



## Research Article

# Stopping anticoagulation for isolated or incidental pulmonary embolism: the STOPAPE RCT protocol

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## Abstract

**Research question:** Is withholding anticoagulation for patients with isolated or incidental subsegmental pulmonary embolism clinically and cost-effective compared with full anticoagulation for 3 months?

**Background:** There has been an increase in the diagnosis of subsegmental pulmonary embolism since the advent of computed tomography pulmonary angiogram to investigate patients with suspected pulmonary embolism. Subsegmental pulmonary embolism is not often detectable with older nuclear medicine-based diagnostic imaging for ventilation/perfusion mismatch. The case fatality of pulmonary embolism has reduced as subsegmental pulmonary embolism diagnoses from computed tomography pulmonary angiogram have increased. There is growing equipoise about the optimal treatment for patients with subsegmental pulmonary embolism, given that full anticoagulation has significant risks of bleeding and subsegmental pulmonary embolism was not often diagnosed previously with ventilation/perfusion scanning and therefore most likely left predominantly untreated prior to the introduction of computed tomography pulmonary angiogram scanning.

### Objectives:

1. Determine whether withholding anticoagulation for isolated or incidental subsegmental pulmonary embolism (i.e. subsegmental pulmonary embolism with no coexisting deep-vein thrombosis) reduces the harms of recurrent thromboembolism and major bleeding compared with 3 months of full anticoagulation at 3, 6 and 12 months.
2. Determine the rate of complications of anticoagulation therapy (predominantly bleeding) in patients with isolated subsegmental pulmonary embolism.
3. Determine whether not treating isolated subsegmental pulmonary embolism is acceptable to clinicians and patients.
4. Determine the reclassification rate of subsegmental pulmonary embolism diagnoses made by general reporting radiologists when reviewed by specialist respiratory radiologists and develop a set of rules to improve general radiologists' diagnoses of subsegmental pulmonary embolism.
5. Assess cost-effectiveness of not treating patients with isolated subsegmental pulmonary embolism with anticoagulation, taking a health service perspective.

**Methods:** Prospective individually randomised open controlled trial with blinded end-point committee assessment for outcomes, powered for non-inferiority for recurrent venous thromboembolism and for superiority for bleeding events. An internal pilot phase is included for feasibility and acceptability of no anticoagulation. We planned to recruit

1466 patients from at least 50 acute hospital sites. Allowing for a dropout rate of 15%, this would have given us 90% power to detect a reduction in major and clinically relevant non-major bleeding from 7.3% in the anticoagulation arm to 3% in the intervention arm. We were powered to determine that a strategy of no anticoagulation was non-inferior to anticoagulation with an upper margin of a 2.3% increase in recurrent venous thromboembolism from an expected rate of 2% in those who receive full anticoagulation.

We also planned to undertake a study comparing acute reporting radiologists' diagnoses of subsegmental pulmonary embolism from all computed tomography pulmonary angiograms with specialist respiratory radiologists. This would have allowed us to determine safety in the pilot study (i.e. patients with pulmonary embolism that was in fact larger than subsegmental would have been identified) and develop guidance for subsegmental pulmonary embolism diagnosis for general radiologists. Patients with lived experience of thrombosis contributed to all aspects of the trial design and were part of the Trial Management Group.

**Progress of study:** The STOPAPE trial was stopped prematurely due to a low recruitment rate in the wake of the COVID pandemic and prioritisation of recovery of the National Institute for Health and Care Research research portfolio. There are no outcome data available for this trial. Separate NIHR Library publications will detail the linked qualitative study examining the views of patients and clinicians around withholding anticoagulation for isolated subsegmental pulmonary embolism as well as presenting all collected data of recruited patients.

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## Introduction

### Background and rationale

Acute pulmonary embolism (PE) is associated with significant mortality and morbidity and has a wide range of clinical impact from sudden death through to no symptoms.<sup>1</sup> There is growing equipoise over the value of treating smaller pulmonary emboli which are confined to subsegmental arteries when they are isolated, that is without a coexisting deep-vein thrombosis (DVT).<sup>2</sup> With the introduction of computed tomography pulmonary angiogram (CTPA), more PEs are being diagnosed but this is associated with a fall in case fatality, suggesting over-diagnosis.<sup>3</sup> Furthermore, the complication rates from anticoagulation treatment have increased by 80%, suggesting over-treatment.<sup>4</sup>

