for both devices is comparable.[14] In the multi-centre prospective FLASH registry of 800 American patients with intermediate-high or high risk PE treated with FlowTriever, 63% of the patients did not need an overnight stay in the ICU post-procedure, and a reduction in RV/LV ratio and in the number of patients with severe dyspnea were observed.[15] Major adverse events, including major bleeding, and death occurred in 1.8% and 0.8%, respectively.

These studies highlight that the potential health benefit for patients may well outweigh the burden of a catheterization procedure including radiation exposure and contrast fluid load. Importantly, such a procedure may further include some delay in treatment time as compared to systemic thrombolysis, since thrombectomy requires the (fast) deployment of a (24/7 available) catheterization team. Other important clinical endpoints that were insufficiently explored and reported in the abovementioned studies are 'treatment failure' (a lack of improvement or deterioration[16]) and 'ischemic stroke', mostly from migrating emboli from the venous circulation to the arterial system through a patent foramen ovale or atrial septal defect.

2. OBJECTIVES

Primary Objective:

The primary objective of the TORPEDO-NL study is to test the hypothesis that CDT in high-risk PE patients relative to systemic thrombolysis is more effective and safe in terms of a reduction of the composite endpoint on all-cause mortality and adverse events defined as treatment failure, major bleeding and all-cause stroke at day 30.

Secondary Objective(s):

The secondary objectives of the TORPEDO-NL study are to evaluate, after randomization, whether CDT in high-risk PE patients relative to systemic thrombolysis is:

- associated with a better survival at day 7 and day 30
- associated with a lower incidence of treatment failure at day 7 and day 30
- associated with a lower incidence of all-cause stroke at day 7 and day 30
- associated with a lower incidence of all-cause mortality at day 7, 30 and day 90
- associated with a lower incidence of BARC3b and BARC3c bleeding, at day 7 and day 30
- associated with a lower incidence of ISTH major and non-major clinically relevant bleeding at day 7 and day 30
- associated with a lower composite incidence of the binary endpoints of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 7
- associated with a better Desirability of Outcome Ranking (DOOR) at day 7
- associated with a lower level of oxygen supplementation at 48 hours
- associated with shorter LOS at the ICU and in hospital
- associated with better patient-relevant outcomes such as QoL, functional recovery and
- symptom burden at day 7 and after 3, 6, 9 and 12 months according to the ICHOM-VTE set
- cost-effective after a time horizon of a year

- associated with an impact on budget

3. STUDY DESIGN

TORPEDO-NL will be an investigator-initiated, academically sponsored, multicentre, open-label, randomized controlled trial (RCT) to show superiority of CDT (2 commercially available systems; technical variant) on top of regular anticoagulation over systemic thrombolysis plus regular anticoagulation in patients with high-risk PE in the Netherlands. A 2:1 (thrombectomy: systemic thrombolysis) randomization will be applied. The randomization procedure will be web-based, using randomly sized blocks consisting of 3,6 or 9 patients. Randomization will occur after the verification that a thrombectomy procedure can be started (randomisation-to-needle time) within 60 minutes. Randomization will be stratified by centre. Patients will be followed for 1 year after randomisation. The primary outcome will be assessed after a 30-day follow-up period (**Figure 1**). The inclusion is estimated to take 2.5 years. Finally, all primary study outcomes will be adjudicated, blinded, by an independent critical events committee, a more detailed description will be provided in paragraph 8.1.1.

