University Hospitals Plymouth NHS Trust

TiPE
Thrombectomy in Pulmonary Embolism

PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE THE USE OF COMPUTER AIDED VACCUM THROMBECTOMY WITHIN THE CONTEXT OF INTERMEDIATE AND HIGH-RISK PE.

Version 1.0 (draft 11): 19 Oct 25

IRAS Number:	XXX
REC Reference:	XXX
SPONSORS Number:	24RAD100
FUNDERS Number:	XXX
Trial Registration:	XXX

Put people first
Take ownership
Respect others
Be positive
Listen, learn, improve

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research (2017). It will be conducted in compliance with the protocol, the Data Protection Act (2018) and other regulatory requirements as appropriate.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature: .....

Date: Date of signature

Name (please print): .....

Chief Investigator:

Signature: .....

Date: Date of signature

Name (please print): .....

Statistician:

Signature: .....

Date: Date of signature

Name (please print): .....

For and on behalf of the Study Sponsor:

Signature: .....

Name (please print): .....

Date: Date of signature

Position: .....

PRINCIPAL INVESTIGATOR PROTOCOL SIGNATURE PAGE

Trial Title: Prospective observational study to evaluate the use of computer aided vacuum thrombectomy within the context of intermediate and high-risk PE.

IRAS: IRAS number

Protocol Date and Version No: Protocol date; Version number

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol, any relevant laws and regulations.

Please print name.	Insert signature	Site name	Signature date
Principal Investigator	**Signature**	**Site name or ID No.**	**Date**

This page will be given as a separate document to the Principal Investigators to sign prior to commencement of the study.

KEY CONTACTS

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TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
BNP	B-type Natriuretic Peptide
BP	Blood Pressure
CAG	Confidential Advisory Group (CAG advises on both research and non-research uses of confidential patient information without consent).
CAVT	Computer Aided Vacuum Thrombectomy
CI	Chief Investigator
CRP	C-Reactive Protein
CT	Computed Tomography
DCS	damage control surgery
DVT	Deep Vein Thrombosis
ECMO	Extra Corporeal Membrane Oxygenation
ECS	European Society of Cardiology
GCS	Glasgow Coma Scale
GFR	Glomerular Filtration Rate
GI	GastroIntestinal
HDU	High Dependency Unit
HRA	Health Research Authority
ICH	IntraCerebral Haemorrhage
ICMJE	International Committee of Medical Journal Editors
IM&T	Information, Management & Technology
IR	Interventional Radiology
IVC	Inferior Vena Cava
MTCs	Major Trauma Centres
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PAT	Pulmonary Artery Thrombectomy
PI	Principal Investigator
PE	Pulmonary Embolism
PERT	Pulmonary Embolism Response Team
PESI	Pulmonary Embolism Severity Index
PFO	Patent Foramen Ovale
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

RBC	Red Blood Cell
RV/LV	Right Ventricle to Left Ventricle diameter ratio
Dendrite	Dendrite clinical systems, electronic research database
Section 251	The purpose of section 251 support is to give the data controller a legal means of providing access to confidential patient information without consent.
SOP	Standard Operating Procedure
SPSS	Statistical Product and Service Solutions (statistical software suite)
UHP	University Hospitals Plymouth NHS Trust
USS	UltraSound Scan
WBC	White Blood Cell

KEY WORDS:

Pulmonary embolism, Thrombectomy.

STUDY SUMMARY

Study Title	TiPE
Study Design	Prospective observational study to evaluate the use of Computer aided vacuum thrombectomy (CAVT) within the context of intermediate and high-risk PE.
Study Participants	Patients presenting with intermediate or high-risk PE (as defined by European Society of Cardiology (ESC) guidelines[1]) at one of the participating hospitals.
Eligibility Criteria	Study Site Criteria: 1. Availability of 16Fr Penumbra Flash 2. Operational PE Response team 3. Operator experience treating a minimum of 2 previous PE's and experience with Penumbra indigo systems (defined as 3 cases). Inclusion Criteria Participants: 1. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less 2. Patients who present with CT confirmed PE 3. Defined as intermediate or high-risk PE (according to ESC guidelines[1]) 4. Date of CT imaging from within the two-year period 5. Patient is ≥ 18 years of age 6. Informed consent obtained 7. Evidence of cardiac dysfunction (Either biochemical or imaging features of RHS) Exclusion Criteria: 1. Known serious, uncontrolled sensitivity to radiographic agents 2. CT not available to evaluate PE 3. Low Risk PE as defined by ESC guidelines[1] 4. Current participation in another investigational drug or device study that may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies 5. Other medical, social, or psychological conditions that, in the opinion of the Investigator, precludes the patient from appropriate consent, could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study
Planned Sample Size	2000 eligible patients and 200 thrombectomy patients