Computed tomography pulmonary angiogram imaging diagnoses more, and smaller, PEs than the older technology of ventilation/perfusion (V/Q) scanning. In a trial that compared these two scanning strategies, there were no recurrent VTEs during follow-up of patients whose initial V/Q scan was negative, compared with those whose CTPA was negative.<sup>5</sup> A meta-analysis of observational studies (i.e. without internal control groups) of treating or withholding treatment in subsegmental pulmonary embolism (SSPE) reported no clinically important difference between pooled incidences of recurrent VTE between these two treatment strategies.<sup>6</sup> More recent observational data of routine care for SSPE showed high complication rates of anticoagulation, but in patients where no anticoagulation treatment was given, this proved to be a safe in terms of

recurrent VTE.<sup>7</sup> An international survey of clinicians using clinical scenarios found up to 30% would not treat an isolated SSPE,<sup>8</sup> yet there have been no completed clinical trials to determine the benefits and harms of treating isolated SSPE.<sup>3</sup>

Current guidelines for the management of PE from the National Institute for Health and Care Excellence (NICE) (2020)<sup>1</sup> and from the British Thoracic Society (BTS)<sup>9</sup> recommend CTPA to confirm a diagnosis of PE; 9 studies in 648 patients showed sensitivity 80–100% and specificity 78–100%. However, there are concerns that over-diagnosis of SSPE may occur in CTPAs due to incorrect interpretation of small artefacts, with some case series showing that 10% of diagnoses made by general radiologists are not confirmed on review by specialist thoracic radiologists.<sup>10</sup> Furthermore, the extent to which SSPEs cause the initial presenting symptoms is uncertain as over 80% of patients with SSPE have abnormalities on CTPA that could also generate chest pain and chest pain.<sup>11</sup> The STOPAPE trial offers the first opportunity to determine the accuracy of initial reporting of SSPE in a large generalisable population, and also to develop diagnostic criteria for SSPE.<sup>3</sup>

The National Institute for Health and Care Excellence recommends treatment with anticoagulation for all PEs, initially with low-molecular-weight heparin (LMWH), changing to either a directly acting oral anticoagulant (DOAC) or vitamin K antagonist, for example warfarin for 3 months afterwards.<sup>1,12</sup> The BTS guidelines specifically considered risk stratification for outpatient management,<sup>9</sup> concluding that the pulmonary embolism severity index (PESI) is the most

appropriate for general use; in the validation studies, no patients in low or very low risk categories had recurrent VTE at 90 days.<sup>13</sup> Furthermore, blood levels of B-type natriuretic peptide and troponin both have prognostic utility in addition to demographic and physiological variables in PESI<sup>14</sup> and have been included in the European Society of Cardiology guidelines on risk stratification of PE.<sup>15</sup>

The only current guidance specifically for SSPE comes from the American College of Chest Physicians Antithrombotic Therapy for VTE, which recommends clinical surveillance, that is no intervention, as opposed to anticoagulation in patients who have a low risk of recurrent VTE and no concurrent DVT.<sup>16</sup> However, this was not based on evidence from randomised controlled trials (RCTs) but based on consensus opinion.

Hospital admissions for PE rose by 30% in the period 2008–12, and evaluation for PE often includes clinical decision rules, laboratory tests and several imaging modalities. The introduction of CTPA has significantly increased the rates of PE diagnosis but without any change in mortality from PE.<sup>17</sup> The increased sensitivity of CTPA and the increase in use of CTPA have led to an increase in diagnoses of SSPE and incidental PE.<sup>17</sup> This means that understanding the balance of benefit and harms of anticoagulating patients with SSPE is vital if we are to avoid the impact of over-diagnosis and minimise the side effects of over-treatment.<sup>3</sup>

COVID-19, the disease caused by the novel coronavirus SARS-CoV-2,<sup>18</sup> is associated with VTE in both acute and convalescent phases of the disease.<sup>19</sup> While the data in reviews cited above are from before the COVID-19 pandemic, the issue of anticoagulating isolated subsegmental pulmonary embolism (ISSPE) 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 pragmatic randomised trial of withholding anticoagulation in ISSPE compared with the usual care of full anticoagulation for at least 3 months would be the first study to adequately address the clinical and cost-effectiveness of these two treatment strategies recommended only by consensus in international guidelines.<sup>3</sup>

### **Justification for participant population**

There is equipoise about treatment with anticoagulation for patients with ISSPE who are low risk for recurrent VTE and do not require inpatient care. Suitability for ambulatory (i.e. outpatient) management is determined

by physiological measures (heart rate, blood pressure and oxygen saturation). A low risk for recurrent VTE is assessed by the absence of coexisting proximal DVT, active malignancy (defined below), pregnancy, thrombophilia and advanced renal failure.

Cohort studies show a higher rate of larger vessel PE than SSPE in patients with actively treated cancer<sup>20</sup> and, furthermore, the overall incidence of incidental PE in patients with active cancer may be lower than previously suspected.<sup>21</sup> Cancer is not a single condition however, and certain cancers are associated with higher rates of VTE.<sup>22</sup> Given that active treatment (chemotherapy and surgery) is the primary driver of VTE risk, there is no equipoise in these groups of patients and so we have used an exclusion criterion of active treatment of cancer in progress or planned. However, we have included patients who are not undergoing active treatment or have treatment planned. We have adopted the definition of active cancer used in the CARAVAGGIO trial,<sup>23</sup> that is cancer diagnosed within the past 6 months, anticancer treatment being given at the time of enrolment or during 6 months beforehand, or recurrent locally advanced or metastatic cancer.

