TRIAL PROTOCOL

STOPping **A**nticoagulation for isolated or incidental subsegmental **P**ulmonary **E**mbolism

This protocol has regard for the HRA guidance and is compliant with SPIRIT

Version Number: 4.0

Version date: 28th June 2021

Protocol development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
01	12-Feb-2021	2.0	Non-substantial amendment	New sites added to the IRAS form. PI information added for existing sites. Sites that have declined to participate in the trial have been removed. Minor changes made to the protocol and trial summary that do not affect trial design or scientific value.
03	15-Apr-2021	3.0	Non-substantial amendment	Clarification to the operational procedure of uploading the patient's CTPA/CT thorax imaging to the online cloud based system following registration.
04	28-Jun-2021	4.0	Non-substantial amendment	Addition of "Equivocal for SSPE" as an outcome for the central radiology review. Analyses of outcome measures will also be based on modified intention to treat. New sites added to the IRAS form.

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trial design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical 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.

This protocol has been approved by:

Trial Name:	STOP-APE
Protocol Version Number: Protocol Version Date:	Version: 4.0 28 / June / 2021
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Trial Role:	Chief Investigator
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Sponsor statement:

By signing the IRAS form for this trial, University of Birmingham, acting as Sponsor of this trial confirms approval of this protocol.

Compliance statement:

This protocol describes the STOP-APE trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the STOP-APE trial.

The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive and laid down in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

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The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

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 clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	STOP-APE
Protocol Version Number:	Version: 4.0
Protocol Version Date:	28 / June / 2021
PI Name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

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Trial social media	https://twitter.com/StopapeTrial

ABBREVIATIONS

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
ACCP	American College of Chest Physicians
AE	Adverse Event
AMU	Acute Medical Unit
APR	Annual Progress Report
AR	Adverse Reaction
BCTU	Birmingham Clinical Trials Unit
BNP	Brain Natriuretic Peptide
BTS	British Thoracic Society
CI	Chief Investigator
CIAC	Central Blinded Independent Adjudication Committee
CRF	Case Report Form
CRN	Clinical Research Network
CRNMB	Clinically Relevant Non-major Bleeding
CRO	Contract Research Organisation
CT	Computed Tomography
CTIMP	Clinical Trial of Investigational Medicinal Product
CTPA	Computed Tomography Pulmonary Angiogram
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DOAC	Direct Oral Anticoagulant
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
eGFR	Estimated Glomerular Filtration rate
GCP	Good Clinical Practice
GP	General Practitioner
Hb	Haemoglobin
HCP	Health Care Professionals

HES	Hospital Episode Statistics
HRA	Health Research Authority
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISSPE	Isolated Subsegmental Pulmonary Embolism
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
LMWH	Low Molecular Weight Heparin
MR	Magnetic Resonance
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR HTA	National Institute for Health Research Health Technology Assessment
NT-proBNP	N-terminal pro B Type Natriuretic Peptide
PACS	Picture Archiving and Communication System
PE	Pulmonary Embolism
PESI	Pulmonary Embolism Severity Index
PI	Principal Investigator
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
RBA	Role Based Access
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
RGT	Research Governance Team
RSI	Reference Safety Information
RUSAE	Related and Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics

SSPE	Subsegmental Pulmonary Embolism
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
V/Q	Ventilation/Perfusion
VTE	Venous Thromboembolism

DEFINITIONS

Term	Description
Computed Tomography Pulmonary Angiogram (CTPA)	A medical diagnostic test that employs computed tomography to obtain an image of the pulmonary arteries.
Subsegmental Pulmonary Embolism (SSPE)	A symptomatic or incidental pulmonary embolism (single or multiple) occurring in a subsegmental pulmonary arterial branch but no larger order of vessels.
Isolated SSPE (ISSPE)	An SSPE with the absence of proximal deep vein thrombosis (DVT).
Venous thromboembolism (VTE)	A thrombus that has formed within the venous system in a limb and or the pulmonary circulation.
Major bleeding	A fatal bleeding, and/or Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in haemoglobin level of 20g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.
Clinically relevant non-major bleeding (CRNMB)	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: i. requiring medical intervention by a healthcare professional ii. leading to hospitalisation or increased level of care iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

	ISTH major bleeding in non-surgical patients is defined as having a symptomatic presentation and: iv. Fatal bleeding, and/or v. Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or vi. Bleeding causing a fall in haemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more or leading to transfusion of two or more units of whole blood or red cells.
Net clinical benefit	Composite of recurrent VTE and clinically relevant bleeding events.
Active cancer	Cancer diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrolment or during 6 months before randomisation, or recurrent locally advanced or metastatic cancer.
Withholding	In relation to this trial withholding is defined as stopping the current treatment strategy of anticoagulation for at least 3 months.

TRIAL SUMMARY

Title:
STOPping Anticoagulation for isolated or incidental subsegmental Pulmonary Embolism (STOP-APE)

Primary objective:
To determine if withholding anticoagulation is non-inferior to standard anticoagulation therapy in the treatment of isolated subsegmental pulmonary embolism (ISSPE) for preventing recurrent venous thromboembolism (VTE), or death related VTE, or superior for clinically relevant bleeding over 3 months, compared with at least 3 months of full anticoagulation.

Secondary objectives:
- Determine whether withholding anticoagulation for isolated subsegmental PE reduces harm (recurrent VTE, bleeding events) compared with at least 3 months of full anticoagulation at 6 and 12 months and impact on diagnoses of pulmonary hypertension at 12 months.
- Determine the reclassification rate of SSPE diagnoses made by acute reporting radiologists when reviewed by thoracic radiologists and formulate a set of rules to improve acute reporting radiologists' diagnoses of SSPE.
- Determine whether any radiological parameters correlate with clinical presentations or outcomes.

Economic Aims and Objectives
- Healthcare resource use: hospitalisations, bed days, unscheduled primary and secondary care visits for recurrent VTE, clinically relevant bleeding or potentially related symptoms.
- Healthcare costs.
- Health-related quality of life (EQ-5D-5L at baseline, 12 and 24 weeks).
- Cost-utility at 24 weeks (cost per QALY) and cost-effectiveness at 52 weeks (cost per VTE avoided).

Mechanistic (behavioural) Aims and Objectives
- To determine whether not treating SSPE is acceptable to patients and clinicians.
- To determine the health seeking behaviours and health utilisation of a no anticoagulation treatment strategy for isolated SSPE.

Trial Design:
An investigator led, multicentre, prospective, randomised controlled, open-label, pragmatic clinical trial designed to test both the non-inferiority and superiority objectives. A 12-month internal pilot will assess feasibility and acceptability with safety of randomisation based on acute reporting radiologists' diagnoses assessed as part of a nested computed tomography pulmonary angiogram (CTPA) study.

Participant Population and Sample Size:
1466 consenting adult patients with ISSPE diagnosed on computed tomography pulmonary angiogram (CTPA) or computed tomography (CT) thorax with intravenous (IV) contrast.

Setting:
There will be approximately 50 trial sites from secondary care clinical settings of emergency departments, ambulatory care and acute medical units within NHS hospitals in the UK.

Eligibility Criteria:

Inclusion

- Age ≥18 years
- SSPE diagnosed by the radiologist at the trial site by CTPA or CT thorax with IV contrast
- No evidence of proximal deep vein thrombosis based on lower limb ultrasonography or CT / MR venography
- Heart rate (<110bpm)
- Systolic blood pressure (≥100 mmHg)
- Oxygen saturation (≥90%)
- Written signed informed consent to the trial

Exclusion

- Indication for hospital admission
- >7 days empirical anticoagulation treatment immediately prior to randomisation
- <28 days since first symptoms of proven or clinically suspected COVID-19
- Known stage 5 chronic kidney disease
- Patients with active cancer defined as cancer diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrolment or during 6 months before randomisation, or recurrent locally advanced or metastatic cancer
- Patients with previous unprovoked PE, thrombophilia or requiring long term anticoagulation for another reason
- Patients with a DVT / thrombus of an unusual site (e.g. upper limbs, associated with a line) that requires anticoagulation
- Patients with active bleeding
- Any condition which, in the opinion of the investigator, makes the participant unsuitable for trial entry due to prognosis/terminal illness with a projected survival of less than 3 months
- Pregnancy confirmed by positive pregnancy test or post-partum period or actively trying to conceive
- Inability to comply with the trial schedule and follow-up
- Participation in a CTIMP study

Intervention arm
Withholding anticoagulation for ISSPE for at least 3 months.

Control arm
Full dose anticoagulant treatment as standard care for at least 3 months.

Outcome Measures:

Primary Outcome
The joint (multiple) primary outcomes are a composite of;
Recurrent VTE

- recurrent VTE (non-fatal)
- VTE related death (primary safety outcome)

Clinically relevant bleeding

- composite of major and clinically relevant non-major bleeding (CRNMB) (primary efficacy outcome).

Secondary Outcomes

- Recurrent VTE at 6 and 12 months.
- Clinically relevant bleeding at 6 months and 12 months (as assessed through HES records).
- Net clinical benefit - composite of clinically relevant bleeding and recurrent VTE at 3 and 6 months.
- New diagnosis of pulmonary hypertension or right ventricular dysfunction within 12 months of SSPE, defined from HES clinical coding and supported where possible by additional radiological data and echocardiograms undertaken in tertiary pulmonary hypertension centres.
- All-cause mortality at 3, 6 and 12 months.
- VTE related mortality at 3, 6 and 12 months.
- Cardiovascular mortality at 3, 6 and 12 months defined as cardiac deaths (e.g., cardiogenic shock, fatal arrhythmia, cardiac rupture) and vascular deaths (e.g., VTE-related, fatal stroke, ruptured aortic aneurysm, aortic dissection).
- Reclassification rate from thoracic radiologist review.