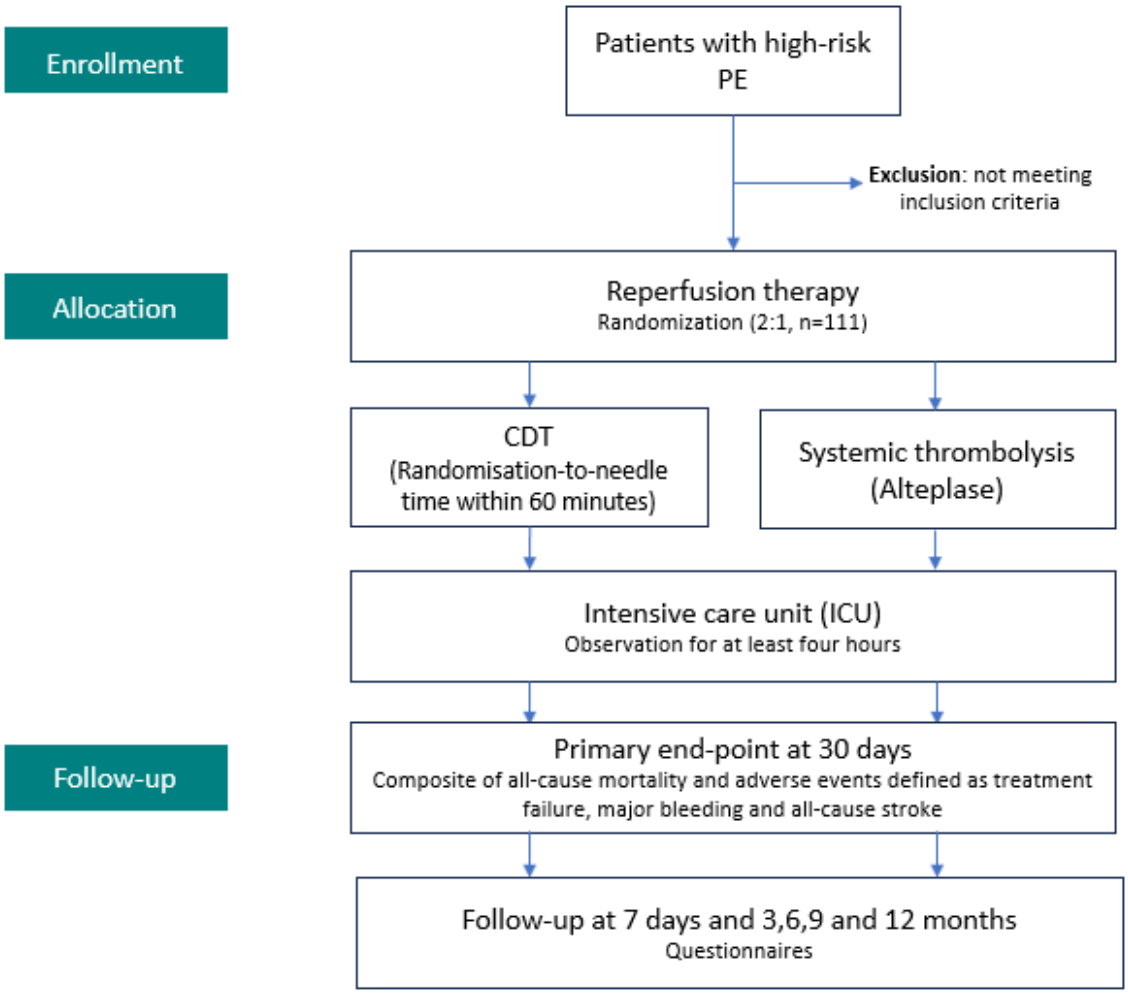

Figure 1: Study flowchart

4. STUDY POPULATION

4.1 Population (base)

The TORPEDO-NL trial will enrol consecutive adult patients with acute PE presenting with respiratory failure, persistent hypotension or shock who do not have a contraindication for systemic thrombolysis or CDT.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Adult patients with confirmed acute PE, i.e. contrast filling defect in a lobar or more proximal pulmonary artery on computed tomography pulmonary angiography (CTPA), or obstructive shock with echocardiographic confirmed dilatation of the right ventricle and a congested vena cava inferior, both with/without echocardiographic signs of clot in transit or deep vein thrombosis of the leg.
2. High risk for mortality, i.e.
    a. post cardiac arrest (after temporary need for cardiopulmonary resuscitation), OR
    b. obstructive shock (systolic blood pressure <90 mmHg and signs of end-organ hypoperfusion (e.g. elevated lactate levels >2 mmol/l) or the need for vasopressors (noradrenalin or adrenalin) to maintain an adequate blood pressure), OR
    c. persistent hypotension (systolic blood pressure <90 mmHg or systolic blood pressure drop ≥40 mmHg for at least 15 minutes) not caused by new onset arrhythmia, hypovolemia, or sepsis, OR
    d. abnormal RV function on transthoracic echocardiography or CTPA AND elevated cardiac troponin levels AND respiratory failure defined as hypoxemia (SaO2 <90%) refractory to O2 supplementation by nasal cannula or Venturi mask, requiring full face mask O2 supplementation (100% FiO2), high-flow nasal O2, or (non-)invasive mechanical ventilation.
3. CDT available and technically feasible so as to allow for a randomization-to-needle time of 60 minutes or less.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. “Catastrophic PE”, i.e. ongoing cardiac arrest and/or need for extracorporeal cardiopulmonary resuscitation (ECPR) and/or immediate indication for venoarterial extracorporeal membrane oxygenation (VA-ECMO) as judged by the responsible physician(s)
2. Glascow Coma Scale <8 following resuscitation for cardiac arrest

3. Alternative diagnosis than acute pulmonary embolism contributing largely to the acute hemodynamic and/or respiratory failure, e.g. sepsis, COPD GOLD 3 or 4, or known heart failure with NYHA Functional Classification of 4, as judged by the treating physician.
4. A known “do not admit to the ICU” or “do not resuscitate” directive
5. An absolute contraindication to systemic thrombolysis, i.e.
   - ✓ History of hemorrhagic stroke
   - ✓ Ischemic stroke in past 6 months
   - ✓ Central nervous system neoplasm
   - ✓ Major trauma, major surgery or major head injury in past 3 weeks (note: mild external laceration of the head after, e.g. syncope, does not count as major head injury, especially when a CT scan of the head shows no hematoma)
   - ✓ Active bleeding, life-threatening or into a critically organ/area; OR known severe bleeding diathesis with previous bleeding fulfilling these criteria
6. Reperfusion therapy (systemic thrombolysis, surgical thrombectomy or CDT/other catheter directed therapy), or placement of a non-retrieved inferior vena cava filter for acute pulmonary embolism in the past 3 months
7. Thrombus in transit through a patent foramen ovale.
8. Known chronic thromboembolic pulmonary hypertension (CTEPH), or strong suspicion of CTEPH based on pre-existing clinical findings and combinations of signs of PE chronicity on echocardiography and/or CTPA.[2,17]
9. Known hypersensitivity to systemic thrombolysis, heparin, or to any of the excipients
10. If, in the Investigator’s opinion, or after consultation with the local PERT-team or EC-members, the patient is not appropriate for thrombectomy
11. Chronic use of full-dose oral or parenteral anticoagulation before presentation.
12. Pregnancy
13. Current participation in another study that would interfere with participation in this study
14. Previous enrolment in this study
15. Refusal of deferred consent by the next of kin or by the patient himself to use the data. Deferred consent will not be asked to relatives of patients who die in scene, but are included in the study.