The DiPEP study of PE in pregnancy demonstrated a small percentage of SSPE among confirmed diagnoses (3.7%).<sup>24</sup> Our preliminary work with obstetric physicians showed that the methodology for STOPAPE would need to be adapted for patients who are pregnant with SSPE. Firstly, we would need to rule out DVT with magnetic resonance venography (rather than Doppler ultrasound) to visualise iliac vein thrombosis. Secondly, the comparator treatment for equipoise would be prophylactic anticoagulation with LMWH, rather than no treatment (i.e. a different comparator arm than that used in STOPAPE). As a result, patients with pregnancy are excluded from the trial as they would have different treatment than the main group of recruited patients – a separate trial would be needed for pregnant patients with ISSPE.

Data from the International Severe Acute Respiratory and emerging Infections Consortium show that for patients with COVID-19, clinical deterioration requiring hospital admission occurs at a mean of 14.6 days after symptom onset with a standard deviation of 8 days.<sup>18</sup> Therefore, we planned to recruit patients who have most likely passed a phase of deterioration if they have ISSPE and COVID-19, using the inclusion criterion of at least 28 days after COVID-19 symptom onset.

### **Justification for trial design**

The design is a prospective randomised open blinded end-point trial, with individual level randomisation. We used an open design because we needed to understand

how the knowledge of a diagnosis of SSPE without taking anticoagulation affects health seeking behaviour. If the results of the trial were to support withholding anticoagulation, patients would know they have a diagnosis of SSPE and also know they are not taking anticoagulation. If we had designed a placebo-controlled trial, we would not be able to assess the wider impact of this management strategy in routine practice. An internal pilot will inform progression criteria to the main trial, and a nested study of diagnostic accuracy will ensure safety for participants.

As the intervention arm involved withholding treatment, the patient and research team were unable to be blinded from the treatment allocation (patients diagnosed with ISSPE during an inpatient stay or who require hospitalisation for reasons other than newly diagnosed ISSPE will continue to be treated as per standard of care including prophylactic anticoagulation for the duration of their inpatient stay). In order to minimise bias from an open-label trial, we planned to have a blinded end-point committee to adjudicate outcomes.

A nested study of all CTPAs was planned to compare the diagnosis of SSPE made by the reporting radiologists at trial sites with specialist thoracic radiologists. This would allow us to determine safety in the pilot phase (patients with larger than subsegmental clots could be rapidly identified), determine whether our assumptions about study power and sample size were accurate (e.g. patients with breathing artefact may be recruited instead of true SSPE), and develop guidance for acute reporting radiologists to improve accuracy of SSPE diagnosis.

An internal pilot phase was planned to evaluate recruitment rates, acceptability of the intervention (see [Internal pilot study objectives](#)) and programme reach.

## Aims and objectives

### Co-primary objectives

To determine if withholding anticoagulation in the treatment of ISSPE compared with at least 3 months of full anticoagulation is:

- non-inferior to standard anticoagulation therapy preventing recurrent VTE or death-related VTE
- superior for clinically relevant bleeding over 3 months.

### Secondary objectives

- To 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.<sup>25</sup>

- To 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.<sup>25</sup>
- To determine whether any radiological parameters correlate with clinical presentations or outcomes.<sup>25</sup>

### Economic aims and objectives

- An economic evaluation to assess the cost-effectiveness of no treatment versus full dose anticoagulation in patients with ISSPE.<sup>25</sup>
- An additional analysis, using decision modelling, to explore the cost-utility and cost-effectiveness of a pragmatic treatment policy (without expert thoracic radiological review) over a 52-week time horizon.<sup>25</sup>

### Mechanistic 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.

### Internal pilot study objectives

The internal pilot was planned for the first 12 months of recruitment with 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 (nested CTPA study).
4. To refine recruitment target based on misclassification rates.

The stop/go criteria are informed by the Medical Research Council Hubs for Trials Methodology Research workshop,<sup>26</sup> namely, 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 recruitment progression criteria would be based on rates per centre per unit time that can be extrapolated, rather than specifying an absolute number by a specific date.

**TABLE 1** RAG rating for internal pilot

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

RAG, red, amber, green.

Our first major progression criterion was the proportion of otherwise eligible patients excluded due to declining no treatment (green ≤ 30%, amber = 30–69%, red ≥ 70%). Our second criterion was recruitment rate. If sites, overall, recruited 1.5 patients per month on average, and each site has a target of 30 patients, each site would 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 per site per month, we would approach more sites to open, and if there were < 0.5 patients per site per month, this represents red (stop). We planned to collect safety data about VTE outcomes at 4 weeks after randomisation. The Database Monitoring Committee (DMC) safety data for trial progression also included SSPE diagnosis (see nested CTPA study) and recurrent VTE.