TRIAL SCHEMA

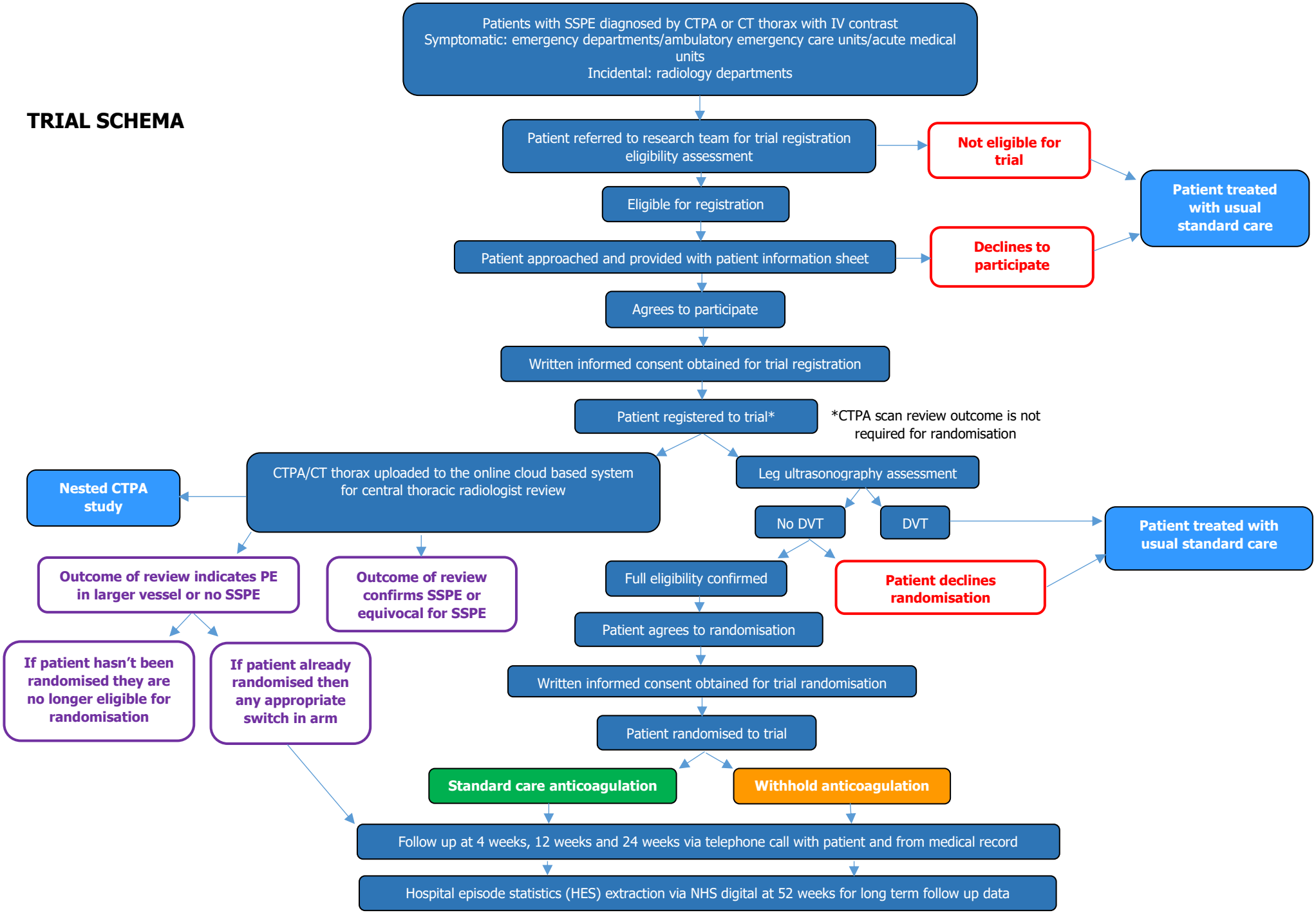


TABLE OF CONTENTS

Table Contents:

1. BACKGROUND AND RATIONALE

1.1. Background

Pulmonary embolism (PE) is a potentially serious condition, whereby blood clots cause a blockage of the blood supply to the lungs. PEs are often caused by blood clots in the legs and occasionally the arms (deep vein thrombosis (DVT)) breaking off and travelling to the lungs. A number of risk factors increase the chances of developing PE and/or DVT, including cancer, major surgery, pregnancy, some medications (e.g. the combined oral contraceptive pill or hormone replacement therapy), dehydration, long-distance travel and prolonged immobility. The symptoms of a PE depend on the size and location of the blood clot. A large PE can cause symptoms of breathlessness and chest pain, and the diagnosis is made using blood tests and a scan of the lungs. The treatment of PE includes anticoagulant medication ("blood thinners") that are taken over months and include: warfarin, an injectable form of heparin and direct oral anticoagulants (DOACs). These medications work by preventing new clots from forming whilst the body's own mechanisms break down the clots.

Acute pulmonary embolism (PE) is associated with significant mortality and morbidity and has a wide range of clinical severity from sudden death or haemodynamic instability through to no symptoms. The increased use and improving sensitivity of computed tomography (CT) imaging has resulted in a large increase in identification of both subsegmental PE (SSPE; embolism confined to subsegmental pulmonary vasculature) as well as incidental PE (when the CT was performed for indications other than identification of venous thromboembolism (VTE)).

To date, there have been no randomised trials to assess how subsegmental emboli should be managed, and current guidelines are based on non-randomised studies and clinical consensus. Anticoagulation of these patients may reduce short or longer term thromboembolic risk but this must be balanced against the potential increased risk of major and potentially life threatening bleeding which can occur with anticoagulant therapy.

There is growing equipoise over the value of treating small pulmonary emboli which are confined to subsegmental arteries when they are isolated, i.e. in the absence of a co-existing DVT (4). With the introduction of CT pulmonary angiography (CTPA), substantially more PEs are being diagnosed but with a fall in case fatality, suggesting over-diagnosis. Furthermore, the complication rates from anticoagulation treatment have risen by 80%, suggesting over-treatment (5). CTPA imaging diagnoses more, and smaller PEs than traditional ventilation/perfusion (V/Q) scanning.

In a trial comparing these two scanning strategies, there was no excess of recurrent VTEs during follow-up of patients whose initial V/Q scan was negative (6). A meta-analysis of uncontrolled observational studies of treating or withholding treatment in SSPE reported no clinically important difference between pooled incidences of recurrent VTE between treatment strategies (3). More recent observational data of routine care for SSPE showed very high complication rates of anticoagulation but in patients where treatment was withheld, this proved to be a safe strategy in terms of recurrent VTE (7). An international survey of clinicians using clinical vignettes found up to 30% would not treat an isolated SSPE (8). Yet there have been no clinical trials to clarify the benefits and harms of treating isolated SSPE.

Current UK guidelines for PE management from NICE (2015) (9) and from the British Thoracic Society (BTS) (10) recommend CTPA to confirm the diagnosis of PE; 9 studies in 648 patients showed sensitivity 80-100% and specificity 78-100%. This has informed the choice to use CTPA as our imaging modality to confirm subsegmental PE. However, there are concerns that over-diagnosis of SSPE may be due to incorrect interpretation of small artefacts, with some case series showing that 10% of diagnoses made by general radiologists are not supported by review from specialist respiratory radiologists (11). This trial offers the first opportunity to determine the accuracy of general radiology reporting of SSPE at sufficient scale, and clarify diagnostic criteria.

Anticoagulation is the recommended treatment in NICE guidance, initially with low molecular weight heparin (LMWH), changing to a vitamin K antagonist such as warfarin or a direct oral anticoagulant (DOAC) for 3 months thereafter (9, 12). The BTS guideline specifically considered risk stratification for outpatient management and looked at a variety of risk scores (10), concluding that the pulmonary embolism severity index (PESI) is the most well validated; no patients in low or very low risk categories had recurrent VTE at 90 days (13). This has informed our choice of PESI as a way of determining stability.

The only current guidance on the optimal treatment for patients with SSPE comes from the American College of Chest Physicians (ACCP) Antithrombotic therapy for VTE, which recommends those with a low risk of recurrent VTE and no concurrent DVT to have clinical surveillance over anticoagulation (16). However, this was based on consensus opinion rather than trial evidence.

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, has implications for a trial that tests different management strategies in SSPE. VTE is a common complication of COVID-19, in both acute and convalescent phases (31). Whist the data cited above are from patients prior to the existence of COVID-19, the issue of anticoagulating SSPE in an ambulatory convalescent phase of COVID-19 for patients who have not required hospital admission requires consideration on the same terms as other temporary causes of a pro-thrombotic state where there is minimal physiological impact.

Therefore, a rigorous, well-conceived and pragmatic randomised trial would be the first study to adequately address the clinical and cost-effectiveness of withholding anticoagulation in isolated SSPE compared with the usual care of full anticoagulation.

1.2. Trial Rationale

Hospital admissions for PE rose by 30% in the period 2008-2012. No individual risk factor, symptom, or clinical sign can definitively diagnose or exclude PE and therefore evaluation for PE often includes clinical decision rules, laboratory tests, and several imaging modalities. The availability of these tests, in particular the advent of CTPA, has markedly increased rates of PE diagnosis but without an increase in mortality from PE (17). In particular, with increased testing rates for PE and sensitivity of CTPA, the diagnosis of SSPE and incidental PE has increased (17). This means that understanding the utility of correctly diagnosing and treating this patient group is vital if we are to avoid over-diagnosis and excess side effects from over-treatment.

1.2.1. Justification for participant population

Patients with SSPE who are at low risk for recurrent VTE and do not require hospitalisation are those in whom there is equipoise about treatment with anticoagulation. Suitability of

out-patient management is assessed physiologically by heart rate, blood pressure and oxygen saturation. A low recurrence risk for recurrent VTE is assessed by the absence of concomitant proximal deep vein thrombosis, active malignancy (defined below), pregnancy, thrombophilia and advanced renal failure.

Cohort studies show a higher rate of larger vessel PE than SSPE among patients with actively treated cancer (19) and the overall incidence of incidental PE in this cohort may be lower than previously suspected (20). Cancer is not a single condition and certain cancers are associated with high rates of VTE recurrence (21). Given that active treatment (chemotherapy and surgery) is the major driver of VTE risks, there is no equipoise in these groups and so we will exclude patients with active treatment in progress or planned. However there is equipoise for patients who are not undergoing active treatment or have treatment planned, and therefore these patients are eligible for recruitment. In keeping with the CARAVAGGIO trial (30) we defined active cancer as cancer that had been diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrolment or during 6 months before randomisation, or recurrent locally advanced or metastatic cancer.

For patients with confirmed COVID-19, data from the International Severe Acute Respiratory Infections Consortium (ISARIC) show that deterioration requiring hospital admission occurs at a mean of 14.6 days after symptom onset with a standard deviation of 8 days (32). In order to recruit patients who have most likely passed a phase of acute deterioration, we will recruit patients who are diagnosed with SSPE at least 28 days after symptom onset.

1.2.2. Justification for design

Randomised controlled trials are considered the "gold standard" for evidence-based medicine. As the intervention arm will involve withholding treatment the patient and research team are unable to be blinded from the treatment allocation. In order to minimise bias from an open label trial we will have a blinded end point committee to adjudicate outcomes.

A nested study of all CTPAs will be performed, comparing the SSPE diagnosis made by the acute reporting radiologists with specialist thoracic radiologists. This will allow us to determine safety in the pilot study (patients with larger than subsegmental clots are rapidly identified), appropriate powering and sample size (e.g. patients with breathing artefact may be recruited instead of true SSPE) and develop guidance for SSPE diagnosis in routine clinical practice. See section 3.3.1 for further details on this.

1.2.3. Choice of intervention

This trial is testing how a strategy of withholding anticoagulation in ISSPE (either symptomatic or incidental) for at least 3 months compares to standard care which is full anticoagulation for at least 3 months. We have not specified the choice of anticoagulation as there are contra-indications for directly acting oral anticoagulants (DOACs) such as renal impairment where warfarin would be an acceptable alternative. In some patients, low molecular weight heparin (LMWH) injected subcutaneously would also be appropriate. By not specifying the drug class of anticoagulation, we are testing the strategy of full anticoagulation against the strategy of no anticoagulation in the most generalisable and pragmatic way.