Follow-up Duration	6 months from date of PE or date of death, whichever is sooner
Planned Study Period	30 months
Primary Objective	1. To evaluate the effectiveness of PE CAVT as a treatment for intermediate and high-risk PE as measured by change pulmonary arterial pressure and in RV/LV (Right Ventricle to Left Ventricle diameter) ratio at 48 (+ 48 /- 24) hours post procedure. 2. Ascertain the mortality and morbidity profile for CAVT within intermediate and high-risk PE, within 48 (± 12) hours post procedure, 30 (± 7) days, 90 (± 14) days and at 6months (+/- 30 days).
Secondary Objective	1. To identify factors that determine the decision to use thrombectomy within the PERT team 2. To evaluate the factors that predict outcome of CAVT 3. To evaluate the patient tolerance and experience in the form of Patient related outcome measures (PROMS) of CAVT 4. To evaluate the effectiveness and risk profile of CAVT in high-risk patients, including effects of concurrent lytic therapy where given 5. To evaluate the effect of service design on PE CAVT rate and outcomes 6. To compare variability in provision of CAVT between hospitals and its effect on performance and outcomes. 7. To evaluate the relationship between severity and outcome in patients receiving CAVT 8. To determine imaging features that are associated with poor outcomes in patients undergoing CAVT 9. To determine the effectiveness of CAVT in relationship to the age of the thrombus 10. To evaluate the perceived dyspnoea at 30 days, 90 days and 6 months after CAVT, and also in comparison to the non-intervened group 11. To evaluate Quality of life as assessed by EQ-5D-5L and PEmb-QoL at 30 days, 90 days and 6 month, and also in comparison to the non-intervention group 12. Incidence of device related SAE(s)

13. Evaluate the impact of the length of procedure time and the operator decided end point of CAVT, including technical success and its effect on outcomes
14. To evaluate the time to CAVT and its effect on outcomes and resource utilisation.

STUDY FLOW CHART

Identification of cohort

All patients who had intermediate or high-risk PE within the two-year period.

Screening for eligibility

Exclusion criteria:

1. Known serious, uncontrolled sensitivity to radiographic agents
2. CT not available to evaluate PE
3. Low Risk PE as per ESC guidelines[1]
4. Current participation in another investigational study that may confound
5. Other medical, social, or psychological conditions that, in the opinion of the Investigator, precludes the patient from appropriate consent, could limit the patient's ability to participate in the study.

Screening for eligibility

Inclusion criteria participants:

1. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less
2. Patients who present with CT confirmed PE
3. Defined as intermediate or high-risk PE (as per ESC guidelines[1])
4. Date of CT imaging within the two-year period
5. Patient is ≥ 18 years of age
6. Informed consent obtained
7. Evidence of cardiac dysfunction (Either biochemical or imaging features of RHS)

Inclusion criteria Operator:

1. Operator experience treating a minimum of 2 previous PE's and experience with Penumbra indigo systems (defined as 3 cases).

Exclusion
Patient choice

Data collection

Data on patients regarding patient demographics, physiological parameters, PESI score, CT findings, clinical status, procedural information, day 1,3,5 observations, length of stay, readmission rates, further procedures and outcome at 30 days, 90 days and 6months.

Final cohort for analysis

Full cohort analysis will be performed on anonymised data set.

1 INTRODUCTION

1.1 LAY SUMMARY

Pulmonary embolism is a blood clot on the lung, which can cause death or significant reduced quality of life. Sucking the clot out with a special tube (catheter) is a relatively new procedure that can be performed but doesn't have the data required to properly support its use in some patients. We know this procedure works in patients who have no other options and would almost certainly die without intervention. We currently don't know how well this procedure is tolerated, how well it works and what its complications are in patients who are moderately to severely unwell. The National Institute of Clinical Excellence (NICE), an advisory body, suggests more data is required to support its use in patients who are sick or very sick. This registry aims to support this growing evidence base to workout if the treatment is effective and the associated risks that come with using it. We are collecting data about this procedure and other treatments patients get offered to better inform clinicians and researchers.