## Methods

### Trial design

STOPAPE was an investigator led, multicentre, prospective, randomised, controlled, open-label, pragmatic clinical trial with central, blinded, independent adjudication committee (CIAC) end-point 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 were randomised to either the control arm: full dose anticoagulant treatment as standard care, or the intervention arm: withholding anticoagulation. The choice of anticoagulant was determined by the responsible treating clinician as part of the standard of care. Pre-randomisation empirical therapeutic anticoagulation treatment was allowed for up to 7 days immediately prior to randomisation. For patients randomised to the intervention arm during hospitalisation (i.e. admitted to hospital at ISSPE diagnosis, or ISSPE diagnosis made during admission for another reason), standard general care of patients continued including prophylactic doses of anticoagulants during their inpatient stay.

The joint (multiple) primary outcomes of recurrent VTE and clinically relevant bleeding were 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 conducted 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 were performed by the local research team via telephone to complete case report forms and questionnaires. A window of ± 2 weeks was permitted for follow-ups.

A 12-month internal pilot was planned to 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 was planned to continue for the full duration of the trial.

### Trial setting

Recruitment was planned at approximately 50 trial sites from secondary care clinical settings of emergency departments, ambulatory care units, acute medical units and inpatient wards within National Health Service (NHS) hospitals in the UK. The recruitment rates were planned to be assessed during the pilot phase and additional sites recruited if required.

The trial schema is shown in [Figure 1](#) and schedule of events in [Table 2](#).

### Identification of participants

Potential trial participants were identified from participating centres, in the UK, by members of their normal clinical team via the following two routes:

- Adult patients presenting at secondary care clinical settings of emergency departments, ambulatory care units and acute medical units with acute symptomatic SSPE diagnosed with CTPA/CT thorax with IV contrast or while being treated as an inpatient.
- 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.

Inclusion criteria were:

- Age ≥ 18 years.
- Subsegmental pulmonary embolism diagnosed by the radiologist at the trial site by CTPA or CT thorax with IV contrast.