4.4 Sample size calculation

For the primary endpoint, which is the composite incidence of all-cause mortality and adverse events defined as treatment failure, major bleeding and all-cause stroke at day 30, we calculated the desired sample size largely based on the data from the FLAME prospective registry.[13] This study used a somewhat different composite primary endpoint of all-cause mortality, bailout to alternative thrombus removal strategy, clinical deterioration and major

bleeding. These endpoints were however not well enough defined and the clinically important endpoint of stroke was not a component of the primary outcome. We can however basically state that “bailout” and “clinical deterioration” may match our proposed component of treatment failure. The primary endpoint in FLAME occurred in 17.0% and in 63.9% (AR difference 46.9%) in the FlowTriever and context arms, respectively. Including ischemic stroke, the event rates were 18.9% and 67.2% (AR difference 48.3%), respectively. This study suffered from selection bias and confounding by indication, and therefore the treatment effect is likely overestimated. Patients were enrolled in the FlowTriever arm in the years 2021 and 2022 where event rates in the Context arm were obtained from historical data (years 2010-2020) derived from a meta-analysis.

To assess statistical power, the probability of the primary outcome was assumed to be 0.19 in the thrombectomy arm (based on the most recent data available) and 0.46 in the systemic thrombolysis arm (corresponding with a treatment OR of 3.71 and a risk difference of 27.5%; number needed to treat 3.6). The minimum clinically important difference was set at 27.5% based on discussion within the project group, scientific societies and patient representatives, and on clinical relevance for the difference facets of the composite endpoints. The assumed ARR of 27.5% consists of 5% decrease in mortality, 21.5% reduction in treatment failure or major bleeding and 1% reduction in ischemic stroke (the latter both based on expert opinion).[18] Given a power of 80%, a two-sided α-level of 5%, and a 1:2 (systemic thrombolysis:CDT) patient allocation, 35 patients are needed in the systemic thrombolysis and 70 patients in the CDT arm. Assuming 5% drop-out, 37 patients (systemic thrombolysis) and 74 patients (CDT; total 111 patients) will be recruited. The calculation was done using G*Power (version 3.1.9.6) and is based on proportion difference tested with an anticipated OR.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The standard of care for the patients eligible for the TORPEDO-NL trial is parenteral anticoagulation and systemic thrombolysis (Actilyse® [manufactured by Boehringer Ingelheim Pharmaceuticals, Inc., Ingelheim am Rhein, Germany] 10mg bolus followed by 90mg in two hours). The intervention consists of parenteral anticoagulation and immediate CDT (FlowTriever or Indigo) without systemic or locally administered systemic thrombolysis. Thrombectomy is performed according to the IFU for the particular device and occurs via echoguided femoral or jugular venous access by an interventional cardiologist, interventional radiologist or vascular surgeon. The catheter is advanced over a preplaced guidewire across the right heart into the pulmonary arteries to the location of proximal thrombus. After removal

of the dilator, the thrombus is extracted by controlled volume aspiration through an aspiration catheter using either a syringe or the dedicated aspiration system depending on the device of choise, with multiple aspirations performed as needed. Investigators will determine when to terminate the procedure based on their assessment patients respiratory and hemodynamic status. Procedural objectives will be clearly stated prior to the intervention and respiratory and hemodynamic parameters, including pulmonary artery pressures, will be evaluated pre- and post-thrombectomy per protocol to inform each operator's decision to determine completion. Revaluation of the patient's condition should be carried out using blood loss as a reference, establishing 400 cc of blood loss as a cut-off value. The type and dosage of anticoagulant prescribed to each patient at discharge will be determined by local practice but administration will initially be parenteral for at least 24h after randomization. Participating centres have an institutionalized multidisciplinary Pulmonary Embolism Response Team (PERT) or EXPERT-PE team in place. The intervention team should have ample experience with endovascular interventions. At least one member of the intervention team should have sufficient experience with thrombectomy for PE and should have completed at least 3 full procedures (logged) with one of the devices. Procedures that have been carried out by two team members (for example, in a training setting) do count.