1.2 RATIONALE FOR CURRENT STUDY

Acute intermediate-risk pulmonary embolism (PE) and high-risk PE (1) can be life threatening. The incidence of PE is increasing (2), and patients who survive the acute presentation may experience significant morbidity including reduced exercise tolerance, and decreased quality of life (QoL) (3). Often patients are treated with anticoagulation to stop the clot getting worse and encourage the body to slowly break up the clot. However in more severe cases thrombolysis medication can be given to actively break up the clot. Catheter directed thrombolysis can be used to target the lytic medication into the pulmonary arteries and reduced the systemic effects. Percutaneous thrombectomy is a newer treatment option that aspirates the clot, providing a faster and potentially lytic free solution to sick patients. Pulmonary artery thrombectomy (PAT) is a treatment option that is variably utilised and has unclear evidence base (4,5,6,7). The penumbra device uses a computer modulated vacuum aspiration system to both fatigue, breakup and aspirate the clot. This has been shown to be safe and effective in small cohorts (8). CAVT can prevent acute hemodynamic decompensation, alleviate acute PE-related symptoms, accelerate right ventricular recovery, and improve quality of life as measured by patient-reported outcomes (PROs) (4,5). Despite existing literature addressing clinical outcomes with PE treatment, comprehensive data on PE-related morbidity, PROs and longer-term outcomes after mechanical thrombectomy are still lacking.

1.3 PARTICIPANT AND PUBLIC INVOLVEMENT

Several patients who suffered from significant PEs, either receiving thrombectomy or other treatments including catheter directed thrombolysis were asked to review the protocol who considered the study

worthwhile and the involvement not onerous on patients. Lay person representative will be further involved in ongoing meetings.

In order to assess participants' lived experience of receiving vacuum thrombectomy for PE, a qualitative sub-study is planned. This study will build upon the existing literature (9, 10), that suggests patients suffer adverse physical and psychological consequences of PE and its management. To our knowledge, there is no literature exploring patients' experience of PE thrombectomy procedures specifically, thus highlighting an important gap in the literature. The qualitative sub-study will therefore provide insight into the experience of CAVT as a therapeutic intervention, deliver insights into how the patient experience may be optimised by IR providers, and infer whether there are any subjective differences in short-term morbidity and psychological sequelae as result of undergoing CAVT. The qualitative sub study will be protocolised separately as the 'TiPE-views' study.

1.4 Diversity and Inclusion

The study will involve 12 sites, including remote costal population and cities. The 12 sites will include centres in the Southwest, North England and Scotland. This will help with capturing a diverse national population along with patients from deprived areas. As this is a hospital study, all adult patients referred to the PERT team will be screened. The study will collect data from intermediate and high-risk patients who are affected by cancer and pregnant women who have an increased risk of clotting (11). Both populations were excluded from previous clinical trials, although the risk of radiation during pregnancy needs to be acknowledged.

2 STUDY OBJECTIVES

2.1 Primary Objectives

1. To evaluate the effectiveness of PE CAVT as a treatment for intermediate and high-risk PE as measured by change pulmonary arterial pressure and in RV/LV (Right Ventricle to Left Ventricle diameter) ratio at 48 (- 24 / + 48) hours post procedure.
2. Ascertain the mortality and morbidity profile for CAVT within intermediate and high-risk PE, within 48 (± 12) hours post procedure, 30 (± 7) days, 90 (± 14) days and 6 months (+/- 30 days).

2.2 Secondary Objectives

1. To identify factors that determine the decision to use thrombectomy within the PERT team
2. To evaluate the factors that predict outcome of CAVT
3. To evaluate the patient tolerance and experience in the form of patient related outcome measures (PROMS) of CAVT

4. To evaluate the effectiveness and risk profile of CAVT in high-risk patients, including effects of concurrent lytic therapy where given
5. To evaluate the effect of service design on PE CAVT rate and outcomes
6. To compare variability in provision of CAVT between hospitals and its effect on performance and outcomes.
7. To evaluate the relationship between severity and outcome in patients receiving CAVT
8. To determine imaging features that are associated with poor outcomes in patients undergoing CAVT
9. To determine the effectiveness of CAVT in relationship to the age of the thrombus
10. To evaluate the perceived dyspnoea at 30 days and 6 months after CAVT, and also in comparison to the non-intervened group
11. To evaluate Quality of life as assessed by EQ-5D-5L and PEmb-QoL at 30, 90 days and 6 months for all participants.
12. Incidence of device related SAE(s)
13. Evaluate the impact of the length of procedure time and the operator decided end point of CAVT, including technical success and its effect on outcomes
14. To evaluate the time to CAVT and its effect on outcomes and resource utilisation.