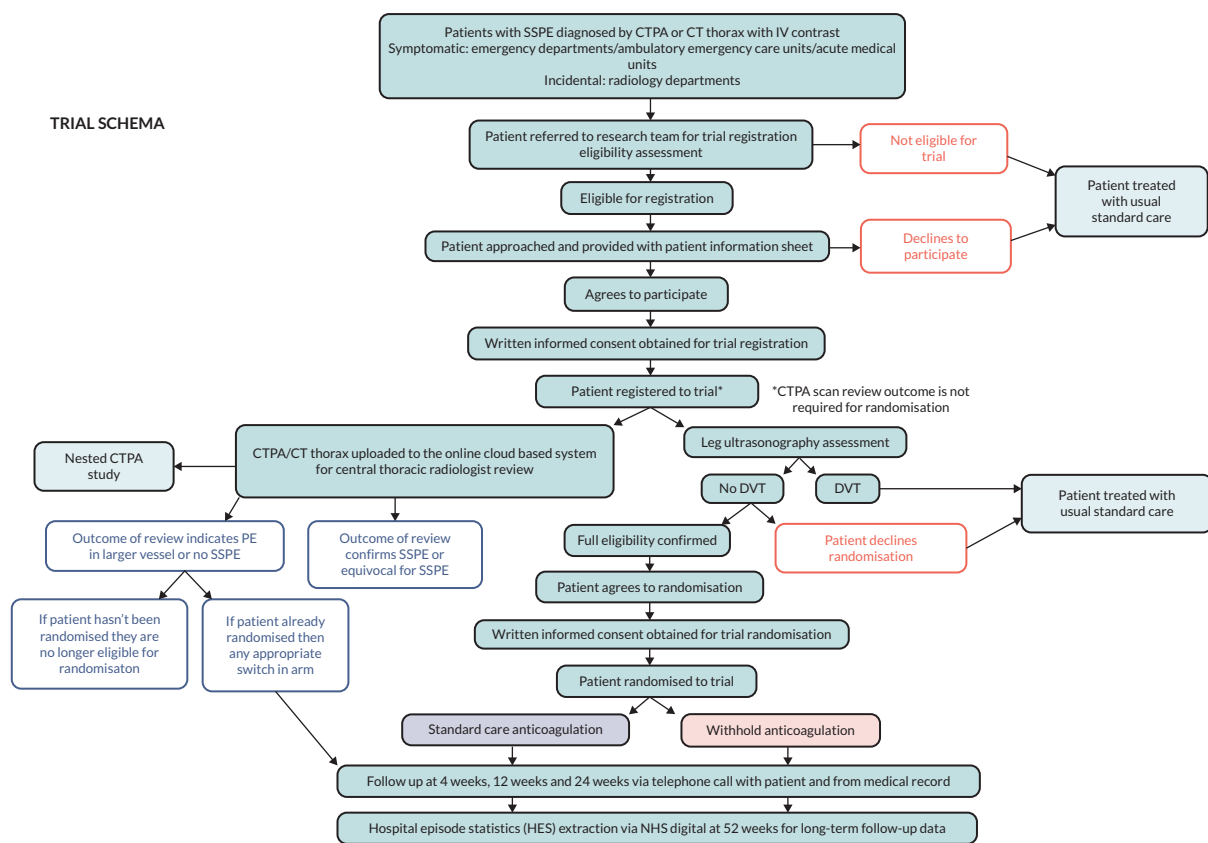


FIGURE 1 Flow of patients through the trial.

TABLE 2 Schedule of events

Activity	Acute care episode		Follow-up in community		
	Screening	Baseline	Telephone call 1	Telephone call 2	HES data requested by BCTU
	Day 1	Day 1	3 months	6 months	12 months
Medical history	X				
Medications	X		X	X	
Bloods – BNP and troponin	X				
Pregnancy test	X				
Physical exam	X				
Vital signs	X				
CTPA	X				
PESI	X				
Inclusion	X				
Exclusion	X				
Consent	X				
Leg Doppler		X			
Randomisation if leg Doppler normal		X			
EQ-5D-5L		X	X	X	
Adherence			X	X	

TABLE 2 Schedule of events (continued)

Activity	Acute care episode		Follow-up in community		
	Screening	Baseline	Telephone call 1	Telephone call 2	HES data requested by BCTU
	Day 1	Day 1	3 months	6 months	12 months
Fidelity of delivery of advice			X		
VTE recurrence			X	X	X
Bleeding events			X	X	X
Hospitalisation			X	X	X
Primary care usage			X	X	

BCTU, Birmingham Clinical Trials Unit; BNP, B-type natriuretic peptide.

- No evidence of proximal DVT based on lower limb ultrasonography or CT/MR venography.
- Heart rate (< 110 b.p.m.).
- Systolic blood pressure ( $\geq$  100 mmHg).
- Oxygen saturation ( $\geq$  90%).
- Patients can be recruited from acute assessment settings (ambulatory care or acute medical units, emergency departments). At the time of trial close, we applied for extension of inclusion criteria to include patients who developed ISSPE while being treated as an inpatient.
- Written, signed informed consent to the trial.

#### Exclusion criteria were:

- Requiring oxygen therapy.
- Hospital admission due to PE as the only acute medical problem.
- Less than 28 days since first symptoms of proven or clinically suspected COVID-19.
- Empirical therapeutic anticoagulation treatment for > 7 days 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 < 3 months.

- Pregnancy confirmed by positive pregnancy test or postpartum period or actively trying to conceive.
- Inability to comply with the trial schedule and follow-up.
- Participation in clinical trial of an investigational medicinal product (CTIMP) study.

In order to retain the pragmatic nature of the trial and to ensure generalisability of results, detailed diagnostic criteria for SSPE were not issued to general radiology departments. However, an audit of CTPA reports showed that in 15% of PE reports, the arterial distribution was not specified (a binary report is given of 'positive for PE'). Therefore, simple guidance was issued to radiology departments to specify arterial distribution of PE as either subsegmental (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).

#### Patient consent and additional screening tests

We operated a two-stage consent for the STOPAPE trial. The first stage of consent to register for the trial involved obtaining consent for patients with SSPE diagnosed via CTPA or CT thorax with IV contrast to have:

- Venous ultrasound of both proximal legs using compression ultrasonography from the sapheno-femoral junction to the popliteal fossa sampling at three points. If computed tomography/magnetic resonance (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.
- Computed tomography pulmonary angiogram or CT thorax imaging to be uploaded to the

online cloud-based system for central thoracic radiologist review.

Optional consent (i.e. not required to register or to be randomised into the main trial) was also 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.

Once eligibility was confirmed after the additional tests above, a further consent was then sought to participate in the main trial and be randomised to one of the two treatment strategies.

### Randomisation

Participants were randomised by computer at the level of the individual in a 1 : 1 ratio to either intervention (withhold anticoagulation treatment) or control arm (full dose anticoagulation treatment as standard of care).

A minimisation algorithm was 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)<sup>27</sup> (Yes/No)
- randomising site.

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

Randomisation was provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (available at <https://bctu-redcap.bham.ac.uk>). The online randomisation system was available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance.

The STOPAPE patient card was provided to the patient following randomisation. The patient card included a guide of symptoms related to a potential VTE recurrence, to prompt the patient to seek medical attention should they suffer any symptom in the list. 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 in the event of seeking healthcare during the trial follow-up period.