5.2 Use of co-intervention (if applicable)

All study patients will be treated with parenteral therapeutic anticoagulation. Patients will receive an intravenous (IV) bolus of 80 U/kg unfractionated heparin (UFH) immediately upon confirmation of the diagnosis 'high risk PE', before of immediately after randomisation, not to exceed a total of 8,000 U. During the CDT procedure, UFH is continued. Within 4 hours (or immediately upon completion of the reperfusion therapy), the patient should have been transitioned to either full-dose parenteral anticoagulation, either therapeutically dosed LMWH or UFH (based on local protocols). Upon stabilization (no longer need for organ support, transition to normal hospital ward) and after at least 24 hours, the anticoagulation therapy may be switched to oral anticoagulation.

5.3 Escape medication

As soon as a patient meets the predefined primary study outcome, further therapeutic management decisions will be left to the discretion of the treating physician, and are not part of this study protocol.

6. INVESTIGATIONAL PRODUCT

In this study, endovascular reperfusion of the pulmonary artery will be performed using thrombectomy and thromboaspiration. A detailed description of the investigational product will be given in Appendix D2.

6.1 Name and description of investigational product(s)

The 2 most used catheter thrombectomy devices are the FlowTriever (Inari Medical) and Indigo Aspiration/Lightning (Penumbra Inc.). Both systems are CE Mark approved for the treatment of (central) PE. A detailed description of the investigational product will be given in Appendix D2.

6.2 Summary of findings from non-clinical studies

N.A.

6.3 Summary of findings from clinical studies

We refer to Appendix K4 the 2023 NICE document on “Interventional procedure overview of percutaneous thrombectomy for massive pulmonary embolism”.

6.4 Summary of known and potential risks and benefits

We refer to Appendix K4 the 2023 NICE document on “Interventional procedure overview of percutaneous thrombectomy for massive pulmonary embolism”.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable, as all other products used (such as cannulas, vascular dilators, echo machines, are all used in the clinical ICU setting, and all are CE marked and used within the intended use.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study endpoint

The primary outcome is the composite incidence of the binary endpoints of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 30.

Treatment failure in the first six hours after randomization is defined as life-threatening hemodynamic or respiratory deterioration. This deterioration is the clinical scenario if, following randomisation, the patient develops overt cardiorespiratory instability over at least 15 minutes necessitating CPR, escalation of respiratory support, or ECMO. After these first six hours, treatment failure will also be defined by increasing dosages of cardiorespiratory support (e.g. oxygen, catecholamines), and lack of improvement. Lack of improvement is defined by the presence of at least one of the following criteria: i) an equal or rising SCAI SHOCK stage (**Table 1**), ii) an equal or rising Fraction of Inspired Oxygen (FiO_2) level to maintain adequate oxygen saturation (i.e. ≥ 92%), or iii) an equal or decreasing P/F ratio. Treatment failure will be determined every 6 hours starting at the moment of randomisation, until the patient is considered stable and transferable to the ward.

Upon establishing the outcome 'treatment failure' physicians are allowed to escalate therapy in whatever way they consider appropriate. Therapy crossover without meeting the primary outcome is not allowed. Major bleeding is defined as Bleeding Academic Research Consortium (BARC)3b and BARC3c bleeding (=intracranial haemorrhage).[21] Ischemic stroke is defined as any stroke (National Institutes of Health Stroke Scale ≥1).

All primary study outcomes will be adjudicated by an independent critical events committee. This committee will consist of an independent group of three individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant AEs reported by study investigators. The committee will be blinded to treatment assignment and review safety event dossiers, which may include copies of subject source documents provided by study sites, for all reported cases where the primary outcome was met. Committee members may include (interventional) cardiologists, intensivists, pulmonologists, vascular medicine specialists, and (interventional) radiologists, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above.

8.1.2 Secondary study endpoints

The secondary endpoints are:

- Survival at day 7 and day 30
- Treatment failure at day 7 and day 30
- All-cause mortality at day 7, day 30 and day 90
- All-cause stroke at day 7 and day 30
- The composite incidence of the binary endpoints of all-cause mortality, treatment failure, major bleeding and all-cause stroke at day 7
- Desirability of Outcome Ranking (DOOR) at day 7[22]

- BARC3b and BARC3c bleeding, at day 7 and day 30
- ISTH major and non-major clinically relevant bleeding at day 7 and day 30
- Oxygen supplementation (LO2/min) at 48 hours
- Length of stay (days) at the ICU and in hospital at day 30
- Quality of life, functional status and symptom burden symptom burden at day 7 and after 3, 6, 9 and 12 months according to the ICHOM-VTE set[23]
- Cost-effectiveness analysis after a time horizon of one year and budget impact analysis

The DOOR concept provides assessment of benefits and harms using endpoints of efficacy, safety, and functional outcomes. Patients are classified into an ordinal global outcome based on the overall outcome desirability. When patients have been classified, the probability of a more desirable result in one treatment relative to the other is assessed. The superiority of the investigated treatment is calculated by tabulating the pairwise comparison results after further ranking by the number of days that a patient needs organ support. Organ support is defined as respiratory organ support with high-flow nasal cannula or (non-)invasive mechanical ventilation, or cardiovascular organ support with a vasopressor or inotropic agent. The following DOOR outcomes (from most to least desirable) are evaluated: 1. Survival with no new severe functional limitations, no treatment failure and no adverse event; 2. Survival with new severe functional limitations, but no adverse events and no treatment failure; 3. Survival with BARC3b bleeding; 4. Survival with BARC3c bleeding or all-cause stroke; 5. Survival with treatment failure; 6. Death. Functional limitations are defined according to the post-venous thromboembolism functional status (PVFS) scale; grade 4 = severe limitations.[24,25] All secondary endpoints will be evaluated after randomization.

