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THRIVE

THRomboprophylaxis in Individuals undergoing superficial endoVEnouos treatment (THRIVE): a multicentre assessor-blind randomised controlled trial

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Revision summary

Protocol version	Date	Revision summary
2.0	18 August 2023	• Removal of COVID-19 exclusion criteria • Removal of the ability to include patents lacking capacity to consent • Exclusion criteria amended to clarify specific exclusions to anticoagulants • Updated study flow chart in light of amended exclusion criteria • Clarification that the choice between LMWH or DOAC for the extended thromboprophylaxis arm is site-specific and dependent on local preference. • Dose modifications section added in line with the relevant SmPCs • Updated Reporting Procedures to clarify that all AEs should be recorded from the time of informed consent to study completion • Updated guidance regarding the recommendation to use effective contraception while taking DOACs • Correction of typographical errors
1.0	17/01/2023	N/A – original protocol

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SPONSOR

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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FUNDER

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (NIHR152877).

This protocol describes the THRIVE study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CHEERS	Consolidated guidelines for economic evaluation
CI	Confidence interval
CTU	Clinical trials unit
DMC	Data monitoring committee
DHRA tool	Department of Health Risk Assessment tool
DOAC	Direct-acting oral anticoagulant

DVT	Deep venous thrombosis
EQ-5D	Euroqol 5D instrument for measuring generic health status
GCS	Graduated compression stocking
HAT	Hospital-acquired thrombosis
ICC	Intraclass correlation
ICER	Incremental cost-effectiveness ratio
IMP	Investigation medicinal product
LMWH	Low-molecular weight heparin
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
PE	Pulmonary embolism
PPI	Patient and public involvement
PTS	Post-thrombotic syndrome
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RGIT	Research governance and integrity team
SAE	Serious adverse event
SAP	Statistical analysis plan
SVT	Society for Vascular Technology
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse event
TSC	Trial steering committee
VTE	Venous thromboembolism

STUDY SUMMARY

TITLE

THRomboprophylaxis in Individuals undergoing superficial endoVEnouos treatment (THRIVE): a multicentre assessor-blind randomised controlled trial

TRIAL DESIGN

Multi-centre, assessor-blind randomised controlled trial with a superiority comparison.

AIMS AND OBJECTIVES

To establish whether in patients undergoing endovenous varicose vein procedures:

1) A single dose of pharmacological thromboprophylaxis decreases the risk of VTE
2) An extended course of pharmacological thromboprophylaxis further decreases the risk of VTE
3) Pharmacological thromboprophylaxis is associated with an increased rate of bleeding events
4) Providing pharmacological prophylaxis is cost effective
5) There is a signal to suggest the pharmacological agent used affects the rate of VTE

OUTCOME MEASURES

Primary outcome

Imaging confirmed lower limb DVT with or without symptoms, or PE with symptoms within 90 days of varicose vein treatment.

Secondary outcomes

- Individual components of the composite outcome
- Comparisons of quality of life at 7- and 90-days post-procedure using the EQ-5D
- Mortality rates in each group
- Cost-effectiveness of providing pharmacological thromboprophylaxis
- Sub-group analyses of the following risk assessment tools: DHRA tool, Caprini score

POPULATION

Adults undergoing endovenous interventions for varicose veins under local anaesthesia.

PATIENT ELIGIBILITY

Inclusion criteria

- Adults (>18 years)
- Scheduled to undergo endovenous intervention of truncal varicose veins under local anaesthesia
- Treatment technologies including radiofrequency, laser, mechanochemical, foam sclerotherapy and cyanoacrylate glue

Exclusion criteria

- Clinical indication for therapeutic anticoagulation e.g., atrial fibrillation
- Previous personal or first-degree relative history of VTE
- Thrombophilia
- Female patients of childbearing potential who have a positive pregnancy test
- A history of allergy to heparins or direct oral anticoagulants
- A history of heparin-induced thrombocytopenia
- Inherited and acquired bleeding disorders
- Evidence of active bleeding
- Concomitant major health problems such as active cancer and chronic renal and/or liver impairment
- Thrombocytopenia (platelets less than 50 x 10^9/l)
- Surgery or major trauma in the previous 90 days
- Recent ischemic stroke in the previous 90 days