### Nested computed tomography pulmonary angiogram study

Expert thoracic radiologists based at Royal United Hospitals Bath NHS Foundation Trust reviewed all CTPAs for patients registered in the trial.

For patients found not to have SSPE on review of their CTPA, this finding was fed back to their clinical treating team who will make an assessment with regard 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 continued on the treatment arm allocated to them at randomisation, and they were followed up as per the trial protocol.

We planned a nested study of CTPAs within this trial for four purposes.

### Safety assessment during internal pilot study

Subsegmental pulmonary embolism 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:

1. artefact (e.g. from breathing) may be misinterpreted as a filling defect due to PE leading to a false positive diagnosis of SSPE
2. 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 did not 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.

### Reclassification rate from thoracic radiologist review

After 500 CTPA scans, we planned to determine the agreement between the thoracic radiologist review and the 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 Trial Steering Committee (TSC).

### Determine a set of diagnostic criteria for SSPE

At the end of the trial, we planned to draw up pragmatic guidelines through consensus meetings of the thoracic radiologists reporting the trial CTPAs. These would then have been 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.

### 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 misclassified as SSPE.

## Process evaluation

### Acceptability of the intervention

Our proposed research adopted 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. We believe our work meets this definition as we are assessing the impact of not anticoagulating (deductive work in the trial), while 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 would have been taken up in practice after the trial.

We planned to conduct interviews with up to 30 patients and 30 healthcare professionals (HCPs) to allow for data saturation. Face-to-face, telephone or video 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.

The topic guide was informed by existing literature on the reporting of,<sup>28</sup> attitudes to<sup>8</sup> and outcomes from incidental diagnoses.<sup>29</sup> We explored attitudes and practical issues surrounding patient understanding of PE and its management, tolerance of risk by patients and HCPs, preferences for content and delivery of information and any potential concerns. If having a PE and knowingly not being treated (which will be the 'real life' situation if the trial achieves its primary goal 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 were audio recorded and transcribed verbatim, prior to qualitative analysis using the framework method, as described in previous work.<sup>30</sup> 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.<sup>30</sup>

### Programme reach

Sites were 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.

### Treatment modification

There were four circumstances that may lead to treatment modification:

1. A PE is identified on expert radiologist review 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 co-ordinator 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 regard to treatment with anticoagulation as part of standard of care.
2. No SSPE is identified on expert radiologist review (i.e. the absence of any PE). This information will be communicated to the local research team via e-mail who will make an assessment with regard to treatment as part of standard of care.
3. 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.
4. Change to anticoagulation treatment strategy will occur if:
  - a. 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.
  - b. 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.

### Outcome measures

Outcomes were planned to be assessed by the CIAC.

#### Multiple (joint) primary outcomes

A composite of recurrent VTE (non-fatal) 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 would have been used by the CIAC:

1. Venous thromboembolism recurrence: Composite of non-fatal VTE (PE or DVT) recurrence and/or VTE-related death
2. Pulmonary embolism 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 SSPE 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 V/Q lung scan
  - symptoms suggestive of PE but with an inconclusive CTPA, CT thorax with IV contrast or V/Q scan for PE, and with evidence of a new DVT in the lower extremities by compression ultrasound or venography.
3. Deep vein thrombosis recurrence: Suspected (recurrent) DVT with one of the following findings:
  - abnormal compression ultrasound
  - an intraluminal filling defect on venography (CT/MR/invasive).

In keeping with other pragmatic treatment trials of patients with VTE where follow-up for recurrent VTE is included in the outcomes,<sup>31</sup> we did not mandate additional imaging to confirm the presence of recurrent VTE. Patients have already had the radiation exposure from one CTPA prior to recruitment to the trial, and it would be unethical to mandate additional imaging in situations where the treating clinician can make a clinical diagnosis of recurrent VTE. Pragmatically, if confirmatory imaging was not available, we determined a clinically relevant VTE recurrence in the intervention arm if full dose anticoagulation was started during the 3-month follow-up period. This is in keeping with other trials of anticoagulation strategies after acute PE to adjudicate VTE recurrence in the absence of imaging.<sup>31</sup>

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

1. Venous thromboembolism-related death:
  - pulmonary embolism 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).

2. Clinically relevant bleeding: Composite of major bleeding and clinically relevant non-major bleeding (CRNMB)
3. Major bleeding: Was defined by ISTH criteria:<sup>27</sup>
  - a. Fatal bleeding, and/or
  - b. 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
  - c. Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of 2 or more units of whole blood or red cells.
4. Clinically relevant non-major bleeding (CRNMB) was 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:
  - requiring medical intervention by a HCP
  - leading to hospitalisation or increased level of care
  - prompting a face-to-face (i.e. not just a telephone or electronic communication) evaluation.