8.2 Randomization, blinding and treatment allocation

A 2 (CDT: systemic thrombolysis) :1 (TT) randomisation will be applied. The randomization procedure will be web-based (castor), using randomly sized blocks consisting of 3,6 or 9 patients. Randomization will occur after the verification that a thrombectomy procedure can be started (randomisation-to-needle time) within 60 minutes. Randomization will be stratified by centre.

8.3 Study procedures

The study starts as soon as the patients is identified as eligible for inclusion and randomised. All patients, i.e. both study arms, will be treated with an UFH bolus after diagnosis. Patients randomised to the usual care arm will be treated with UFH or LMWH with systemic thrombolysis. Patient randomised to the intervention will be treated with UFH or LMWH (see

paragraph 5.2 for specifics) and transferred to the cath lab and subjected to the thrombectomy. All further diagnostic tests (e.g. echocardiography, repeated blood test) are used along clinically relevant but not dictated by this protocol. No biomarkers or imaging test at baseline or follow-up will be required for the study. The SCAI SHOCK stage will be assessed at baseline and every 6 hours starting from randomization until the patient is stabilized and transferable to a normal ward (**Table 1**).[26,27] At 48 hours following randomisation, the amount of oxygen supplementation (l O_2/min) is noted in the medical chart. Patients will be contacted by the Sponsor on day 7 (± 2 days), at 3 months (± 1 week), at 6 months (± 1 week), at 9 months (± 1 week) and at 12 months (± 2 weeks) by e-mail to complete the PROMS questionnaire(s) (**Table 2**).

Stage	**A**	**B**	**C**	**D**	**E**
Condition	Hemodynamically stable	Hemodynamically unstable	Hypoperfusion = Shock	Failure to stabilize with initial therapy	Extremis / refractory shock
Hypotension:					
- **SBP**	>90 mm Hg	60-90 mm Hg	60-90 mm Hg	60-90 mm Hg	<60 mm Hg
- **MAP**	>65 mm Hg	50-65 mm Hg	50-65 mm Hg	50-65 mm Hg	<50 mm Hg
		OR	AND	AND	OR
Hypoperfusion					
- **Arterial lactate**	<2 mmol/L	2-5 mmol/L OR	2-5 mmol/L OR	>5-10 mmol/L	>10 mmol/L
			200-500 U/L	OR	OR
- **ALAT**	<200 U/L	200-500 U/L	≥ 7.2	>500 U/L	< 7.2
- **pH**	≥ 7.2	≥ 7.2		≥ 7.2	
		AND	AND	OR	OR
Treatment intensity	No Drugs No Devices	No Drugs No Devices	No Drugs No Devices	2 Drugs	≥3 Drugs OR Device
			OR	OR	OR
			1 Drug without hypotension or hypoperfusion	1 Drug with persistent hypotension or hypoperfusion	Out-of- or in-hospital cardiac arrest

Table 1: SCAI SHOCK stage overview. SBP = systolic blood pressure; MAP = mean arterial pressure; ALAT = alanine aminotransferase, Drugs = intravenous vaso-active drugs, Devices = RV support or VA-ECMO; hypotension = SBP ≤90 mm Hg or MAP ≤65 mm Hg

	7 Days	3 Months	6 Months	9 Months	1 Year
EQ-5D-5L	X	X	X	X	X
ICHOM-VTE – Core set – Individual Questions (Satisfaction with treatment / Changes in life view)	X	X	X	X	X
PEMB-QoL 40 items	X	X	X	X	X
PROMIS GH ten items	X	X	X	X	X
PROMIS Numeric Rating Scale v1.0 - Pain Intensity 1a_DUT_FLE	X	X	X	X	X
PROMIS SF v1.0 - Dyspnea Severity short form 10a	X	X	X	X	X
PVFS scale one item	X	X	X	X	X

Table 2: Questionnaire overview. The y-axis represents the type of questionnaire, while the x-axis indicates the time points at which the patient receives the questionnaires.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.5 Replacement of individual subjects after withdrawal

The study will be continued until 111 patients have been randomized and completed the first 30 days of follow-up (or met the primary outcome within that period).

8.6 Follow-up of subjects withdrawn from treatment

The primary outcome will be assessed following the principles of intention to treat (ITT). Hence, if the reperfusion treatment to which the patient is allocated to receive is not provided, the patient will still be followed for the occurrence of primary and secondary outcomes.

