ISRCTN15645679 https://doi.org/10.1186/ISRCTN15645679

A trial to determine if withholding anticoagulation is not worse than standard anticoagulation therapy in the treatment of blood clots in the lungs

Submission date
24/09/2020

Recruitment status
Stopped

Registration date
23/10/2020

Overall study status
Stopped

Last Edited
28/02/2025

Condition category
Circulatory System

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Pulmonary embolism (PE) is a condition where blood clots cause a blockage of the blood vessels in the lungs. PEs are often caused by blood clots in the legs (deep vein thrombosis [DVT]) breaking off and travelling to the lungs. The symptoms of a PE depend on the size and location of the blood clot and can include breathlessness and chest discomfort. The standard treatment for PE includes anticoagulant drugs commonly referred to as “blood thinners”. Anticoagulants include a drug called warfarin, direct oral anticoagulant (DOACs) tablets, or a type of drug called “low molecular weight heparin” that is injected under the skin. These drugs stop new clots from forming while the body breaks down clots that may have already formed. A PE is diagnosed by a scan of the lungs, which is most commonly a computed tomography pulmonary angiogram (CTPA). This gives doctors images of the pulmonary arteries, a small PE in these blood vessels is called a “subsegmental pulmonary embolism” (SSPE).

As the CTPA scanning technology for PE has become more sensitive, smaller clots are being diagnosed. The CTPA scans are now able to detect smaller blood clots in blood vessels of the lungs; these clots are only a few millimetres in size and are the subsegmental pulmonary embolisms (SSPE).

The current standard treatment for pulmonary embolism is anticoagulant drugs. The aim is to reduce future blood clots (PEs and DVTs). It is unclear if the smaller clots, the SSPEs, require treatment with anticoagulation as these smaller PEs may be broken down by the body itself without the need for any treatment. Patients with SSPE who are treated with anticoagulation could be more at harm due to the risk of bleeding than they are helped by preventing future blood clots. This study will compare the outcomes among people with SSPE who have no anticoagulation treatment with those that are anticoagulated. The results of this will help us find out which is the best treatment plan for patients with SSPE.

Who can participate?

Patients aged 18 and older with a subsegmental pulmonary embolism

What does the study involve?
Participants are randomly allocated to either continue with standard anticoagulation or to have no anticoagulation treatment at all and are assessed after 12, 24 and 52 weeks.

What are the possible benefits and risks of participating?
Although participants may not receive any individual benefit from taking part in the study, the results may help to improve the treatment of patients with SSPE in the future. If the participant is allocated to have anti-coagulation treatment then the potential risks are the same as usual care which will have already been discussed with the participant. The participant may experience bleeding from the anticoagulants, which can be minor like a small nose bleed or sometimes more severe (where the participant might need to come to hospital to have a blood transfusion). If the participant is allocated to the no treatment group then they are less likely to have either bleeding as they will not be on anticoagulants, but they may get another blood clot in the lungs (PE) or legs (DVT). The participant will be given a patient card that explains the symptoms to look out for which should prompt them to seek healthcare in case they have had another PE or DVT.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
October 2019 to March 2024

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
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Study website
https://www.birmingham.ac.uk/stop-ape

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
280586

ClinicalTrials.gov number
NCT04727437

Secondary identifying numbers
CPMS 46105, IRAS 280586

Study information

Scientific Title
STOPping Anticoagulation for isolated or incidental subsegmental Pulmonary Embolism

Acronym
STOP-APE

Study objectives
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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/09/2020, Wales REC 6 (c/o Public Health Wales, Building 1, Jobswell Road, St David' s Park, SA31 3HB, UK; +44 (0)1267 61 1164; Wales.REC6@wales.nhs.uk), REC ref: 20/WA/0256

Study design
Randomized; Interventional; Design type: Treatment, Diagnosis, Drug, Management of Care

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Available at https://www.birmingham.ac.uk/stop-ape

Health condition(s) or problem(s) studied
Isolated or incidental subsegmental pulmonary embolism

Interventions
The design is a prospective randomised open blinded end point (PROBE) trial, with individual level randomisation. The researchers have used an open design because of the importance of understanding how the knowledge of a diagnosis of SSPE yet being sent home without anticoagulation affects health seeking behaviour. This would be the situation in real clinical practice, were the results of the trial to support no anticoagulation. If the researchers had opted for a placebo-controlled trial they would not be able to predict the impact of the management strategy in routine practice. An internal pilot (first 12 months of recruitment) will inform progression criteria to the main trial and a nested study of diagnostic accuracy will ensure safety for participants.