1.2.4. Process Evaluation

A process evaluation will be carried out to evaluate (1) the acceptability of the intervention (delivered during the internal pilot, see pilot objectives in the next section), (2) programme reach.

2. AIMS AND OBJECTIVES

2.1. Pilot Stage Objectives

The internal pilot will be conducted during the first 12 months of recruitment and has the following objectives:

1. To assess recruitment rates, the nature of exclusions and patients who decline.
2. To assess acceptability of the study to patients and clinicians and early identification of recruitment barriers.
3. To assess safety with respect to SSPE diagnosis (see 3.3.1 Nested CTPA Study).
4. To refine recruitment target based on misclassification rates.

Table 1: RAG rating for internal pilot

	% of patients declining no treatment	Patients recruited per site
Red	≥70%	< 0.5 per month
Amber	30-69%	0.5 – 1.5 per month
Green	<30%	≥1.5 per month

We have taken guidance from a Medical Research Council Hubs for Trials Methodology Research workshop into account when determining stop/go criteria and will report our pilot results according to their suggestions (27). Areas considered by the workshop as suitable progression criteria included recruitment rate, protocol adherence and outcome rate. As described in Table 1, the traffic light system of green (go), amber (amend) and red (stop) was deemed preferable to a simple stop/go approach when specifying progression criteria for internal pilot studies, and they suggested recruitment progression criteria should be based on rates per centre per unit time that can be extrapolated, rather than specifying an absolute number by a specific date.

Our first major progression criterion is the proportion of otherwise eligible patients excluded due to declining no treatment (green=<30%, amber= 30-69%, red= ≥70%). Our second criterion is recruitment rate. If sites, overall, recruit 1.5 patients per month on average, and each site has a target of 30 patients each site will complete recruitment in 20 months; this represents green as recruitment would complete by 32 months, assuming a linear rate of site opening. If overall recruitment was 1 patient/site/month we would approach more sites to open, and if there were <0.5 patients/site/month this represents red (stop). We will collect safety data about VTE outcomes at 4 weeks after randomisation. The DMC will review safety data with respect to SSPE diagnosis (see 3.3.1 Nested CTPA Study) and recurrent VTE and recommend whether the trial should progress or not.

2.2. Main Trial Objectives

2.2.1. Clinical Aims and Objectives

2.2.1.1. Primary Objective

To determine if withholding anticoagulation is non-inferior to standard anticoagulation therapy in the treatment of ISSPE for preventing recurrent VTE, or death related VTE, or superior for clinically relevant bleeding over 3 months, compared with at least 3 months of full anticoagulation.

2.2.1.2. Secondary Objectives

- Determine whether withholding anticoagulation for isolated subsegmental PE reduces harm (recurrent VTE, bleeding events) compared with at least 3 months of full anticoagulation at 6 and 12 months and impact on diagnoses of pulmonary hypertension at 12 months.
- Determine the reclassification rate of SSPE diagnoses made by acute reporting radiologists when reviewed by thoracic radiologists and formulate a set of rules to improve acute reporting radiologists' diagnoses of SSPE.
- Determine whether any radiological parameters correlate with clinical presentations or outcomes.

2.2.2. Economic Aims and Objectives

An economic evaluation will be undertaken to assess the cost-effectiveness of no treatment versus full dose anticoagulation in patients with ISSPE. The base-case evaluation will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY) over a 24 week follow up and a cost-effectiveness analysis to estimate cost per VTE avoided over 52 weeks using routine data sources. Both analyses will be from a health services perspective. Additional analysis, using decision modelling, will explore the cost-utility and cost-effectiveness of a pragmatic treatment policy (without expert thoracic radiological review) over a 52 week time horizon.

2.2.3. Mechanistic (behavioural) Aims and Objectives

1. To determine whether not treating SSPE is acceptable to patients and clinicians.
2. To determine the health seeking behaviours and health utilisation of a no anticoagulation treatment strategy for isolated SSPE.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

STOP-APE is an investigator led, multicentre, prospective, randomised controlled, open-label, pragmatic clinical trial with central, blinded, independent adjudication committee (CIAC) endpoint assessment over 3 months for efficacy of withholding anticoagulation for ISSPE. The trial is designed to test the superiority for bleeding events and non-inferiority for recurrent VTE.

Participants will be randomised to either the control arm: full dose anticoagulant treatment as standard care, or the intervention arm: withholding anticoagulation. The choice of anticoagulant will be determined by the responsible treating clinician as part of the standard of care. Pre-randomisation empirical anticoagulation treatment will be allowed for up to 7 days immediately prior to randomisation.

The joint (multiple) primary outcomes of recurrent VTE and clinically relevant bleeding will be established from the trial site clinical notes and electronic health records, patient trial follow-ups and centralised data from hospital episode statistics (HES). The local research team will conduct a safety telephone follow up at 4 weeks, with a permitted window of 1 week either side. Trial follow-ups at 12 and 24 weeks will be performed by the local research team via telephone to complete case report forms and questionnaires. A window of ± 2 weeks will be permitted for follow-ups.

A 12-month internal pilot will assess feasibility and acceptability with safety of randomisation based on acute reporting radiologists' diagnoses, assessed as part of a nested CTPA study. Note: The nested CTPA study will not stop after the 12-month internal pilot phase and so will be conducted for the full duration of the trial.

3.2. Trial Setting

Participants will be recruited from approximately 50 trial sites from secondary care clinical settings of emergency departments, ambulatory care and acute medical units within NHS hospitals in the UK. The recruitment rates will be assessed during the pilot phase and additional sites will be recruited if required (see section 2.1).

3.3. Identification of participants

Patients aged 18 years or over with ISSPE will be enrolled into the STOP-APE trial. Potential trial participants will be identified from participating centres, in the UK, by members of their normal clinical team via the following two routes:

1. Adult patients presenting at secondary care clinical settings of emergency departments, ambulatory care units and acute medical units with acute symptomatic SSPE diagnosed with CT pulmonary angiogram/CT thorax with IV contrast.

2. Radiology departments who can flag patients to the research team where they identify SSPE as an incidental diagnosis on a contrast enhanced scan undertaken as part of surveillance after any active treatment for cancer.

In order to retain the pragmatic nature of the trial and to ensure generalisability of results, detailed diagnostic criteria for SSPE will not be issued to general radiology departments. However, an audit of CTPA reports showed that in 15% of PE reports, the arterial distribution is not specified (a binary report is given of 'positive for PE'). Therefore, simple guidance will be issued to radiology departments to specify arterial distribution of PE as either sub-segmental (in which case patients can be considered for potential inclusion in the trial), or at least segmental in size (in which case patients do not meet recruitment criteria).

Patients identified via either of the above routes will be referred to the research team for confirmation of full eligibility. It is the responsibility of the PI or suitably qualified delegate in accordance with local practice as identified on the Site Signature and Delegation Log to confirm eligibility.

3.3.1. Nested Computed Tomography Pulmonary Angiogram (CTPA) study

We will conduct a nested study of CTPAs within this trial for four purposes:

1. Safety assessment during Internal Pilot

SSPE is diagnosed at acute presentation by radiologists with a spectrum of expertise in thoracic imaging. There have been no studies on the accuracy of acute reporting radiologists' interpretation of CTPA scans for SSPE compared with thoracic radiologists using a standard reporting checklist. Disagreement could arise because

a. artefact (e.g. from breathing) may be misinterpreted as a filling defect due to PE leading to a false positive diagnosis of SSPE.

b. because PE is present but is in fact affecting larger vessels (e.g. segmental or lobar) in which case patients should be given full anticoagulation.

The greater risk to patients is where larger vessel PE is misclassified as SSPE as these patients will have a 50% chance of receiving no anticoagulation in this trial and it is therefore crucial that this potential misclassification is detected as soon as possible. After recruitment and randomisation into the trial which is based on the acute reporting radiologist's diagnosis of SSPE, the CTPA will be subject to an initial safety check within 48 hours by a trial thoracic radiologist using a structured reporting template. This will continue for the entire duration of the study.

We have not opted to have expert review of the CTPA scan prior to randomisation in order to deliver the trial within a pragmatic framework of acute clinical care, minimising barriers to recruitment and also yielding important information about the impact of applying trial results with general acute reporting radiologists determining the presence of SSPE. The design of recruitment prior to expert review balances the minimisation of barriers to recruitment with rapid detection of low prevalence misclassification through early discontinuation of an inappropriate treatment arm but continuation in the trial.

Protocol for review of CTPA

i. Reporting guidance

We will issue simple guidance for radiology departments at recruiting sites to specify arterial distribution of PE as either sub-segmental (in which case patients can be considered for potential inclusion in the trial), or at least segmental in size (in which case patients do not meet recruitment criteria).

ii. Mechanism of CTPA retrieval

Each patient that is initially registered in the trial (consented prior to ultrasonography of the legs) will have their CTPA tagged with a study identifier and then uploaded to an online cloud based system which will be remotely accessed by trial thoracic radiologists. A database will be set up within the Bath Hospital Radiology department to receive the CTPA scans from the online cloud based system for long term storage.

iii. Reading of CTPA images and communication to trial sites

The online cloud based system will be used for image presentation to trial radiologist reviewers. They will log on through a secure portal and rate the scans using a standard case report form which will include the largest order of arterial vessel containing a filling defect, an assessment of clot burden, if artefact is present mimicking the presence of SSPE, pulmonary artery size, right sided cardiac dimensions and parenchymal lung changes. Each CTPA will be reviewed by two thoracic radiologists who will come to a consensus decision.

In the unlikely event that segmental vessels or larger contain filling defect (as detected by either reviewer), then this will be communicated immediately to a central clinical coordinator who will then immediately contact the patient to make them aware that they need to attend hospital immediately, in addition to the local research team (or on call acute medical team at the weekend) who will make an assessment with regards to treatment with anticoagulation as part of standard of care (as this is a prospective randomised open blinded end-point study design, the prescribing of anticoagulation will be in the hospital discharge summary).

For patients found not to have SSPE on review of their CTPA this will be fed back to their clinical treating team who will make an assessment with regards to treatment as part of standard of care. Patients will continue in the trial and be followed up as per the trial protocol.

Patients found to have confirmed SSPE or "equivocal for SSPE" on review of their CTPA will continue on the treatment arm allocated to them at randomisation, and will be followed up as per the trial protocol.