8.7 Premature termination of the study

The study will be prematurely terminated if recommended by the DSMB for safety reasons in the intervention arm. The DSMB charter of the trial explains the specific discontinuation criteria.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Only adverse events related to the study (i.e. as a consequence of the reperfusion therapy the patient is randomized to, e.g. bleeding and per procedure complications) will be reported to the METC, as no patient benefit is expected from reporting non-study related adverse events.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The lead investigator (or his/hers representative) of each participating site will report all SAEs related to participation in this study protocol to the lead investigator of the LUMC. Since the patients under study are expected to be at high risk for developing SAEs, we would like to

suggest line-listing every 6 months for reporting SAEs. The main reason for line-listing applies to the feasibility of reporting the SAEs besides all other study activities, which is expected to be of burden for the accredited METC. If there is an SAE that is thought to be in direct relation with the safety of the study we will follow the usual regulations of reporting SAEs. The lead investigator of the LUMC will report all SAEs related to participation in this study protocol to the sponsor without undue delay after obtaining knowledge of the events. The sponsor will report the SAEs related to participation in this study protocol through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs related to participation in this study protocol that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report.

SAEs that are considered study specific include:
- Laceration of a blood vessel
- Haemothorax
- Cardiac tamponade
- Damage to the heart valve
- Pneumothorax

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

The independent Data and Safety Monitoring Board (DSMB) is responsible for the oversight review of all AEs. The DSMB will include leading experts in interventional cardiology/cardiology, vascular medicine, pulmonology and biostatistics not participating in the study. During the course of the study, the DSMB will review accumulating safety data to

monitor the incidence of adjudicated events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DSMB Charter.

Data will be supplied to and reviewed by the DSMB in unblinded fashion. Any DSMB recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Executive Committee for consideration and final decision. However, if the DSMB at any time determines that a potentially serious risk exists to subjects in this study, the DSMB chairperson will immediately notify both the sponsor and the Lead Investigators. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

The data will be analyzed on an ITT basis in several steps. The ITT populations consist of all subjects who have been randomized, i.e. when the subject number and allocated regimen are recorded in the eCRF. Patients will be analyzed in accordance with the randomized treatment assignment irrespective of the factual implementation of the assigned treatment regimen. The baseline characteristics in each trial arm will be described. Continuous variables will be described as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables depending on their normality of distribution. The Shapiro–Wilk test will be used to assess normality. Categorical variables are presented as numbers and percentages.
On top of the ITT analyses a per-protocol (safety population) analysis will be performed.
A detailed description of the statistical analysis will be provided in the Statistical Analysis Plan.

10.1 Primary study parameter(s)

For the primary composite endpoint, we will provide the cumulative incidence (number and percentage) for each trial arm and estimate the Odds Ratio (OR, including the 95% Confidence Interval using a binary logistic regression) to compare trial arms. In case of imbalance in background characteristics we can adjust the logistic regression analysis for the respective confounders.

10.2 Secondary study parameter(s)

For continuous secondary endpoints (e.g., DOOR in the first 7 days after randomization), we will estimate mean or median difference between trial arms using an Independent Samples t

Test (mean difference) or a Mann Whitney-U test (median difference), depending on the normality of the distribution. Regarding categorical secondary outcomes, differences between the trial arms will be analyzed using a Chi-square test or Fisher's exact test, when appropriate. Repeated measures secondary outcomes are analyzed using mixed-effects (longitudinal) regression models. Outcomes will be (numerically) stratified according to the type of thrombectomy (FlowTriever vs. Indigo). A per-protocol analysis is performed as a sensitivity analysis. Both R studio and Graphpad software will be used for statistical analysis and making graphs, respectively. A two-sided p-value <0.05 is considered statistically significant. Missing data, where applicable, will be imputed with the use of multiple imputation under the missing-at-random assumption with chained equations. Outcome variables will not be imputed, as is the convention in randomized controlled trials. Patient safety will be monitored by a Data Safety Monitoring Board (DSMB) that will include several senior researchers. Subgroup analyses will be performed (if feasible, i.e. if numbers per subgroup are sufficiently large) for man versus women, age below 75 or 75 and older, different devices used and subtype of high-risk PE.

A cost effectiveness analysis (CEA) will be performed after a time horizon of one year for the primary outcome and QALYs. QALYs will be estimated using the EQ-5D-5L administered at day 7 and after 3, 6, 9 and 12 months, the Dutch tariff, and the "Area under the Curve" approach.[28,29]
The economic evaluation will be performed in accordance with the 'Dutch Guideline for economic Evaluations'.[18] In the main analysis, the societal perspective will be applied, meaning that all costs will be included irrespective of who pays or benefits (i.e. the cost of the intervention, other healthcare use, informal care, as well as productivity losses from unpaid and paid work). Intervention costs will be micro-costed, all other costs will be measured using cost questionnaires administered at 7 and after 3, 6, 9 and 12 months, and valued using standard prices provided by the 'Dutch Manual for Costing Studies in Health Care'.[30]