2.2 OUTCOMES

Effectiveness of CAVT will be determined by the change in RV/LV ratio on Echocardiography and the reduction in direct invasive measurement of the Pulmonary artery pressure at the beginning and end of the procedure.

Technical success will be determined by the operator comparing pre and post imaging and pulmonary artery pressures. Morbidity and mortality will be expressed as percentage of the cohort. Imaging features, service design, PERT team decision and comorbidities effect on outcomes will be assessed via regression analysis.

The service design and effect on thrombectomy will be assess by service questionnaire at site set up describing the service design factors. Patient reported outcomes like quality of life and breathlessness will be assessed to determine improvement as per their validated questionnaires.

3 STUDY PARTICIPANTS

3.1 SCREENING PROCEDURES

All patients identified as having an CT confirmed PE and referred to the hospitals PERT team will be screened. Patients who attend hospital over a 2-year period with a CT diagnosed pulmonary embolism will be stratified, into low, intermediate or high risk as per normal standard of care using the PESI score. This is an internationally regarded score that enables PEs to be categorized according

to severity. All patients who are intermediate or high risk and referred to the local Pulmonary Embolism Response Team (PERT) and if eligible will be approach for consenting to enter the study.

3.2 INCLUSION CRITERIA

Patient:

1. Clinical signs and symptoms consistent with acute PE with duration of 14 days or less
2. Patients who present with CT confirmed PE
3. Defined as intermediate or high-risk PE (as defined within the ESC Guidelines[1])
4. Date of CT imaging within the two-year study period.
5. Patient is ≥ 18 years of age
6. Informed consent obtained
7. Evidence of cardiac dysfunction (Either biochemical or imaging features of RHS)

Operator:

1. Operator experience treating a minimum of 2 previous PE's and experience with Penumbra indigo systems (defined as 3 cases).

3.3 EXCLUSION CRITERIA

1. Known serious, uncontrolled sensitivity to radiographic agents
2. CT not available to evaluate PE
3. Low risk PE as defined by ESC guidelines[1]
4. Current participation in another investigational drug or device study that may confound the results of this study. Studies requiring extended follow-up for products that were investigational but have since become commercially available are not considered investigational studies.
5. Other medical, social, or psychological conditions that, in the opinion of the Investigator, precludes the patient from appropriate consent, could limit the patient's ability to participate in the study.

4 STUDY DESIGN, PROCEDURES AND INTERVENTIONS

4.1 STUDY DESIGN

We estimate that each centre will see around 130 eligible patients per year and perform approximately 13 thrombectomies per year (4). Therefore, across the 12 centres we expect to see around 3000 eligible patients and around 300 thrombectomy patients across the two years. We expect around 70% of patients to consent to take part in the study due to its observational nature and therefore we expect between 2000 of PERT referred patients and 200 thrombectomy patients across the two years.

4.2 RECRUITMENT

Patients will be assessed for inclusion into the study by the research nursing team or trained member of the PERT team at point of referral to the local PERT team. Consent for inclusion in the data recording can be sought retrospectively in an out of hours setting, up to 96 hours post referral. All patients referred with an intermediate or high-risk PE (according to ESC guidelines (1)) will be included (after consent) into the wider dataset, with more specific data collected on those undergoing CAVT treatment.

4.3 CONSENT

Consent for inclusion into the trial dataset will be obtained by the research nurse or PERT team, only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Consent can be sought up to 96 hours after the referral to the PERT to allow for out of hours setting. No study specific data will be collected before a consent form is signed. The right of the participant to refuse to participate without giving reasons must be respected. There will be no change in the patients' treatment pathway. Patients will be able to withdraw from the study at any point. If a patient loses capacity, no further information will be obtained but their data already included will not be deleted. Patients who are unable to consent will be able to be included if a appropriate proxy consent is available. Patients who die within the 96 hours will also be able to be included if appropriate proxy consent available.

4.4 STUDY ASSESSMENTS

Data will then be collected regarding admission information, imaging parameters, decisions to treat and how the patient was treated. Data will be collected by the research nursing team and will be maintained on anonymised electronic research specific (Dendrite) database.