The data to be collected and stored in the online cloud based system from CTPAs by each trial radiologist are as follows:

1. Breathing artefact (categorised into 4 levels)
2. Thrombus distribution, burden and location (if thrombus is present)
3. At thrombus level - size of upstream/downstream vessel, contrast density, signs of artefact.
4. CT quality

5. Protocol variations, dose and technique across sites
6. Cardiac calcifications (Aortic Valve, Mitral Valve, coronary arteries)
7. Size of Pulmonary Artery, Right Atrium, Right Ventricle, Left Atrium, Left Ventricle, (including ratio or right ventricle / left ventricle) and Aorta.
8. Grading of an emphysema present using a standardised system
9. Changes consistent with COVID-19 infection
10. Incidental findings

2. Reclassification rate from thoracic radiologist review

After 500 CTPA scans, we will determine the agreement between thoracic radiologist review and initial acute reporting radiologist's diagnosis. Where two thoracic radiologists disagree about the presence of SSPE, a third review will be used to achieve consensus. At this stage, we will determine if, in spite of adequate recruitment to the trial based on our initial powering, we may need to increase the recruitment target due to reclassification of patients and a reduction in the number of 'true SSPE' scans. We will maintain power in the trial for the non-inferiority outcome by applying our recruitment target to the numbers of patients with true SSPE. The DMC will advise on changes to total recruitment based on an interim analysis. If recruitment is green, and rate of site initiation is linear, we will increase the number of sites in order to increase recruitment target to a rate feasible as determined by the DMC and TSC.

3. Determine a set of diagnostic criteria for SSPE

At the end of the trial, pragmatic guidelines will be drawn up through consensus meetings of the thoracic radiologists reporting the trial CTPAs. These can then be utilised in subsequent radiological reporting practice to improve diagnosis of SSPE in routine emergency care as well as in future research studies where SSPE are reported.

4. Future artificial intelligence studies

The trial database will be used for automated image analysis and artificial intelligence (AI) studies (not charged to this grant). Potential applications of the CTPA images with clinical correlation are to investigate risk of recurrent VTE in patients without anticoagulation, to train automated algorithms to diagnose SSPE and to act as clinical decision support so that larger vessel PE is not mis-classified as SSPE.

3.3.2. Process evaluation (qualitative research)

Acceptability of the intervention: Our proposed research adopts a mixed methods approach, recommended when concepts examined are broad and complex, with some facets best explored using a deductive approach, and others an interpretive approach (1). We believe our work meets this definition as we are assessing the impact of not anticoagulating (deductive work in the trial), whilst recognising that the patients' psychology around their own attitude to risk, medication and the disease (understood by interpretive work) will impact on outcomes relevant to the health service, namely how this intervention will be taken up in practice after the trial.

We will conduct interviews with up to 30 patients and 30 healthcare professionals to allow for data saturation. Face-to-face, telephone or Skype interviews either in the participant's home or the clinical site will be used to accommodate participant preference and convenience. Interviewing will be concentrated on the first year of the study in order to

inform optimal recruitment and information presentation to potentially eligible patients. We will also ask permission to recruit patients for interview who declined to be randomised in the study after an initial discussion.

Within our sample we will aim for maximum variation to include the range of characteristics of eligible participants (e.g. site, symptomatic/incidental/COVID-19 patients). The topic guide will be informed by existing literature on reporting of (24), attitudes to (8) and outcomes from, incidental diagnoses (25). We will explore attitudes and practical issues surrounding patient understanding of PE and its management, tolerance of risk by patients and health care professionals (HCPs) particularly in relation to COVID-19, preferences for content and delivery of information and any potential concerns. We will seek to include primary care physicians in our mainly hospitalist sample of HCPs. If having a PE and knowingly not being treated (which will be the 'real life' situation if the trial achieves its primary outcome and changes clinical guidelines) changes how one responds to transient symptoms (e.g. leg or chest pain) then a potential outcome beyond the trial may be excess scans and emergency presentations in the untreated group. The psychology around this and the 'harm' of repeated diagnostic imaging in this context will therefore be important to assess. Interviews will be audio recorded and transcribed verbatim, prior to qualitative analysis using the framework method, as described in previous work (26). This is a systematic approach well suited to interdisciplinary health research and to working with clinical and lay collaborators which will facilitate comparison of and similarities and differences between patient and HCP views in a timely manner to inform the ongoing recruitment process (26).

Programme reach: Sites will be asked to collect data on the number of exclusions due to each of our specified exclusion factors, and the number of patients who are felt suitable but decline participation, and if so why.

3.4. Assessment of Risk

All clinical trials can be considered to involve an element of risk and, in accordance with BCTU operating procedures this trial has been risk assessed, to clarify any risks relating uniquely to this trial. This risk assessment concluded:

- Type A = Comparable to the risk of standard medical care.

4. ELIGIBILITY

4.1. Inclusion Criteria

- Age ≥18 years
- SSPE diagnosed by the radiologist at the trial site by CTPA or CT thorax with IV contrast
- No evidence of proximal deep vein thrombosis based on lower limb ultrasonography or CT / MR venography
- Heart rate (<110bpm)
- Systolic blood pressure (≥100 mmHg)
- Oxygen saturation (≥90%)
- Written, signed informed consent to the trial

4.2. Exclusion Criteria

- Indication for hospital admission
- <28 days since first symptoms of proven or clinically suspected COVID-19
- >7 days empirical anticoagulation treatment immediately prior to randomisation
- Known stage 5 chronic kidney disease
- Patients with active cancer defined as cancer diagnosed within the past 6 months, cancer for which anticancer treatment was being given at the time of enrolment or during 6 months before randomisation, or recurrent locally advanced or metastatic cancer
- Patients with previous unprovoked PE, thrombophilia or requiring long term anticoagulation for another reason
- Patients with a DVT / thrombus of an unusual site (e.g. upper limbs, associated with a line) that requires anticoagulation
- Patients with active bleeding
- Any condition which, in the opinion of the investigator, makes the participant unsuitable for trial entry due to prognosis/terminal illness with a projected survival of less than 3 months
- Pregnancy confirmed by positive pregnancy test or post-partum period or actively trying to conceive
- Inability to comply with the trial schedule and follow-up
- Participation in a CTIMP study

4.3. Co-enrolment

Patients cannot participate in a CTIMP study. Participation in other non-CTIMP studies is allowed.

5. CONSENT

5.1. Health Care Professional Consent

Consent for relevant health care professionals to participate in qualitative interviews for the process evaluation study will be obtained using the STOP-APE Health Care Professional Interview Study Consent Form. Research nurses or the qualitative researcher will obtain written consent from all staff prior to their interview.

5.2. Patient Consent

It will be the responsibility of the PI or suitably qualified delegate in accordance with local practice as identified on the Site Signature and Delegation Log to obtain written informed consent for each participant prior to performing any trial related procedure.

Consent will be a two-stage process for the STOP-APE trial. The first stage consent to registration will involve obtaining consent for patients with SSPE diagnosed via CTPA or CT thorax with IV contrast to have lower limb ultrasonography as part of the eligibility assessment and for their CTPA or CT thorax imaging to be uploaded to the online cloud based system for central thoracic radiologist review. Additionally if the patient is female and pre-menopausal consent will be obtained to perform a pregnancy test. Optional consent will also be sought for participation in qualitative interviews and transfer of the imaging to Royal United Hospitals Bath NHS Foundation Trust for long term storage for future research. This will be formally documented using the registration Informed Consent Form (ICF). If eligibility is confirmed at the second stage, consent will be sought to participate in the main trial. This will be formally documented using the main trial ICF.

A single Participant Information Sheet (PIS) will be provided to facilitate this process. Investigators or delegate(s) will ensure that they adequately explain the aim, trial intervention, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given adequate time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before signing and dating the latest version on the Consent Form. If the participant expresses an interest in participating in the trial they will be asked to sign and date the latest version of the ICF. The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is registered into the trial, the participant's registration number will be entered on the registration ICF maintained in the ISF. If the participant is subsequently randomised the participant's randomisation number will be entered on to the main trial ICF maintained in the ICF. In addition, if the participant has given explicit consent, a copy of the signed registration and main trial ICFs will be sent to the Birmingham Clinical Trials Unit (BCTU) Trial Office for review. If a suitable secure

electronic consent system is introduced by BCTU in the future then this can be used as an alternative to obtaining written consent in person.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of registration and main trial ICFs signed and date each respective consent was received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each telephone contact conducted by the local research team, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICFs will be available from the Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all participants approached about the trial will be recorded on a **STOP-APE Participant Screening Log** and with the participant's prior consent their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. ENROLMENT AND RANDOMISATION

6.1. Screening

The research team will screen the patient for eligibility and record information on the **STOP-APE Participant Screening Log** accordingly, this will be kept in the ISF and should be available to be sent to the Trials Office upon request. The following assessments form part of screening in order to confirm the patient's eligibility for trial registration:

- CTPA or CT thorax with IV contrast confirming the presence of a subsegmental pulmonary embolism, without the presence of PE in the segmental, lobar or main pulmonary arteries.
- Medical history
- Physical examination
- Blood pressure, oxygen saturation, heart rate

The following procedures should be performed as part of screening in order to confirm the patient's eligibility for randomisation:

- Venous ultrasound of both proximal legs using compression ultrasonography from the sapheno-femoral junction to the popliteal fossa sampling at three points. If CT/MR venography has already been performed including both proximal legs ultrasonography is not required.

    - In the event of clinically suspected upper limb DVT or line associated thrombus appropriate imaging including lower limb ultrasonography to exclude DVT
- Pregnancy test in pre-menopausal women.

The PI will electronically sign the **Registration and Randomisation Forms** to document the eligibility assessment.. All information on the randomisation form is required to randomise the patient.

Details of the trial enrolment will be recorded in the participant's medical notes/electronic patient record. This will include confirmation of eligibility, name of the individual that confirmed eligibility and the date of registration and randomisation into the trial.

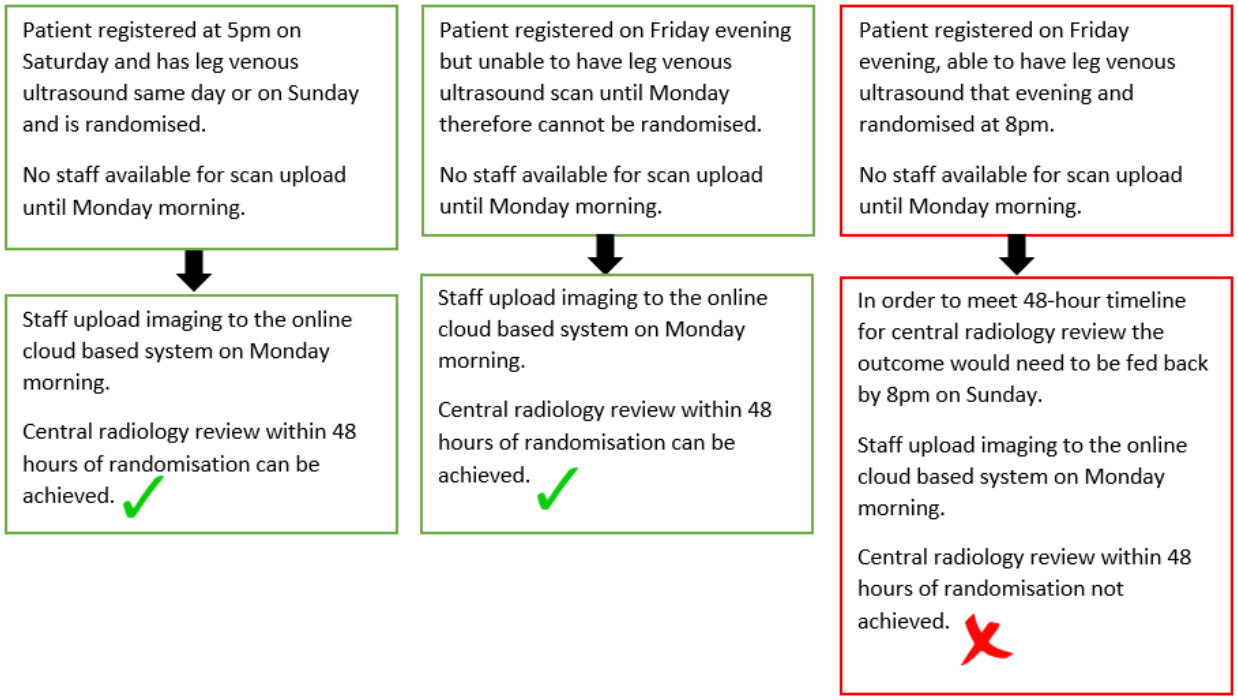
6.2. Registration process

After eligibility for registration has been confirmed (as specified above) and informed consent has been received the patient will be registered to the trial. A Registration Form will be provided to investigators (or delegates) and must be used to collate the necessary information prior to registration. All questions and data items on the Registration Form must be answered before a Registration Number can be given.