Cost and effect differences will be estimated, while appropriately accounting for the skewed nature of costs (bootstrapping), correlated costs and effects (bivariate regression model), missing data (multiple imputation), baseline imbalances (baseline adjustment), and the clustered nature of data (mixed model), if applicable.(38) Then, incremental cost-effectiveness ratios (ICER) will be calculated by dividing the difference in costs by the difference in effects. The uncertainty stratified around the ICER and will be estimated using bias-corrected and accelerated bootstrapping with 5.000 replications and graphically presented on cost-effectiveness planes. These planes will indicate the probability that an intervention is cost-effective compared to usual care at different values of willingness to pay (cost-effectiveness acceptability curve).[29] To assess the robustness of the results, various sensitivity analyses will

be performed (e.g. healthcare perspective, complete-case analysis, per-protocol analysis, human capital approach versus friction cost approach).[29]

A budget impact analysis (BIA) will be conducted according to ZonMw's 'BIA, leidraad en rekentool' and ISPOR's principles of good practice.[31] The budget impact analysis will be based on the Dutch population, and hence Dutch incidence data will be used. Perspectives that will be considered are the societal, government (Budget Kader Zorg), and insurer perspective. The cost of the intervention mix will be valued using Dutch standard costs for the societal perspective, actual NZA tariffs for the government perspective, and average tariffs NZA for the insurer perspective. Different scenarios will be evaluated including the following: 1) the intervention is not implemented, i.e. all patients will receive usual care, 2) the intervention is offered to the whole patient population, and 3) the intervention is only offered to specific subgroups of the potential patient population. These subgroups will be defined based on the results of the study, e.g. subgroups who particularly benefitted from the intervention (e.g., type of thrombectomy, sex, presence of cancer). Uncertainty will be estimated using probabilistic sensitivity analyses.

10.3 Other study parameters

Not applicable.

10.4 Interim monitoring

As the anticipated sample size is relatively small, a formal interim analysis is not feasible to reach a solid conclusion. For this reason, an interim monitoring will be performed after the inclusion of 50 patients.[32] This monitoring will entail (i) an evaluation of the consent procedures, (ii) a data quality check, (iii) a review of process measures (e.g., screening, drop out rates, and adherence), and (iv) safety and serious adverse events. The DSMB will review the data of these parameters and report their advice to the sponsor of the trial.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (as amended in Tokyo, Venice and Hong Kong, Somerset West and Edinburgh; version of 2013), in accordance with the Guideline for Good Clinical Practice (CPMP/ICH/135/95 - 17th July 1996), the Medical Research Involving Human Subjects Act (WMO) and the European regulation (EU) 2017/745 on medical devices (MDR).

11.2 Recruitment and consent

Patients will be screened for inclusion upon arrival of the local EXPERT-PE team. The patients eligible for this study are in shock and often respiratory insufficient. Both the study intervention and the systemic thrombolysis are emergency interventions that have to be applied without delay and the intervention fulfils the ethical requirement of clinical equipoise. The study participant can benefit from the intervention, but up to now there is a state of honest, professional uncertainty in the community of expert practitioners as to the effect of the intervention. All in all, the eligible patients have an extremely high risk of dying (up to 70% if left untreated or if appropriate treatment is delayed) and the legal representatives will therefore be in a disturbed mental state complicating an immediate informed decision. The patient will therefore be randomized upon confirmation by the treating physicians that the patients fulfils the criteria of study participation.

The investigator or treating physician will inform the patient about the study and will ask for deferred proxy consent for use of the study and medical data (deferred consent) immediately if and when the patient is deemed susceptible for this (for the majority of patients, this will be shortly after the reperfusion therapy has been delivered), or the legal representative if the patient remains unable to communicate within 72 hours after randomisation. If the patient has died by that time, the legal representatives will be informed that the patient participated in the study. This can be done either by the local principal investigator or the treating physician, provided that the physician has been explicitly informed of the ethical and legal nuances of the trial. The legal representatives will not be asked for consent to use the data, since: (1) the legal representatives have no independent right on inspection of or say on therapeutic or study data (CCMO: “De nabestaanden hebben geen zelfstandig recht op inzage van de tijdens de behandeling en het onderzoek verkregen gegevens en hebben daar ook geen zeggenschap over. Van toestemming voor het gebruik van de data door de nabestaanden kan daarom ook geen sprake zijn”); (2) possible refusal may cause selection bias and this is ethically unwanted (CCMO: het introduceren van selectiebias door het moeten vragen van toestemming aan de nabestaanden, mocht daar een grond voor zijn, ethisch niet wenselijk is). These patients are essential for the internally validity of the study; 3) the data will be coded. Use of the data has no implications for the patient or legal representatives; and (4) we consider it unethical to burden the grieving relatives with a decision that has no impact on the already performed treatment and only pertains the use of already gathered and coded data.
The legal representatives will be given a letter containing information about the trial. They will also receive an invitation for an appointment with the supervising doctor and an investigator after 6 to 8 weeks, to answer any remaining questions.

11.3 Objection by minors or incapacitated subjects (if applicable)

Minors will not be included. This study is not including incapacitated subjects. Deferred consent will be asked to when the patient becomes susceptible and/or the legal representative, as described above.