Process evaluation: The researchers will focus on acceptability and the potential consequences of a no treatment approach, through conducting interviews with a range of patients (n=30) and healthcare professionals (HCP; n=30). The topic guide will be developed drawing on existing literature on reporting of, attitudes to, and outcomes from incidental diagnoses. The researchers will explore attitudes and practical issues surrounding tolerance of risk by patients and HCPs. If having a PE and knowingly not being treated changes how one responds to transient symptoms (e.g. leg or chest pain) then a potential outcome may be excess scans and emergency presentations in the untreated group. Distress at receiving a diagnosis of VTE, particularly as an incidental finding 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. If patient/health care professional consents to this they will be interviewed by a researcher at a place that is convenient for them, either face-to-face in their own home or a hospital site, or by telephone /video call. The interview will take around one hour and will be tape recorded.

The potential for an increase in emergency presentations and diagnostic tests, may mean that there are additional NHS costs of no treatment, in spite of the cost savings in medication. Therefore, the researchers will undertake an economic evaluation to assess the cost-effectiveness of no treatment versus full dose anticoagulation in patients with isolated SSPE.

Nested CTPA study: 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 clot 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.

Estimated total trial duration is 54 months comprising of setup (6 months), recruitment (32 months), follow-up (12 months) and analysis/write up (4 months).

Patients will be approached by a member of the local research team who will introduce the trial to them and provide the patient information sheet for their consideration. Patients will then be asked to sign an informed consent form to consent to the screening procedures and for their CTPA imaging to be transferred for central radiology review.

Screening:
Patients who also have DVT as well as a SSPE cannot take part in the trial. If they have already had a computed tomography (CT) scan or magnetic resonance imaging (MRI) to confirm DVT status they will need to have a ultrasound scan of their legs to look for DVT.

Pregnant patients cannot participate in the trial therefore women likely to become pregnant will be required to take a pregnancy test.

As part of the eligibility assessment patients will be required to have a physical examination, they will have their medical history, vital signs and current medication assessed.

Patients will be asked to complete the EQ-5D-5L health questionnaire at baseline.

If following screening the patient is found to be eligible they will be asked if they are willing to be randomised and sign an additional informed consent form.

The patient will be randomized 1:1 to either anti-coagulation treatment for at least three months or no anti-coagulation treatment.

Follow up:
Primary outcome analysis at 3 months with patient follow up assessments via telephone at 30 days, 3 and 6 months post randomization.

At the 4 week assessment patients will be contacted to provide data on recurrent VTE.

At the 3 and 6 months assessment patients will be contacted and asked to complete the EQ-5D-5L health questionnaire. They will also be asked about symptoms relating to VTE, bleeding events, hospitalisations and bed days for VTE or bleeding, VTE recurrence, EQ-5D-5L, unscheduled visits to primary/secondary care for symptoms potentially related to VTE, whether anti-coagulation treatment has been stopped or started.

The researchers will use an efficient design for 12 month follow-up through targeted extractions from NHS Digital and consent to access medical records. These extractions will include VTE recurrence at 12 months, rate of new diagnosis of pulmonary hypertension or right ventricular dysfunction (coded in hospital or HES record), death due to PE/VTE.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
-

Primary outcome measure
Recurrent venous thromboembolism (VTE), death-related VTE, or clinically relevant bleeding, assessed using case report forms at the 12 and 24 week follow up timepoints