Follow up

Follow up data, including 30 days, 90 days and 6-month outcomes will be assessed. The follow up with the questionnaires will be administered by the Dendrite platform.

Organisation

A short service-based questionnaire will be sent to each centre to establish centre-specific systems such as on call rota, PERT team activation, reporting practices and capture data around routine decision-making at that site. This will be completed by the site team at registration at each site and will take approximately 5 minutes to complete.

4.5 Definition of End of Study

This is defined as the date of the last data submitted by the site. The sponsor will notify the REC, in writing, within 90 days of the end of the study.

Recruitment will be monitored with specific review at 1 year and 18 months. If recruitment at >120 thrombectomies at 1 year or >180 thrombectomies (i.e. greater than 20%) then the study will complete upon the final (200 thrombectomy) admission into the database unless an amendment to increase the specified end point is agreed with the sponsor, funder and with approval of the REC. In the event of under recruitment at 1 year or 18 months (<90 thrombectomies or <150 respectively then an extension or additional sites will be considered in conjunction with the sponsor, funder and with approval of the REC.

5 SAFETY REPORTING

5.1 Definitions of Adverse Events

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study participant.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 Reporting Procedures

At each data collection (30 days, 90 days and 6 months from the thrombectomy) the investigator will determine whether adverse events about the device and procedure have occurred. Subjects participating in the study should be encouraged to report these AEs spontaneously or in response to general, non-directed questioning.

Relevant events will be collected from the signing of informed consent to the completion of the follow up 6 months post index procedure.

Adverse Events

AEs will be recorded for the CAVT and relevant procedure only.

Any AEs related to the CAVT will also be reported to the company Penumbra and MHRA.

Please find in Appendix 3 expected adverse events of CAVT and relevant procedure.

Serious Adverse Events

Death due to any pre-existing conditions will not be reported as SAEs.

Serious adverse events will be recorded.

Only CAVT related SAEs will be reported to the Principle Investigator, the Chief Investigator and Sponsor within 24 hours of being aware of the event. An Independent Medical Reviewer for the SAEs will also be appointed and the opinion will be recorded along with the PI / CI opinion. A SAE form should be completed.

All CAVT related SAEs should be reported to the Name of REC and copied to the Sponsor, and Penumbra where in the opinion of the Chief / Principal Investigator and the Independent Medical Reviewer, the event was:

- **'related'**, i.e. resulted from the administration of any of the research procedures; and
- **'unexpected'**, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief / Principal Investigator becoming aware of the event, using the Non-CTIMP safety report to REC form for non-IMP studies.

Sponsor contact details for reporting SAEs

Please send SAE forms to: R&D Governance / R&D Office

Tel: 01752 432195 / 01752 432196 (Mon to Fri 09.00 – 17.00)

6 STATISTICS

6.1 THE NUMBER OF PARTICIPANTS

Target sample size is based on recruitment of 12 centres, based on estimates from current PE Response team referrals and previous year thrombectomy numbers. We estimate that each centre will see around 130 eligible patients per year and perform approximately 13 thrombectomies per year (4). Therefore, across the 12 centres we expect to see around 3000 eligible patients and around 300

thrombectomy patients across the two years. We expect around 70% of patients to consent to take part in the study due to its observational nature and therefore we expect between 2000 of PERT referred patients and 200 thrombectomy patients across the two years. These allow for approximately 30% of eligible patients to decline to participate in the study which is higher than the STRIKE PE (8) rate.

The interim analysis of the STRIKE PE (8) study demonstrated a change of LV/RV ratio of (mean reduction of 0.38 (SD ± 0.27) ($P < .001$)) at 48 hours, which is equivalent to an effect size of d >1 (Cohen's d). However, the STRIKE PE study was within a European setting and with different thresholds for treatment than current UK based guidelines. We are therefore conservatively anticipating approximately 25% of the thrombectomy group being classified as high risk. Therefore, our patient group, we anticipate a smaller change in LV/RV ratio which is still clinically significant. With a sample size of 200 we would be able to detect a standardised effect size of d=0.2 (Cohen's d) at 90% power with an alpha 0.05. As a key comparison of interest of the high-risk subgroup at 90% power a small effect size will be detectable.