### Secondary outcomes (reproduced with permission from Birmingham Clinical Trials Unit)

There were a number of secondary outcome measures from the time of randomisation including:<sup>25</sup>

- 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
- venous thromboembolism-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.

### Economic outcomes

1. Healthcare resource use: hospitalisations, bed days, unscheduled primary and secondary care visits for recurrent VTE, clinically relevant bleeding or potentially related symptoms.
2. Healthcare costs.
3. Health-related quality of life [EuroQol-5 Dimensions, five-level version (EQ-5D-5L) at baseline, 3 and 6 months].
4. Cost-utility at 6 months [cost per quality-adjusted life-year (QALY)] and cost-effectiveness at 12 months (cost per VTE avoided)

### Mechanistic (behavioural) outcomes

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

### Sample size and statistical analysis

#### Sample size

Given that both effectiveness and harm need to be considered, we decided on co-primary efficacy and safety outcomes. 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)<sup>32</sup> in the anticoagulation group to 3% in the no treatment group using a two-sample proportions test, 1244 patients (622 per group) were required [Stata 13 (StataCorp LP, College Station, TX, USA)]. We also aimed to detect whether no treatment is non-inferior to treatment 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)<sup>32</sup> and a non-inferiority margin of 2.5%, 1320 patients would be needed (Stata 13). Taking the largest of the two sample sizes computed, after allowing for 10% attrition, a total of 1466 patients (733 per arm) were required.

#### Statistical analysis

The primary comparison groups would have been composed of those treated without anticoagulation versus those treated with anticoagulation. All analyses would have been 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 that the multiple (joint) primary outcomes for recurrent VTE have a non-inferiority hypothesis, the decision for claiming non-inferiority would have been based on the results from the per-protocol set for this outcome.

For all outcome measures, appropriate summary statistics would have been presented by group (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). Intervention effects would have been adjusted for the minimisation variables listed in [Randomisation](#) and baseline scores where possible. Ninety-five per cent confidence intervals (95% CIs) and *p*-values would have been presented for all outcomes. No adjustment for multiple comparisons was made.

The multiple (joint) primary outcomes were both binary outcomes (i.e. yes/no) and would have been analysed using a generalised linear model (with binomial distribution and log link), adjusting for minimisation variables used in randomisation. Treatment effects would have been expressed as adjusted risk ratios with 95% CIs. If the model did not converge, then a Poisson regression model with log link and with robust variance estimation would have been used.<sup>33</sup> We also planned to 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) would have been fitted adjusting for minimisation variables.

#### **Reclassification rates from radiologist review**

Reclassification rates for all recruited patients would have been calculated with 95% binomial exact confidence intervals for (1) no SSPE diagnosis, (2) SSPE diagnosis or equivocal and (3) PE identified in arteries larger than subsegmental level. These rates would have been analysed without any adjustment. These reclassification rates by trial arm would have been included in the table of baseline characteristics. Variation between centres would have been 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 was required as a safety check to ensure randomised patients receive appropriate treatment, that is anticoagulation of patients with no SSPE randomised to anticoagulation could have been halted and anticoagulation of patients with PE, where required, could have been initiated.

#### **Subgroup analyses**

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

#### **Missing data**

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

#### **Interim analysis**

Interim analyses of safety and efficacy for presentation to the independent DMC would have taken place during the study. The committee met prior to study commencement to agree the manner and timing of such analyses and included the analysis of the primary and major secondary outcomes and full assessment of safety (serious adverse events) at least at annual intervals. Criteria for stopping or modifying the study based on this information would have been ratified by the DMC.

#### **Planned final analysis**

The primary analysis for the study was planned once all participants had completed the 12-week assessment and corresponding outcome data has been entered on to the study database and validated as being ready for analysis. This analysis would have included 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) would have been analysed separately once participants had completed the corresponding assessments.

#### **Health economics analysis**

An economic evaluation would have been undertaken to assess the cost-effectiveness of no treatment versus full dose anticoagulation in patients with ISSPE. The evaluation would have taken the form of an incremental cost-utility analysis to estimate cost per QALY over 6-month follow-up and a cost-effectiveness analysis to estimate cost per VTE avoided over 12 months using routine data sources. Both analyses would have been from a health services perspective.

#### **Data collection**

Data was collected on all related healthcare resource use, concentrating on VTE and bleeding events and investigation of symptoms. This concentrated 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 was 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, were sought for all healthcare resource use items.

In order to calculate QALYs, the EQ-5D-5L questionnaire was administered to participants at baseline, 12 and 24 weeks. The crosswalk value set was 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 would have been applied from the date of death to 6 months. Information on VTE recurrence (for the cost-effectiveness analysis at 12 months) was collected during the trial and planned from NHS digital records as previously stated.