Secondary outcome measures

1. Reduction in recurrent VTE and bleedings event assessed using case report forms at the 12, 24 and 52-week timepoints
2. Reclassification rate of SSPE diagnoses made by acute reporting radiologists when reviewed by thoracic radiologists, recorded on a case report form at registration/randomisation
3. Healthcare resource use: hospitalisations, bed days, unscheduled primary and secondary care visits for recurrent VTE, clinically relevant bleeding or potentially related symptoms, measured using case report forms at the 12, 24 and 52-week timepoints
4. Healthcare costs assessed using case report forms at the 12, 24 and 52-week timepoints
5. Health-related quality of life measured using the EQ-5D-5L questionnaire at baseline, 12 and 24 weeks
6. Cost-utility (cost per QALY) measured using a case report form at 24 weeks and cost-effectiveness (cost per VTE avoided) measured at 52 weeks
5. Acceptability to patients and clinicians and health-seeking behaviours and health utilisation of a no anticoagulation treatment strategy for isolated SSPE, assessed through audio-recorded interviews which can occur at any point throughout the trial

Overall study start date
01/10/2019

Completion date
31/03/2024

Eligibility

Key inclusion criteria
1. Age ≥18 years
2. SSPE diagnosed by the radiologist at the trial site by CTPA or CT thorax with IV contrast
3. No evidence of proximal deep vein thrombosis on doppler ultrasonography or CT/MR venography
4. Heart rate <110 bpm
5. Systolic blood pressure ≥100 mmHg
6. Oxygen saturation ≥90%
7. Written signed informed consent to the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 1466; UK Sample Size: 1466

Key exclusion criteria
1. Indication for hospital admission
2. >7 days empirical anticoagulation treatment immediately prior to randomisation
3. <28 days since first symptoms of proven or clinically suspected COVID-19
4. Known stage 5 chronic kidney disease
5. 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
6. Patients with previous unprovoked PE, thrombophilia or requiring long term anticoagulation for another reason
7. Patients with a DVT / thrombus of an unusual site (e.g. upper limbs, associated with a line) that requires anticoagulation
8. Patients with active bleeding
9. 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
10. Pregnancy confirmed by positive pregnancy test or post-partum period or actively trying to conceive
11. Inability to comply with the trial schedule and follow-up
12. Participation in a CTIMP study

Date of first enrolment
08/04/2021

Date of final enrolment
30/06/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Airedale NHS Foundation Trust
Airedale General Hospital
Skipton Road
Steeton
United Kingdom
BD20 6TD

Study participating centre

Calderdale and Huddersfield NHS Foundation Trust
Trust Headquarters
Acre Street
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HD3 3EA

Study participating centre
Cardiff & Vale University LHB
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Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
Chelsea & Westminster Hospital
369 Fulham Road
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SW10 9NH

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
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Manchester
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M20 4BX

Study participating centre
NHS Forth Valley
33 Spittal Street
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United Kingdom
FK8 1DX

Study participating centre

Frimley Health NHS Foundation Trust
Portsmouth Road
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GU16 7UJ

Study participating centre
The Royal Wolverhampton NHS Trust
New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
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WV10 0QP

Study participating centre
NHS Lothian
Waverley Gate
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EH1 3EG

Study participating centre
North Bristol NHS Trust
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Southmead Road
Westbury-On-Trym
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BS10 5N

Study participating centre
North Tees and Hartlepool NHS Foundation Trust
University Hospital of Hartlepool
Holdforth Road
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TS24 9AH

Study participating centre
Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Rake Lane
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NE29 8NH

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Nottingham University Hospitals NHS Trust
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The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
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LS9 7TF

Study participating centre
Stockport NHS Foundation Trust
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University Hospitals Birmingham NHS Foundation Trust
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Whittington Health NHS Trust
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Study participating centre

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Study participating centre
Cambridge University Hospitals NHS Foundation Trust
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CB2 0QQ

Study participating centre

County Durham and Darlington NHS Foundation Trust
Darlington Memorial Hospital
Hollyhurst Road
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Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
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NE7 7DN

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
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Study participating centre
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Sponsor information

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Sponsor type
University/education

Website
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ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR128073

Results and Publications

Publication and dissemination plan
1. The study protocol and patient trial documents are available on the trial website: https://www.birmingham.ac.uk/stop-ape
2. Planned publication in a high-impact peer-reviewed journal

Intention to publish date
31/05/2025

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Other publications	Process evaluation	26/02/2025	28/02/2025	Yes	No