Registration will be provided by a secure online registration system at the Birmingham Clinical Trials Unit (BCTU) (available at https://bctu-redcap.bham.ac.uk). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of registering participants into the study as detailed on the STOP-APE Trial Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either the registration process or trial database using another person's login details.

Once registration has been completed the patient's CTPA or CT thorax imaging labelled with their registration number should immediately be uploaded to the online cloud based system for central radiologist review. The central radiology team will perform their review and provide the outcome within 48 hours of the imaging being uploaded to the online cloud based system. It is permissible for imaging to be uploaded to the online cloud based system at the start of the next working day if the patient is registered outside of the working hours of the staff responsible for uploading imaging to the system. However this should not result in the outcome of the scan review by the central radiologists taking longer than 48 hours post randomisation to be fed back to the local research team (please see Figure 1 of example scenarios for added clarity). For this reason patients should not be randomised between Friday 4pm and Saturday 4pm if there are no staff available to upload the imaging to the online cloud based system.

Figure 1. Example scenarios for imaging upload to the online cloud based system



This process is detailed in a separate document called **Instructions for uploading CTPA/CT thorax imaging** which can be found in the ISF.

Patients can be randomised prior to the outcome of this review. This will minimise barriers to recruitment and reflects usual care as closely as possible in keeping with the pragmatic nature of the trial. However, if the outcome of the review is received prior to randomisation and shows the participant either has a PE affecting a larger vessel or no SSPE is present then they should not be randomised.

6.3. Registration records

Following registration, a confirmatory e-mail will be sent to the person registering the patient, PI and Research Nurse.

Investigators (or delegates) must complete the **STOP-APE Participant Recruitment and Identification Log** which links participants with their allocated registration number. The Investigator (or delegates) must maintain this document, which is **not** for submission to the Trials Office. The Investigator or delegate should also add the registration number to the relevant entry on the **STOP-APE Participant Screening Log**. The **STOP-APE Participant Recruitment and Identification Log** and **STOP-APE Participant Screening Log** should be held in strict confidence.

6.4. Randomisation

6.4.1. Randomisation Methodology

Participants will be randomised by computer at the level of the individual in a 1:1 ratio to either intervention (withhold anticoagulation treatment) or control (full dose anticoagulation treatment as standard of care) arm.
A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Age (<50, 50-70, >70 years)
- Cancer (Yes/No)
- Clinically suspected or confirmed COVID-19 (Yes/No)
- Type of SSPE (Symptomatic / Incidental)
- Previous clinically relevant bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) (Yes/No)
- Randomising site

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received.

Full details of the randomisation specification will be stored in a confidential document at the Trial Office.

6.4.2. Blinding

The treatment allocation will not be blinded. This design has been adopted because of the importance of understanding how the knowledge of a diagnosis of SSPE that is not treated with anticoagulation affects health seeking behaviour. This would be the situation in real clinical practice, if the results of the trial support a no anticoagulation strategy. If the trial was to be blinded and placebo-controlled, it would not be able to predict the impact of a no anticoagulation strategy in routine practice.

6.4.3. Randomisation Process

After participant eligibility for randomisation has been confirmed and informed consent has been received, the participant can be randomised into the trial.

A Randomisation Form on the database will be provided to investigators (or delegates) and must be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before a randomisation number can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available. The exception to this is the anticoagulation treatment details which will be provided on the form post-randomisation if the patient is allocated to the control (anticoagulant treatment) arm, in this case the randomisation will not need to be suspended.

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at https://bctu-redcap.bham.ac.uk). Unique log-in usernames and passwords will be provided to those who wish to use the online system and

who have been delegated the role of randomising participants into the study as detailed on the STOP-APE Trial Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either the randomisation process or trial database using another person's login details. The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A back-up telephone randomisation service will be available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days. The contact information will be provided by the trial office.

The STOP-APE patient card should be provided to the patient following randomisation. The patient card provides symptoms related to a potential VTE recurrence to prompt the patient to seek medical attention should they suffer any of these. Additionally it prompts the patient to contact the research team should they be admitted to hospital. It also provides details of the trial including their allocation and the PI contact details to present to their treating clinician.

6.4.4. Randomisation Records

Following randomisation, a confirmatory e-mail will be sent to the Randomiser, PI and Research Nurse.

Investigators (or delegates) must complete the **STOP-APE Participant Recruitment and Identification Log** which links participants with their allocated randomisation number. The Investigator (or delegates) must maintain this document, which is **not** for submission to the Trials Office. The Investigator or delegate should add the randomisation number to the relevant entry on the **STOP-APE Participant Screening Log.** The Investigator or delegate should also add the randomisation number to the relevant entry on the **STOP-APE Participant Screening Log**. The **STOP-APE Participant Recruitment and Identification Log** and **STOP-APE Participant Screening Log** should be held in strict confidence.

6.4.5. Informing Other Parties

Following randomisation of the participant, the participant's GP should be notified that they are participating in STOP-APE trial, using the **STOP-APE GP Letter** clearly indicating whether the patient has been randomised to the treatment or no treatment arm**.**

7. TRIAL TREATMENT / INTERVENTION

7.1. Intervention(s) and Schedule

7.1.1. Intervention Group

Withhold anticoagulation treatment for at least 3 months.

7.1.2. Control Group

Full dose anticoagulant treatment, either Direct Oral Anticoagulant (DOAC), warfarin or low molecular weight heparin (LMWH) subcutaneous injection as standard care for at least 3 months.

7.2. Drug Interaction or Contraindications

The pragmatic trial design allows any concomitant medications (both within and after 3 months) that are part of the trial participant's usual care to be administered to replicate real world practice, with the exception of the use of anticoagulants in the intervention group (see also section 7.3).

7.3. Treatment Modification

Central review of CTPA

There are two scenarios that may lead to treatment modification after central thoracic radiologist review of the CTPA/CT thorax:

1. A pulmonary embolism is identified that is affecting larger vessels (i.e. segmental, lobar or main pulmonary artery). If this situation occurs and the patient has been randomised to the intervention arm, a central clinical coordinator will contact the patient to make them aware that they need to attend hospital immediately. They will also contact the responsible clinical team (the local research team or the on call acute medical team if at the weekend) who will make an assessment with regards to treatment with anticoagulation as part of standard of care.

2. No SSPE is identified (i.e. the absence of any pulmonary embolism). This information will be communicated to the local research team via email who will make an assessment with regards to treatment as part of standard of care.

Pregnancy and other clinical indications

If the patient becomes pregnant during the first 3 months after randomisation then they should be treated according to local clinical protocol which is likely to involve full dose anti coagulation and may necessitate changing arms.

In all other circumstances if a change to the type of anti-coagulation treatment is clinically indicated this will be at the discretion of the treating clinician.

7.4. Cessation of Treatment

If a recurrent VTE is diagnosed during the first 3 months of the trial in the intervention group, then anticoagulation will be started as per the standard care. This will be deemed an end point although follow up will continue up to the 12 months after randomisation.

If patients in the control group have a major bleed, then any cessation of anticoagulation will be at the discretion of the treating clinician. This will be deemed an end point, although follow up will continue up to the 12 months after randomisation.

8. OUTCOME MEASURES AND STUDY PROCEDURES

8.1. Pilot Stage Outcomes

- Recruitment rates
- The nature of exclusions and patients who decline to take part in the study
- Study acceptability and early identification of recruitment barriers
- CTPA outcomes
    - Safety of randomisation based on acute reporting radiologists diagnoses

8.2. Main Trial Outcomes

Outcomes will be assessed by the central blinded and independent adjudication committee (CIAC). Details of outcomes from patient reports and electronic health records will be collated by the trial team for adjudication at regular meetings (frequency to be specified by TSC). The decisions of this committee will then be entered into the trial database.

8.2.1. Multiple (joint) Primary Outcomes

Composite of recurrent VTE (nonfatal) and/or VTE related death (primary safety outcome) and clinically relevant bleeding, which is a composite of major and clinically relevant non-major bleeding (CRNMB) (primary efficacy outcome) within 3 months post-randomisation.

The following primary outcome definitions will be used by the CIAC:

VTE recurrence
Composite of nonfatal VTE (PE or DVT) recurrence and/or VTE-related death.

PE recurrence
Suspected (new or recurrent) PE with one of the following findings:

- A new intraluminal filling defect in a subsegmental or more proximal pulmonary artery on CTPA or CT thorax with IV contrast
- An extension of an existing subsegmental pulmonary embolism on CTPA or CT thorax with IV contrast
- A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan

- Symptoms suggestive of PE but with an inconclusive CTPA, CT thorax with IV contrast or ventilation/perfusion scan for PE, and with evidence of a new DVT in the lower extremities by compression ultrasound or venography.

DVT recurrence
Suspected (recurrent) DVT with one of the following findings:

- abnormal compression ultrasound
- an intraluminal filling defect on venography (CT/MR/invasive)

Objective testing for PE/DVT recurrence will be encouraged, but in the absence of objective testing, a suspected episode of DVT or PE will be considered as confirmed if it led to a change in anticoagulant treatment at therapeutic dosages.

VTE-related death
- PE based on objective diagnostic testing, autopsy, or
- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out (unexplained death).

Clinically relevant bleeding
Composite of major bleeding and clinically relevant non major bleeding (CRNMB).