6.2 ANALYSIS

Patient demographic and clinical characteristics will be summarised using appropriate descriptive statistics. The primary outcome, change in LV/RV ratio before and at 48 hours post baseline will be summarised according to risk group and overall and will be assessed with a two-sided paired t-Test. Linear regression analysis will be used to identify factors, including severity, affecting the change in LV/RV ratio. Survival analysis will be used to model factors affecting mortality. Data will be analysed using R or Stata. An unblinded interim analysis at 100 patients will be performed at 6 month follow up with focus on the primary outcomes. No Stop/Go criteria will be applied as the PE response team decision to treat or not is not protocolised and the study is observational only. A detailed statistical analysis plan will be written with the University of Plymouth Medical Statistics group and finalised before database lock.

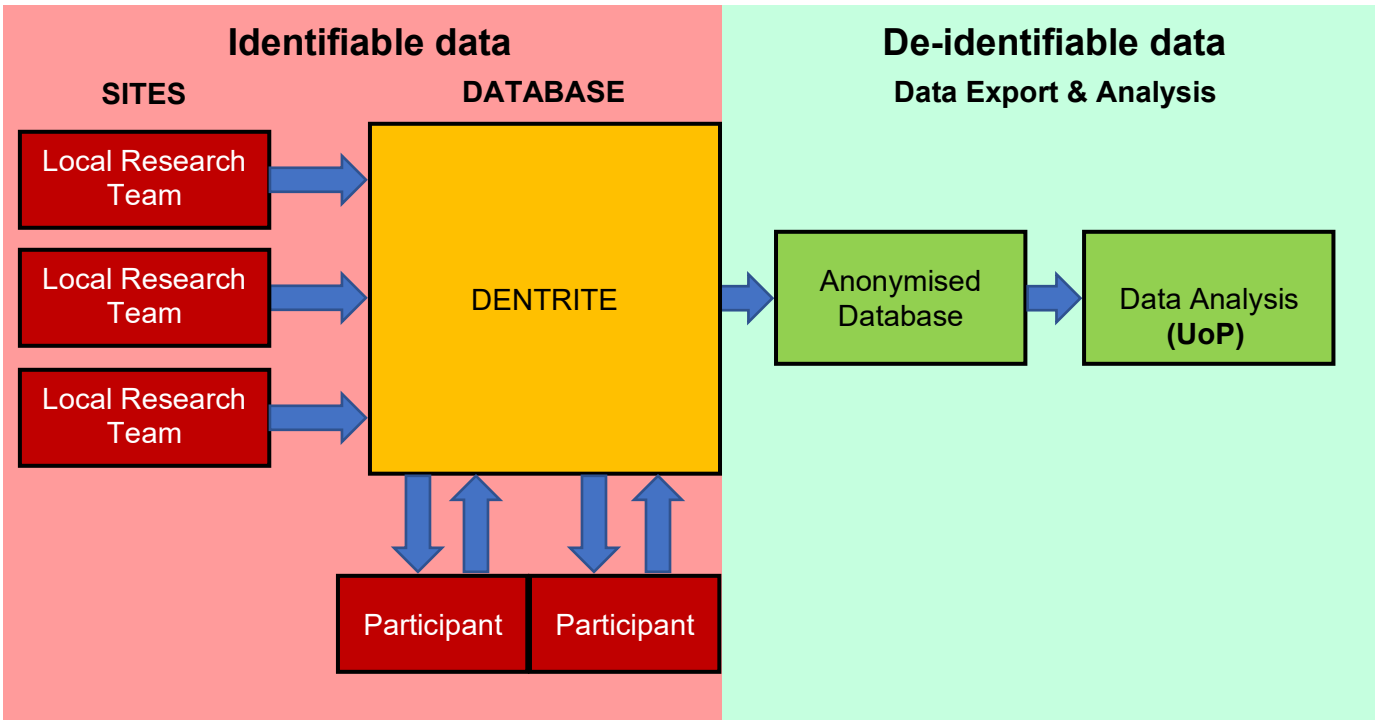
7 DATA MANAGEMENT AND DATA SHARING PLAN

To comply with the Data Protection legislation information will be collected and used fairly, stored safely and not disclosed to any unauthorised person. This applies to both manual and electronically held data.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and ensure the UK General Data Protection Regulation (GDPR) in conjunction with the UK Data Protection

Act 2018, which sets out the statutory requirements for the processing of personal data, is adhered to.

7.1 DATA FLOW DIAGRAM



7.2 DESCRIPTION OF THE DATA

Sample data points will include the following for **ALL** patients:

Patient demographics

Age, Sex, Medical History, Cancer, Pregnancy, Time of first symptoms, presenting hospital, admission from location (e.g. Own Home/nursing home) transfer in, previous PE, Anticoagulation, Concurrent DVT and Position.