### Analysis

Quality-adjusted life-years would have been calculated using responses to the EQ-5D-5L, using the area under the curve approach. Unit costs were applied to all healthcare resource use items, and mean resource use (for each category of healthcare usage) and mean total costs calculated for all trial participants. As cost data are likely to have a skewed distribution, the nature of the distribution of costs would have been explored, and if the data were not normally distributed, a non-parametric comparison of means (using bootstrapping) would have been undertaken. Multiple imputation would have been 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 time frame is not greater than 1 year. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial-based data themselves, the methods employed to analyse the data and the generalisability of the results to other settings. The base-case analysis will be ITT, with a per-protocol analysis conducted as a sensitivity analysis. Cost-effectiveness acceptability curves will also be produced to reflect the probability that the intervention will be cost-effective at different cost per QALY willingness to pay thresholds.

As we would have liked to explore the cost-effectiveness of a pragmatic treatment policy (i.e. without an expert thoracic radiological review), we proposed 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 would have considered bleeding and VTE outcomes only and related deaths. This modelling would allow us to explore the potential impact of this policy where those with the 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.

### Trial close

Due to the effect of the COVID-19 pandemic on wider research capability within the NHS, the STOPAPE trial closed due to low recruitment on 31 December 2022.

### Equality, diversity and inclusion

Due to very low recruitment, we were unable to assess how well subjects recruited to the STOPAPE trial represented the populations served at trial sites.

### Patient and public involvement

We worked with patient partners with lived experience of thrombosis as we designed and delivered the trial, including one funding co-applicant with lived experience of thrombosis. Patients were members of our Trial Management Group and have advised us throughout on trial set-up, patient leaflet design and wording, mechanisms to increase recruitment, interpretation of our qualitative data and ultimately supported the decision of premature cessation of the trial.

### Discussion

The STOPAPE trial closure leaves the question of clinical and cost-effectiveness of withholding anticoagulation in ISSPE unanswered in the NHS context. A similar trial testing withholding anticoagulation in ISSPE based in Switzerland remains open to recruitment across Europe, the SAFE-SSPE trial.<sup>34</sup> There are important methodological differences between STOPAPE and SAFE-SSPE, as SAFE-SSPE uses a placebo-controlled design testing one anticoagulant, rivaroxaban. While STOPAPE did not specify which anticoagulant to use, the majority of patients would be given a DOAC, that is the same class of drug as rivaroxaban.

While the blinded allocation of SAFE-SSPE has some advantages, the health seeking behaviour of patients who have been diagnosed with ISSPE, but know that they are not on an anticoagulant, cannot be assessed. This limits a cost-effectiveness assessment from their trial data as the likely rate of re-attendance during follow-up, were this



treatment strategy to be put into routine practice, could not be estimated.

Another key difference is trial size as while STOPAPE required over 1400 patients for a powered clinical outcome, SAFE-SSPE requires 276. STOPAPE was designed with 90% power for a non-inferiority margin for harm of a 2.5% increase in recurrent VTE events, whereas SAFE-SSPE has 80% power for a non-inferiority margin of 3.5%. Nevertheless, if SAFE-SSPE reaches its recruitment target, the primary outcome could still influence guidance.

We hope that the protocol detailed above will be useful for future trialists who test treatment strategies in ISSPE so that patients and their clinicians will have the optimal information for shared decision-making about treatment.

## Additional information

### Contributions of authors

**Daniel Lasserson** (<https://orcid.org/0000-0001-8274-5580>) (Acute ambulatory care clinician/chief investigator) drafted the initial manuscript, revised the manuscript and approved the manuscript.

**Pooja Gaddu** (<https://orcid.org/0009-0009-4980-1689>) (Trial manager) revised and approved the manuscript.

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### Data-sharing statement

There are no data to share for this protocol of the STOPAPE trial.

### Ethics statement

Research ethics approval was given on 18 September 2020 by Wales Research Ethics Committee 6. REC Reference: 20/WA/026.

### Information governance statement

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### Disclosure of interests

**Full disclosure of interests:** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/HRCW7937>.

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quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

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### List of abbreviations

BTS	British Thoracic Society
CIAC	central, blinded, independent adjudication committee
COVID-19	coronavirus disease 2019
CTPA	computed tomography pulmonary angiogram
DOAC	directly acting oral anticoagulant
DVT	deep-vein thrombosis
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
HCP	healthcare professionals

HES	hospital episode statistics
ISSPE	isolated subsegmental pulmonary embolism
ISTH	International Society on Thrombosis and Haemostasis
ITT	intention to treat
LMWH	low-molecular-weight heparin
PE	pulmonary embolism
PESI	pulmonary embolism severity index
RCT	randomised controlled trial
QALY	quality-adjusted life-year
SSPE	subsegmental pulmonary embolism
V/Q	ventilation/perfusion
VTE	venous thromboembolism

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