Major bleeding
Is defined by ISTH criteria:

1. Fatal bleeding, and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or

3. Bleeding causing a fall in haemoglobin level of 20g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

Clinically relevant non-major bleeding (CRNMB)
Is defined by ISTH criteria:

Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:

i. requiring medical intervention by a healthcare professional

ii. leading to hospitalisation or increased level of care

iii. prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

8.2.2. Secondary Outcomes

There are a number of secondary outcome measures from the time of randomisation including:

- Recurrent VTE or clinically relevant bleeding at 6 months and 12 months (as assessed through HES records)
- Net clinical benefit - composite of clinically relevant bleeding and recurrent VTE at 3 and 6 months.
- New diagnosis of pulmonary hypertension or right ventricular dysfunction within 12 months of SSPE, defined from HES clinical coding and supported where possible by additional radiological data and echocardiograms undertaken in tertiary pulmonary hypertension centres.
- All-cause mortality at 3, 6 and 12 months
- VTE related mortality at 3, 6 and 12 months
- Cardiovascular mortality at 3, 6 and 12 months defined as cardiac deaths (e.g., cardiogenic shock, fatal arrhythmia, cardiac rupture) and vascular deaths (e.g., VTE-related, fatal stroke, ruptured aortic aneurysm, aortic dissection).
- Reclassification rate from thoracic radiologist review

8.2.2.1. Economic

- Healthcare resource use: hospitalisations, bed days, unscheduled primary and secondary care visits for recurrent VTE, clinically relevant bleeding or potentially related symptoms
- Healthcare costs
- Health-related quality of life (EQ-5D-5L at baseline, 3 and 6 months)
- Cost-utility at 6 months (cost per QALY) and cost-effectiveness at 12 months (cost per VTE avoided)

8.2.2.2. Mechanistic (behavioural)

- Themes from qualitative interviews which inform optimal recruitment strategies including information presentation and attitudes to risk.

8.3. Study procedures

The following assessments should be performed at baseline:

- Ethnicity
- Concomitant medications
- Smoking status
- Risk factors for bleeding as defined by ISTH
- VTE symptoms - include pleuritic pain, breathlessness, chest pain – not pleuritic, syncope, haemoptysis, leg pain (unilateral/bilateral), leg swelling or oedema (unilateral/bilateral)
- VTE recurrence risk factors as defined by ACCP
- Height and weight
- Routine blood tests to include Hb, platelet count, creatinine, eGFR, BNP, NT-proBNP, Troponin I, Troponin T, D dimer
- Modified MRC dyspnoea score
- EQ-5D-5L questionnaire - to be completed on paper by patient (only required for patients who will be randomised)

At point of randomisation:

- Provide patient with patient card

The following assessments should be performed at 4 week follow up via telephone call with the patient (a window of one week is permitted) and review of the medical record:

- SAE check
- Survival check
- VTE recurrence
- Anti-coagulation medication check to include cessation of treatment, commencement of treatment and change to type of treatment

The following assessments should be performed at 12 week and 24 week follow up via telephone call with the patient (a window of two weeks is permitted) and review of the medical record:

- SAE check
- Survival check
- VTE recurrence
- Bleeding events - major bleeding and clinically relevant non major bleeding
- Anti-coagulation medication check to include cessation of treatment, commencement of treatment and change to type of treatment
- Modified MRC dyspnoea score
- EQ-5D-5L questionnaire
- NHS usage for VTE recurrence and associated symptoms/bleeding events- to include primary care visits, emergency department/ambulatory care/AMU visits, hospitalisations and diagnostic investigations for VTE.

8.4.Schedule of Assessments

	Screening	Baseline	Telephone Call 1	Telephone Call 2	Telephone Call 3	HES data extraction
			4 weeks (± 1 week)	12 weeks (± 2 weeks)	24 weeks (± 2 weeks)	52 weeks
Consent	X	X				
Eligibility check	X	X				
Registration	X					
Randomisation[2]		X				
CTPA/CT thorax with IV contrast	X					
Medical history[1]	X					
Concomitant medications		X				
Ethnicity		X				
Risk factors for bleeding[3]		X				
VTE symptoms and recurrence risk factors[4, 5]		X				
Routine blood tests[6]		X				
Modified MRC Dyspnoea score		X		X	X	
Pregnancy test	X					
Physical exam[7]	X					
Vital signs[8]	X					
CTPA/CT Thorax upload to the online cloud based system[9]		X				
Leg venous ultrasound[10]	X					
EQ-5D-5L[11]		X		X	X	
Anticoagulant medication check[13]			X	X	X	
VTE Recurrence			X	X	X	X
Bleeding events[12]				X	X	X
NHS usage for VTE related events/bleeding events[14]				X	X	X
SAE check			X	X	X	
Survival check			X	X	X	X

Notes

[1] Medical history - to include smoking status

[2] Randomisation - provide patient card to patient at point of randomisation

[3] Bleeding risk factors as defined by ISTH

[4] Recurrent VTE risk factors as defined by ACCP

[5] VTE symptoms to include pleuritic pain, breathlessness, chest pain - not pleuritic, syncope, haemoptysis, leg pain (unilateral/bilateral), leg swelling or oedema (unilateral/bilateral)

[6] Routine bloods results - to include Hb, platelet count, creatinine, eGFR, BNP, NT-proBNP, Troponin I, Troponin T, D dimer

[7] Physical examination - to include height, weight, pain on lower-limb venous palpation, leg swelling swelling/oedema (unilateral/bilateral), leg erythema (unilateral/bilateral)

[8] Vital signs - to include heart rate, blood pressure, oxygen saturation, respiratory rate

[9] CTPA/CT thorax upload to the online cloud based system - to be done immediately following registration of the patient; or next working day if outside of working hours of staff responsible for upload as long as central thoracic radiology review outcome can be fed back within 48 hours of randomisation.

[10] Venous ultrasound - of both proximal legs using compression ultrasonography from the sapheno-femoral junction to the popliteal fossa sampling at three points. If CT/MR venography has already been performed including both proximal legs ultrasonography is not required.

[11] EQ-5D-5L – only required for patients who will be randomised. To be completed on paper by patient at baseline and follow up via telephone call.

[12] Bleeding events – major bleeding and clinically relevant non major bleeding

[13] Anti-coagulation medication check - to include cessation of treatment, commencement of treatment and change to type of treatment

[14] NHS usage for VTE recurrence and associated symptoms/bleeding events - to include primary care visits, emergency department/ambulatory care/AMU visits, hospitalisations and diagnostic investigations for VTE

8.5.Participant Withdrawal and Changes of Status Within Trial

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation. Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial at any time. A participant who withdraws from the trial does so completely (i.e. from trial treatment and all follow up).

A participant who wishes to cease to participate *in a particular aspect of the trial*, will be considered as having changed their status within the trial.

Patients who lose mental capacity during the trial will be withdrawn as they would not be able to comply with taking the medication or form completion.

The changes in status within the trial are categorised in the following ways:

- No trial intervention: The participant would no longer like to receive the trial intervention, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis).

- No trial related follow-up: The participant would no longer like to receive the trial intervention AND does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes).

- No further data collection: The participant would no longer like to receive the trial intervention AND is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis).

The details of either withdrawal or change of status within trial (date, reason and category of status change) should be provided via trial exit/change of status form within the CRF and clearly documented in the source documents. Patients subsequently found to be ineligible will still have their data analysed.

If following central thoracic radiologist review of the participants' CTPA or CT Thorax, it is found that a randomised participant has a PE affecting a larger vessel or no SSPE is present, providing their continuing consent they should continue to be followed up as part of the trial. All patients will be analysed for the primary outcome, and as per protocol analysis will be undertaken on patients with a confirmed diagnosis of ISSPE.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Table 2: Adverse Event definitions

Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator**
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted
**medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definitions above.

9.2. Adverse Event General Recording Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of definitions in section 9.1. It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of

severity and seriousness and also for causality (relatedness) in relation to the intervention(s) in accordance with the protocol

9.3. Adverse Events Reporting Requirements in STOP-APE

The safety profile for this patient population and anti-coagulation treatment is well established so although it is recommended that the severity, seriousness and causality of all AEs should be recorded in the source documents, a strategy of targeted reporting of AEs will not affect the safety of participants. The reporting of only the following subset of AEs via the Case Report Forms (CRFs), for the appropriate period, is consistent with aims of the trial:

- VTE events, sudden death, bleeding events (categorised as major, or clinically relevant non-major), new diagnosis of pulmonary hypertension or right ventricular dysfunction.

9.4. Serious Adverse Advents (SAE) Reporting in STOP-APE

All AEs that meet the definition of an SAE will be collected and recorded in the participant notes and the Case Report Form (CRF). SAEs will in addition be reported to the trial office immediately and within 24 hours of being made aware of the event.

9.4.1. Events not requiring reporting to BCTU

At whatever time they occur during an individual's participation, from randomisation to end of participant follow-up, the following are not considered to be critical to evaluations of the safety of the trial:

- Elective hospital admissions for a procedure that is not intended to treat or alleviate cardiovascular or respiratory disease

All events which meet the definition of serious must be recorded in the participant notes, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

9.4.2. Events that require reporting to BCTU on the SAE Form

The following events should be reported to the trial office immediately and within 24 hours of being made aware of the event via an SAE form:

- All events that meet the definition of serious, except those listed in section 9.4.1.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial treatment or is being followed up for trial purposes, processes must be in place to *make the trial team at the hospital aware of any SAEs*, regardless which department first becomes aware of the event, *in an expedited manner*.

9.5. Reporting period

Details of targeted AEs as described in section 9.3 will be detected from patient-reported symptoms or clinical records during follow up at 12 and 24 weeks post randomisation and via NHS digital records at 52 weeks post randomisation. Collection of these AEs will help indicate whether the trial intervention is associated with increased adverse events. The reporting timeframe for adverse events is from the date of randomisation until 6 months post randomisation.

9.6. Reporting process – At Site non CTIMPs

9.6.1. Reporting process for SAEs requiring an SAE Form

On becoming aware that a participant has experienced an SAE which requires reporting on a **STOP-APE SAE Form**, the Investigator, (or delegate as indicated on the STOP-APE site signature and delegation log) should report the SAE to their own Trust in accordance with local practice and to the Trial Office as per the requirements of sections 9.4.2 and 9.4.3 above. To report an SAE to the Trials Office the Investigator or delegate must complete, date and sign the SAE form. The completed form together with any other relevant, appropriately anonymised, data should be scanned and emailed to the Trial Office using the email listed below in accordance with the timelines given in section 9.4:

Scan and email the SAE Form to:

stop-ape@trials.bham.ac.uk

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

If the site has not received confirmation of receipt of the SAE from the Trial Office or if the SAE has not been assigned a unique SAE identification number within one working day, the site should contact the Trial Office. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the initial SAE report in the Site File.

9.6.2. Provision of follow-up information

Following reporting of an SAE for a participant, the participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, the final version of the original SAE form completed at site must be returned to the Trial Office and a copy kept in the Site File.

9.7. Assessment of relatedness

When completing the SAE form, the PI or delegate as identified on the STOP-APE site signature and delegation log will be asked to define the causality (relatedness) and the severity of the AE. In defining the causality the PI delegate must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which do not contribute to the event.