Admission / Diagnosis (at point of diagnosis of PE if not on admission)

Admission observations, Biochemistry including Temperature, BP, Pulse, oxygen saturations and GCS, biochemistry including: WCC, RBC, CRP, GFR and BNP and Troponin

CT findings (including Evidence of RHS parameters including IVC contrast reflux, Septal flattening, clot location, reporter grade)

Base line (Day of referral to PERT if not day of admission)

PESI score, , RV/LV ratio CT, RV/LV ratio USS. Presence of right atrial clot, PFO presence on Echocardiography, eligibility for thrombolysis (e.g. recent head trauma/ ischaemic stroke, previous ICH, Intracranial neoplasm, GI malignancy, GI haemorrhage in previous 21 days, Recent surgery, BP >185, active bleeding, infective endocarditis, Clotting abnormalities), If Thrombolysis given, including dose.
PER Team first assessment including date and time
PER Team initial decision outcome, date and time
PER Team review - Change Decision, date and time - and change in observations and Biochemistry
PER Team review - Change Decision 2, date and time - and change in observations and Biochemistry

Discharge

Further procedures, length of stay, (including ICU, HDU, Ward), mortality, Place of discharge to. IVC filter insertion.

Follow up

Day 30 (± 7 days): All cause and PE related Mortality, Local readmission – Patient questionnaire: PEmb-QoL, EQ-5D-5L, Borg Scale
Day 90 (± 14 days): Mortality, Local readmission – Patient questionnaire: PEmb-QoL, EQ-5D-5L, Borg Scale
6 months (+/- 30 days): All cause and PE related Mortality – Patient questionnaire: PEmb-QoL, EQ-5D-5L, Borg Scale

Those undergoing CAVT will have the following additional data collected:

Procedural success and outcome. Procedural time, Access route, Aspiration device used, Separator used, Heparin given, including dose, Concurrent Lysis used, including dose. Thrombectomy time. Pulmonary arterial pressure at start, Pulmonary Arterial pressure at finish. Requiring further procedures, Length of stay, IVC filter insertion, readmission along with:
Day 1 – Observations, including Temperature, BP, Pulse, oxygen saturations and GCS, biochemistry including: WCC, RBC, CRP, GFR and BNP and Troponin (if available)
Day 2 (+ 2 days / - 1 days) – Observations, including Temperature, BP, Pulse, oxygen saturations and GCS (if available). Echocardiogram with LV/RV ratio
Day 3 – Observations, including Temperature, BP, Pulse, oxygen saturations and GCS, biochemistry including: WCC, RBC, CRP, GFR and BNP and Troponin (if available)
Day 5 – Observations, including Temperature, BP, Pulse, oxygen saturations and GCS, biochemistry including: WCC, RBC, CRP, GFR and BNP and Troponin (if available)

7.3 Collection of Data and Study Materials

- Dendrite database
- Patient questionnaire

7.4 Data Storage and Security

- All anonymous patient data will be stored on Dendrite maintained by the CI with oversight from the sponsor.
- The questionnaires will be send by the database Dendrite directly to the participants. Research nurses will call the participant in case of not completion.

7.5 Archiving, Preservation and Curation

Archiving will be authorised by the Sponsor following submission of the end of study declaration. Upon completion of the study, study documents will be archived for a minimum of 5 years as per the participating Trust's Research Archiving SOP. Once the archiving retention period has been reached, the Sponsor will liaise with the CI regarding destruction.

7.6 Data Sharing

Requests for data sharing can be made after publication of the primary results paper. Requests should be made to the Chief Investigator in the first instance. Requesters will be asked to complete an application form detailing specific requirements, rationale, and proposed usage. The CI and study sponsor (including the sponsor's Research Governance Manager (or deputy), the Information Governance Team, Calidcott Guardian, IM&T Security Officer and the researcher funder, as appropriate) will review all requests.

Consideration will be given to:

1. The viability and suitability of the request
2. Appropriate steps have been taken to minimise the risk of identifying participants
3. Data security policies and procedures of recipient organisation (including country if abroad) and other regulatory requirements are applicable
4. The credentials of the requestor

Where access to requested data is granted, requesters organisation must sign a data sharing agreement before they can access any data.