11.4 Benefits and risks assessment, group relatedness

Multiple studies have shown that mortality in high-risk PE patients remains unacceptably high and has not improved much compared to 20 years ago. The current standard of care is underused because of its associated high risk of major and sometimes fatal bleeding. The studies described in chapter 1 of this protocol highlight that the potential health benefit of CDT for patients may well outweigh the burden of a catheterization procedure including radiation exposure (± 5.70 mSv) and contrast fluid load. Notably, such a procedure may further include some delay in treatment time as compared to systemic thrombolysis, since thrombectomy requires the (fast) deployment of a (24/7 available) catheterization team. This fast application of CDT has been shown feasible in cohort studies. The benefits for patients are clear if our hypothesis is proven true: a potential lower mortality and incidence of treatment failure and/or adverse events, lower short-term oxygen requirement, a faster and better relief of functional limitations, a shorter length of stay at the ICU and in-hospital, and better long-term outcomes of care. Importantly, a randomized trial with patient-relevant outcomes is the only way to conform our hypothesis with certainty as the inherent methodological problems of cohort studies in this setting prevent such study designs to provide the necessary level of evidence.

11.5 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 2015). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1) € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2) € 5.000.000,- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3) € 7.500.000,- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

The Insurance company Is CentraMed.
Adress: Postbus 7374, 2719 DB Zoetermeer.
Tel.nr.: +31 (0)70-3017070

11.6 Incentives

Patients will not receive any compensation or other incentives to participate.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

When a potential patient is presented, informed consent procedure will follow as described above in paragraph 11.2. When included in the study all data will be collected, used, and stored. This concerns data such as name, address, contact details and date of birth and medical Information. Diligent efforts will be made to ensure the study data are stored securely and confidential Information is protected. The handling of personal data will comply with the General Data Protection Regulation (GDPR). All study participants will receive a study number which is a unique identifier (not based on patient initials and birth date). The key to the code will be safely stored in the local research institute and safeguarded by the principal investigator. The unique study number will be used on the Case Report Form (CRF; Castor EDC). Baseline characteristics, contact details, and outcomes will be entered in Castor. The data that will be sent to the sponsor/coordinating investigator will include names and contact data as this is relevant for the centralised follow-up via telephone/email beyond the first 30 days. This will be explicitly mentioned in the patient information letter and mentioned in the deferred informed consent conversation. Upon completion of the study for each individual patient, contact details will be deleted. All electronic data and records will be saved under their unique study number and stored in a secured file (in the 'I drive') on the computer. Access to study files and electronic records will be restricted to authorized study personnel only. The local investigators are responsible for ensuring that all sections of the CRF are completed correctly, and that entries can be verified against source data. The principle investigators will archive all study data (subject Identification code list, source data, and investigator's files) and relevant correspondence in the Investigator Site File. Only the principle investigator will have access to the subject Identification code list and source data. The monitor and Flealthcare and Youth Inspectorate also have access to the data in case of safety reviewing. The Investigator Site

File, all source data, and other pertinent documents will be archived for 15 years at the research location.

12.2 Monitoring and Quality Assurance

Monitoring in all sites in the Netherlands will be executed by (internal) monitors of the LUMC according to the monitor plan. Monitors and auditors have permission to see uncoded patients data. Monitoring and auditing procedures will be followed, in order to comply with GCP guidelines. Each center will be monitored at regular intervals to ensure compliance with the protocol, GCP and legal aspects. This will include checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (premature) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Results of this study will be published in open access international peer-reviewed scientific journals and will be presented on (inter)national scientific conferences and meetings. This will be in accordance to the CCMO statement on publication policy.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable as all the investigational products will be used within their registered indication and not in combination with other (investigational) product.

13.2 Synthesis

As described above, we will include a population that is at very high risk of death and for whom the current standard of care (systemic thrombolysis) is considered insufficient. The benefits for patients in this study randomized to the intervention arm seem clear if our hypothesis is proven true. Still, the effectiveness and safety of the intervention are to be proven beyond doubt, even despite the favorable data from observational single-arm studies. The main risks for patients randomized to the intervention are delayed reperfusion because of logistical issues, and per procedure complications. For the first issue, we have very strict criteria for study sites to be able to participate. The multidisciplinary organization of care for patients with severe acute PE via an EXPERT-PE team must be protocolized and proven in place. This will be checked by the principle investigators of this study based on review of relevant local protocols and interviewing the members of the local EXPERT-PE team. Furthermore, the interventional team that will be responsible for the intervention must be available around the clock, well trained and experienced with the intervention, the latter defined as at least 3 uncomplicated procedures in patients with hemodynamic and/or respiratory compromise. The training log of the interventional team will be checked. Finally, the local EXPERT-PE team must make a quick assessment whether it is feasible to initiate the intervention within 1 hour upon randomization. For instance, if the team is performing another procedure, or if the device is technically unavailable, or when catheters are not in stock, patients cannot be included and enrolled. Together with the reported safety and efficacy of the procedure as reported in cohort studies, we are confident that the risk related to unacceptable delay as well as per procedure complications are mitigated. On top of this, we will install a DSMB that will carefully monitor the safety of the study procedures.

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