Table 3: Assessment of relatedness definitions

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) or delegate who will independently review the causality of the SAE. An SAE judged by the PI or delegate or CI or delegate to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI or delegate will not be downgraded by the CI or delegate. If the CI or delegate disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

9.8. Assessment of Expectedness by the CI

The CI or delegate will also assess all related SAEs for expectedness with reference to the following criteria.

Table 4: Definition of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the protocol.
Unexpected	An adverse event that is <u>not</u> consistent with known information about the trial related procedures.

The CI will not overrule the severity or causality assessment given by the PI or delegate but may add additional comment on these If the event is unexpected (i.e. is not defined in the

protocol as an expected event it will be classified as a Related and Unexpected SAE (RUSAE).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

9.8.1. Protocol defined expected SAEs

For participants in control arm, the following events are expected as a consequence of the participant's clinical condition:

- VTE events – recurrent pulmonary embolism, deep vein thrombosis (due to suspected treatment failure of the medication).

The following events are expected as a consequence of anticoagulant therapy

1. Fatal bleeding, and/or

2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra- articular or pericardial, or intramuscular with compartment syndrome, and/or

3. Bleeding causing a fall in haemoglobin level of 20g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

For participants in the intervention arm, the following will be considered expected without anti-coagulation therapy:

- VTE events – recurrent pulmonary embolism, deep vein thrombosis.

9.9. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings. BCTU will report details of all events categorised as Unexpected and Relates SAEs to the main Research Ethics Committee (REC) and the Research Governance team (RGT) within 15 days. The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial. Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the site file and TMF.

9.10. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Table 5: STOP-APE Trial Source Data

Data	**Source**
Participant Reported Outcomes (EQ-5D-5L)	The original patient-completed paper EQ-5D-5L questionnaire is the source at baseline. The interview administration EQ-5D-5L form is the source at 12 and 24 week follow up. These will be kept with the participant's trial record at site.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice. Information will be transcribed onto CRFs.
Imaging	The source is the original imaging usually as an electronic file. Data will be supplied via image upload to the online cloud based system.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be transcribed onto CRFs.
Health Economics data	Obtained by (1) interview directly with the participant for transcription onto the CRF in which case the CRF is source data. (2) To the medical record in which case the original clinical annotation is the source document. Information will be transcribed onto CRFs.
Recruitment	The original record of the registration and randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.

Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the medical records.

10.2.Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual subject. The data held on the completed original CRFs are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties except for authorised representatives or appropriate regulatory authorities without written permission from the sponsor. Appropriate data sharing requests will be considered by the Sponsor.

It will be the responsibility of the PI to ensure the accuracy of all data entered in the CRFs and confirm accordingly. The STOP-APE Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

The CRFs will comprise the following Forms:

Table 6: Data Collection Forms

Form Name	**Schedule for submission**
Registration form	At the point of registration
Randomisation form	At the point of randomisation
Baseline form	For registered patients that are found to be ineligible, at point of becoming aware of ineligibility. For all others at the point of randomisation
Baseline EQ-5D-5L questionnaire	At the point of randomisation
Follow up form (4, 12 and 24 weeks)	Following trial appointment with patient at appropriate time point
Follow up EQ-5D-5L questionnaire (12 and 24 weeks)	Following trial appointment with patient at appropriate time point
Serious Adverse Event Form	Emailed within 24hrs of research staff at site becoming aware of event if expedited. If non-expedited then emailed within two week of awareness.
Trial exit/Change of status form	At the point of withdrawal or death

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to the STOP-APE guide on CRF completion.

For the STOP-APE trial, CRFs will be an electronic record completed at site (except for the baseline patient completed booklet and Serious Adverse events which will be paper), only by those at site delegated the task of doing so. Forms will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data is unobtainable.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI on the CRF. For more information please refer to the **Data Management Plan**.

Data should be submitted according to section 10.4 in a timely manner, therefore if data has not been provided within four weeks of the submission schedule detailed in the above table then a reminder email will be sent to sites. If the data has still not been received within 6 weeks then the trial manager will directly contact the site via telephone to ascertain the reason for the delay. At 8 weeks from expected submission if the data still has not been received this may be escalated to site's senior management and can trigger a monitoring visit.

10.3.Participant completed Questionnaires

Data collected from EQ-5D-5L will be used to inform the heath economic outcome measure. At baseline the EQ-5D-5L will be completed directly by the patient. Questionnaires should generally be completed by the participant alone but physical assistance in completing the form can be given by the research staff or the participant's friends and relatives where appropriate. In such circumstances questions are to be read to the participant verbatim and responses must not be led by the person assisting with the form completion. This requirement must be made clear when the participant's friends and relatives are providing the assistance. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where a questionnaire is returned to the local research staff, in person, with some questions unanswered, research staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

At 12 and 24 week follow up the EQ-5D-5L will be collected from the patient by a member of the local research team telephoning them and asking the questions using the interviewer administered EQ-5D-5L.

10.4.Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed between the trial team and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried using a Data Clarification system in line with the **STOP-APE Data Management Plan**, and will focus on data required for trial outcome

analysis and safety reporting. Single data entry with central monitoring will be employed. Staff at site (as delegated on the **STOP-APE Site Signature & Delegation Log**) will enter and submit data on an electronic CRF online (except serious adverse events). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of CRF completion as detailed on the **STOP-APE Site Signature and Delegation Log**. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the trial database using another person's login details. The trial office will be unable to edit data forms entered by site staff and vice versa. The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and attributable, with a reason for the change documented and will be made by local site staff (except serious adverse events). Serious Adverse Event Forms will be emailed directly to the trial office for trial office staff to enter the data on the electronic CRF online.

Trial office staff will perform self-evident corrections if necessary in the following situations:

- to correct general spelling mistakes
- obvious date errors
- where a response to a question has not been provided but additional "related" data has been supplied and where the correct data is recorded on the CRF but in an incorrect location
- where the trial number is incorrectly recorded on the paper CRF, but the patient can be unequivocally identified from the other patient identifiers on the form, the number may be amended.

Self-Evident corrections will only be made to non-critical data items which must be agreed with the PI prior to implementation.

10.5.Data Security

The security of the trial database is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the study. BCTU has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls used non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.

- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: statisticians will have access to anonymised data.
- System Audit: the System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessments
- Data Protection Registration: the University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

All data captured on and stored by the online cloud based system will be automatically pre-anonymised before upload and will be stored/managed on the Cimar Cloud-PACS system hosted at UK Cloud Ltd secure data centre in the UK. (Company Registration Number 07619797); the following physical security features are in place to guarantee the safety of the data:

- CCTV covering all areas of the data centre
- Security guarded access on duty 24X7X365 days a year
- Role-based access control to manage access to the digital environment, and physical access to the server hosting environment which is controlled by swipe-card system across at the data centre to ensure no un-authorised virtual or physical access is permitted.
- Only authorised people have access to the database and anonymised image library and a full audit trail is captured by the Cloud for every user touch-point to ensure full transparency and accountability.

The online cloud based system (Site-facing upload App and clinician-facing dashboard) will not capture, store or display any personal data. All data transferred to the cloud will be over HTTPS/TLS1.2 only, losslessly compressed and encrypted. All access to the data in the cloud will also be via the same secure access protocol only. Data uploaded to the system will be tested in accordance with the Open Web Application Security Project (OWASP) top 10 vulnerabilities as recommended by NHS data security and information toolkit. Access to the data is controlled by multiple layers of access security:

- login with username and strongly enforced password
- RBA (Roll based access) only, controlling permitted functionality and data rights - per user
- Split/Merge storage – all PHI meta-data is split from imaging data and stored encrypted. Its re-union is only ever in the cloud's RAM and is not written to disc as identifiable data.

The online cloud bases system and end to end solution/workflow is hosted on secure and approved cloud servers at UK Cloud. This state-of-the-art data centre and the Cimar Cloud are accredited with the ISO 27001 certification and periodic penetration testing is carried out to check for any vulnerabilities.

ISO 27001 (formally known as ISO/IEC 27001:2005) is a specification for an information security management system (ISMS). An ISMS is a framework of policies and procedures that includes all legal, physical and technical controls involved in an organisation's information risk management processes. Imaging for the STOP-APE trial will be anonymised when uploaded, stored, managed and viewed using a cloud solution designed for Clinical Trial purpose and is used by over 700 clinical trials globally (including PAREXEL and many other CRO's).

10.6. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, Pharmacy Files, participants' hospital notes, CRFs etc.) at their site are securely retained for at least 10 years. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the Trial Office.

Prior to long term archiving, the TMF will be stored at the Trial Office under controlled conditions. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including a **Site Signature & Delegation Log** between the PI and BCTU, and supply an up to date signed CV and GCP certificate to the Trial Office. All site staff who are performing trial specific tasks are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU and as documented in the monitoring plan.

11.3.Onsite Monitoring

For this trial we will monitor all sites in accordance with the trial Risk Assessment and Monitoring Plan. Investigators will allow the STOP-APE trial staff access to source documents as requested. The monitoring will be conducted by BCTU staff.

11.4.Central Monitoring

Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the **Data Management Plan**. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed ICFs and other documentation for central review for all participants providing explicit consent. This will be detailed in the Monitoring Plan.

11.5.Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify the Trial Office of any relevant inspections.

11.6.Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified may be reported to the Trial Management Group and Trial Steering Committee, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC and/or relevant regulatory bodies.

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

12. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, including DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the REC and RGT within 90 days of the end of trial. Where the trial

has terminated early, the Trials Office will inform the REC within 15 days of the end of trial. The Trials Office will provide the REC and RGT with a summary of the clinical trial report within 12 months of the end of trial.

13. STATISTICAL CONSIDERATIONS

13.1. Sample Size

The trial is powered on the superiority for bleeding events and non-inferiority for recurrent VTE.

Superiority for bleeding events:
With 90% power and two-sided alpha=0.05, to detect a decrease in major bleeding or CRNMB from 7% (based on a meta-analysis of DOAC RCTs)[2] in the anticoagulation group to 3% in the no anticoagulation group using a two-sample proportions test, 1244 patients (622 per group) are required.

Non-inferiority for recurrent VTE:
We also aim to detect whether no anticoagulation is non-inferior to treatment with anticoagulation regarding VTE recurrence. With 90% power, and a one sided alpha=0.025, a VTE recurrence rate of 2% with anticoagulation (also based on the DOAC RCT meta-analysis)[2] and a non-inferiority margin of 2.5%, 1,320 patients would be needed.
Taking the largest of the two sample sizes computed (i.e. sample size for non-inferiority), allowing for 10% attrition, a total of 1466 patients (733 per arm) would be needed. Sample size calculations were performed using Stata 13.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those treated without anticoagulation versus those treated with anticoagulation. All analyses will be based on the intention to treat (ITT) principle as well as the modified ITT set, with modified ITT set being patients with confirmed SSPE or equivocal for SSPE based on CTPA review. Given the multiple (joint) primary outcome for recurrent VTE has a non-inferiority hypothesis, the decision for claiming non-inferiority will be based on the results from the per-protocol set for this outcome. (Please see the SAP for further details on this).