Subject to appropriate data sharing agreements, individual participant's data that underlie the results will be made available (after de-identification) on a controlled access basis. Requested data

will be made available, along with supporting documentation (e.g., data dictionary) on a secure server or through other secure data transfer method.

8 ETHICAL AND REGULATORY COMPLIANCE

8.1 ETHICS AND HRA APPROVAL

The Chief Investigator will obtained approval from the Health Research Authority (HRA) and Research Ethics Committee (REC). The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

8.2 INDEMNITY

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

8.3 SPONSOR

UHP will act as the main sponsor for this study assuming overall responsibility for the initiation and management of the trial. Delegated responsibilities maybe assigned to other relevant parties taking part in this study and appropriately documented.

8.4 FUNDING

Funding for the use of the Dendrite Database, institutional set up and data collection will be obtained from Penumbra Inc. Data will be collected at all centres by research nurses with appropriate funding. Statistics analysis will be performed the University of Plymouth Statistics team.

8.5 MONITORING

The study will be subject to monitoring by UHP under their remit as sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). All UHP studies will be initially monitored before Green Light being given. The subsequent level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited / inspected by regulatory bodies to ensure compliance with national regulations.

9 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Paul Jenkins.

10 PUBLICATION POLICY

Final results of the study will be disseminated via presentations at appropriate scientific meetings, and publication in appropriate peer-reviewed journals. Authorship will involve named individuals involved in study design and manuscript preparation according to the guidelines given by the ICMJE (International Committee of Medical Journal Editors).

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12 APPENDICIES

12.1 APPENDIX 1 – SCHEDULE OF EVENTS

For ALL Participants

Assessments	Visits				
	PERT referral	**Discharge**	**30 (± 7) days post op**	**90 (± 14) days post op**	**6 (± 1) months post op**
Informed consent	X				
Demographics	X				
Admission observations	X				
Biochemistry (WBC, RBC, CRP, GFR, BNP)	X				
PESI score	X				
CT findings	X				
RV/LV ratio	X				
Pulmonary arterial pressure	X				
PERT team assessment	X				
Further procedures		X			
Length of stay		X			
Mortality		X	X	X	X

Assessments	Visits				
	PERT referral	**Discharge**	**30 (± 7) days post op**	**90 (± 14) days post op**	**6 (± 1) months post op**
Readmission			X	X	
Questionnaires					
PEmb-QoL			X	X	X
ED-5D-5L			X	X	X
Borg Scale			X	X	X

Only for CAVT treatment

Assessments	Visits					
	PERT referral	Day 1 post op	Day 2 post op	Day 3 post op	Day 5 post op	Discharge
Procedure outcome	X					
Thrombectomy time	X					
Observations		X	X	X	X	
Temperature		X	X	X	X	
Blood Pressure		X	X	X	X	
Pulse		X	X	X	X	
Oxygen saturation		X	X	X	X	
Glasgow Coma Scale		X	X	X	X	
Biochemistry (WBC, RBC, CRP, GFR, BNP)		X		X	X	
Echocardiogram with LV/RV ratio			X			
Further procedures						X
Length of Stay						X
Mortality						X
Readmission						
Questionnaires						
PEmb-QoL						

Assessments	Visits					
	PERT referral	Day 1 post op	Day 2 post op	Day 3 post op	Day 5 post op	Discharge
ED-5D-5L						
Borg Scale						

12.2 APPENDIX 2 – AMENDMENT HISTORY

List details of all protocol amendments here whenever a new version of the protocol is produced.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of changes made

12.3 APPENDIX 3 – EXPECTED ADVERSE EVENTS

- anaemia
- emboli
- emergent surgery
- haematoma or haemorrhage at access site
- haemoptysis
- hypotension / hypertension
- infection
- ischemia
- pseudoaneurysm
- renal impairment or acute renal failure from contrast media
- residual thrombus due to inability to completely remove thrombus or control blood flow
- vessel spasm, thrombosis, dissection (intimal disruption), or perforation

12.4 APPENDIX 4 – EXPECTED SERIOUS ADVERSE EVENTS

- acute vessel occlusion
- air embolism
- allergic reaction and anaphylaxis from contrast media or device material
- arrhythmia
- arteriovenous fistula
- cardiac injury, cardiac perforation, cardiac tamponade
- cardio-respiratory arrest
- compartment syndrome
- death
- emboli
- foreign body embolization
- haemorrhage
- infarction leading to organ damage
- myocardial infarction
- neurological deficits including stroke
- pneumothorax
- valvular damage