For all outcome measures, appropriate summary statistics will be presented by group (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). Intervention effects will be adjusted for the minimisation variables listed in section 6.4 and baseline scores where possible. 95% confidence intervals (CI) and p-values will be presented for all outcomes. No adjustment for multiple comparisons will be made.

13.2.1. Primary Outcome Measure

The multiple (joint) primary outcomes are both binary outcomes (i.e. yes/no) and will be analysed using a generalised linear model (with binomial distribution and log link), adjusting for minimisation variables listed in Section 6.4. Treatment effects will be expressed as adjusted risk ratios with 95% CIs. If the model does not converge, then a Poisson regression model with log link and with robust variance estimation will be used (28). We will also present the adjusted risk difference alongside the adjusted risk ratio and so to estimate the adjusted risk difference, a generalised linear model (with binomial distribution and identity link) will be fitted adjusting for minimisation variables listed in Section 6.4.

13.2.2. Secondary Outcome Measures

The secondary outcomes are a combination of binary data, continuous data and count data.

Binary outcomes:
The secondary outcomes that are binary (e.g. VTE related death) will be analysed using the same methods described for the co-primary outcomes (see Section 13.2.1).

Count data outcomes:
For those secondary outcomes that are count data types (e.g. SAE's), Poisson regression model will be used for analysis. Time will be used as an offset in the model. Results will be presented as an adjusted incidence rate ratio.

Reclassification rates from thoracic radiologist review:
Reclassification rates for all recruited patients will be calculated with 95% binomial exact confidence intervals for (a) no SSPE diagnosis (b) SSPE diagnosis or Equivocal and (C) PE identified in arteries larger than subsegmental level. These rates will be analysed without any adjustment. These reclassification rates by trial arm will be included in the table of baseline characteristics. Variation between centres will be described anonymously as understanding centre contribution to reclassification rates may be relevant to intervention implementation. Radiological review of the SSPE diagnosis by the acute reporting radiologist is required as a safety check to ensure randomised patients receive appropriate treatment, that is, anticoagulation of patients with no SSPE randomised to anticoagulation can be halted and anticoagulation of patients with PE which requires it can be initiated.

13.2.3. Subgroup Analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm excluding centre (see section 6.4). Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the statistical model) will be performed alongside the effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. In brief, this will include best-case worst-case imputation. Full details will be included in the Statistical Analysis Plan.

13.3.Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 14.5.

13.4.Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the 12 week assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis. This analysis will include data items up to and including the 12 week assessment and no further. Longer term data from further time-points (i.e. 24 and 52 weeks) will be analysed separately once participants have completed the corresponding assessments.

13.5.Health Economics Analysis

An economic evaluation will be undertaken to assess the cost-effectiveness of no treatment versus full dose anticoagulation in patients with ISSPE. The evaluation will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY) over 6 months follow up and a cost-effectiveness analysis to estimate cost per VTE avoided over 12 months using routine data sources. Both analyses will be from a health services perspective.

Data collection: Data will be collected on all related health care resource use, concentrating on VTE and bleeding events and investigation of symptoms. This will concentrate on hospitalisations and bed days related to events, visits to primary and secondary care, diagnostic tests undertaken for symptoms potentially related to VTE and major bleeding, and medication use directly related to anticoagulation. This information will be collected from telephone interviews at 12 and 24 weeks, supplemented by information from trial case report forms and hospital records, with targeted extraction data from NHS digital and medical records providing data from 24 to 52 weeks. Unit costs from standard UK sources, for example NHS Reference costs will be sought for all health care resource use items.

In order to calculate QALYs, the EQ-5D-5L questionnaire will be administered to participants at baseline, 12 and 24 weeks. The crosswalk value set will be applied to patient responses to obtain utility scores, in line with current NICE recommendations. In the event of a death, a utility value of 0 will be applied from the date of death to 6 months. Information on VTE recurrence (for the cost-effectiveness analysis at 12 months) will be collected during the trial and from NHS Digital records as previously stated.

Analysis: QALYs will be calculated using responses to the EQ-5D-5L, using the area under the curve approach. Unit costs will be applied to all health care resource use items, and mean resource use (for each category of health care usage) and mean total costs will be

calculated for all trial participants. As cost data is likely to have a skewed distribution, the nature of the distribution of costs will be explored, and if the data is not normally distributed, a non-parametric comparison of means (using bootstrapping) will be undertaken. Multiple imputation will be used to impute all missing values for the EQ-5D and total cost estimates for non-responders. A cost-consequence analysis will initially be reported, describing all the important results relating to resource use, costs and consequences. Incremental cost-effectiveness and cost-utility analyses will then be undertaken to estimate the incremental cost per QALY gained (6 months) and cost per VTE avoided (12 months) respectively, with adjustment for baseline covariates. Discounting is not required as the timeframe is not greater than one year. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. The base case analysis will be intention to treat, with a per protocol analysis conducted as a sensitivity analysis. Cost-effectiveness acceptability curves will also be produced to reflect the probability the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

As we would like to explore the cost-effectiveness of a pragmatic treatment policy (i.e. without an expert thoracic radiological review), we propose the use of decision analytical modelling using a decision tree with a 12 month time horizon, to consider cost per VTE avoided and cost per QALY. This will consider bleeding and VTE outcomes only, and related deaths. This modelling will allow us to explore the potential impact of this policy where those with biggest clots may be missed (and are not anticoagulated) and those without SSPE are treated unnecessarily with anticoagulation. A modelling framework has the flexibility in allowing the exploration of a range of assumptions, best and worst-case analysis and threshold analysis.

13.6.Qualitative analysis

The interviews will be recorded using a digital recorder from which files will be removed from as soon as possible after interview and stored on a secure computer network until transcribed. Data will be transcribed by a transcription company which has been approved for transcription of medical data. All data and quotes will be anonymised, and each respondent will be allocated a number to ensure that they can be identified if necessary. Digital recordings and corresponding interview transcripts will be stored in an encrypted file on a secure network to which only the primary qualitative researcher will have access. Interview participants will be made aware of this along with their right to withdraw from the interview component up to 7 days following the interview. Data will be managed using NVivo and emerging themes will be identified from the transcripts. A coding framework will be developed to enable analysis of the transcripts and the Framework Method used to summarise the data. Three investigators will separately code a selection of the transcripts to ensure that the codes are triangulated and overall coding will then be carried out by a single researcher.

Analysis will be aimed at understanding whether not treating SSPE is acceptable to patients and clinicians; determining the health seeking behaviours and health utilisation of a no anticoagulation treatment strategy for ISSPE; confirming or challenging existing literature and also at identifying new themes that emerge from the interviews (26). Themes emerging from patient and HCP interviews will be compared both between participants and across the two groups to identify similarities and differences between views in a timely manner to inform the ongoing study (26). A summary of the findings will be sent to the participants.

14. TRIAL ORGANISATIONAL STRUCTURE

14.1. Sponsor

The University of Birmingham is the trial sponsor.

14.2. Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU) based at UoB. Delegation of tasks to the BCTU, from the Sponsor, are documented in the STOP-APE Clinical Trials Task Delegation Log.

14.3. Trial Management Group

The Trial Management Group (membership detailed in the Administrative Information section) will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.4. Trial Steering Committee

A single TSC will be created for the STOP-APE trial and will meet at least annually and as required depending on the needs of the trial office. The TSC will include members who are independent of the investigators, their employing organisations, funders and sponsors.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will: provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the sponsor and investigators. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

14.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter. The DMC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason (e.g. safety phase) and will be recorded in minutes.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The TSC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The DMC may recommend early stopping of the trial if the

interim analyses shows differences between treatments that are deemed to be convincing to the clinical community.

14.6. Central blinded and independent adjudication committee

Data analyses will be supplied in confidence to a central blinded and independent adjudication committee who will assess the end points that inform the primary outcome. The committee will be comprised entirely of independent individuals.

14.7. Finance

The National Institute for Health Research (NIHR) is funding this trial. Clinical Research Network (CRN) support will be sought. Excess cost for the trial remains part of NHS costs while trial resources outside routine care and not covered by the CRN will be funded by the trial in the form of per patient payments to a maximum of £226 per patient.

15. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: *http://www.wma.net/en/30publications/10policies/b3/index.html*).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 2018) and the Principles of GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Participants will always be identified using their unique trial identification number, initials and date of birth on the Case Report Form in correspondence between the Trial Office and site. Participants name and contact number will be collected at the point of registration on the trial registration form in case a central clinical coordinator needs to contact them. Participants will give explicit consent for this information to be provided to the Trial Office. Participants will give their explicit consent for the movement of their consent forms, giving permission for the Trial Office to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The PI (or delegates) must maintain documents not for submission to the Trial Office (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Interviews will be recorded on an encrypted digital recorder which will be locked in a secured cabinet at the University of Birmingham. Recordings will be transferred onto a secured computer and to a password protected University of Birmingham network folder as soon as possible after each interview. Only the qualitative researchers working on this trial will have access to this folder.

Recordings and transcriptions will be named with a trial-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with trial assigned participant numbers. Coding keys matching the name of the participants with their trial participation number will be stored in a password protected spreadsheet, which will be maintained and only accessed by the qualitative researchers. All recordings will be coded and securely transferred to a University of Birmingham approved transcription company or transcriber that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt. The anonymised interview data (transcripts only) will be uploaded to a 'controlled access' data repository, subject to individual written informed consent from the participants. This has been fully explained in the information sheet, and requires participants to initial a specific statement on the consent form (if they agree).

The Trial Office will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party. Representatives of the STOP-APE Trial Office and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. FINANCIAL AND OTHER COMPETING INTERESTS

There are no commercial repercussions related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

18. INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants. With respect to the conduct of the trial at Site and other clinical care of the participant, responsibility for the care of the participants remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19. POST-TRIAL CARE

Following completion of the trial (12 / 24 weeks following an individual's recruitment) patients will be managed according to the standard clinical care that is deemed appropriate by their responsible clinician.

20. PUBLICATION POLICY

All publications and presentations, including abstracts, relating to the main trial will be authorised by the STOP-APE Trial Management Group. The results of the analysis will be published in the name of the STOP-APE Collaborative Group in a peer reviewed journal (provided that this does not conflict with the journal's policy). All contributors to the trial will be listed, with their contribution identified as determined by the trial publication policy. If requested, trial participants will be sent a summary of the final results of the trial, which will contain a reference to the full paper.

All publications using data from this trial to undertake original analyses will be submitted to the Trial Management Group for review before release. To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the Trial Management Group. A study site may not publish results of a study until after a coordinated multicentre publication has been submitted for publication.

21. ACCESS TO FINAL DATA SET

The STOP-APE protocol will be made publicly available via both the STOP-APE webpage, hosted by the Trial Office and subsequently published in an appropriate journal, in advance of the final data set.

The final data set itself will only be available to the direct STOP-APE Trial Office, including the TSC, in the first instance. Following publication of the findings, the final trial dataset will be made available to external researchers upon approval from the TSC and the BCTU data sharing committee in line with standard data sharing practices for clinical trial data sets.

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