TREATMENT

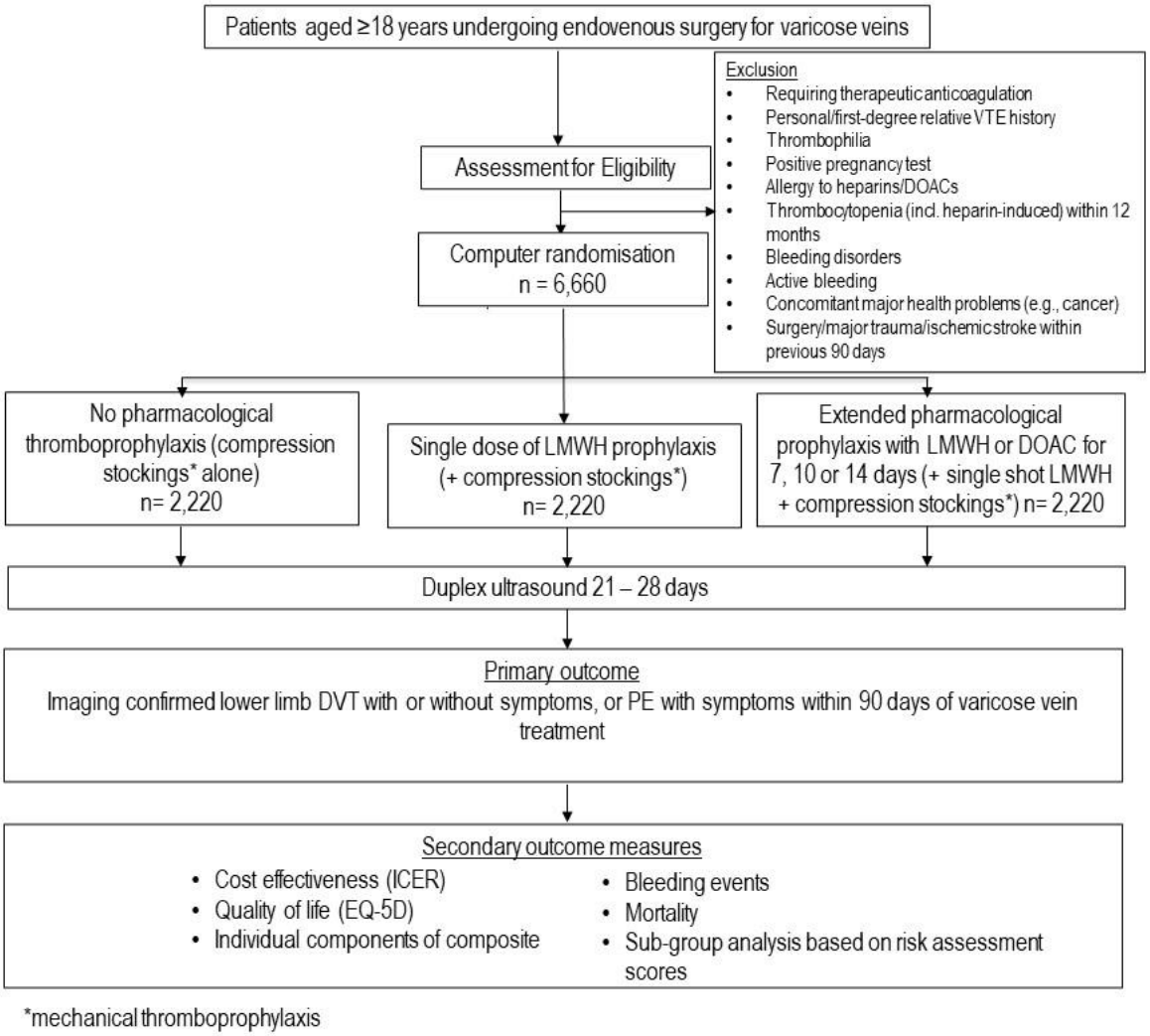
Intervention arms will consist of two different pharmacological thromboprophylaxis strategies in addition to compression therapy (as per local practice).

Control arm will consist of participants receiving compression therapy (as per local practice) alone.

DURATION

The total study duration will be 39-months in length.

Figure 1: Study Flow Diagram



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1. INTRODUCTION

1.1 Background

Varicose veins, also known as superficial refluxing veins, are common affecting up to 45% of the UK population (1). Varicose veins are known to reduce physical and mental health-related quality of life (2), with the burden of disease far greater when considering its contribution to chronic venous disease accountable for half (52%) of all those with leg ulcers (3,4). Endovenous surgery has a solid evidence base and is the recommended first choice management of symptomatic varicose veins in NICE guidelines [CG168] (5). This recommendation is mirrored in the European Society for Vascular Surgery Clinical Practice Guidelines providing a level I recommendation (6). Superficial endovenous interventions not only improve quality of life and healing of venous ulceration but are also cost saving to healthcare providers (7-10). Hence, endovenous interventions for varicose veins are commonly performed, with 26-30,000 procedures undertaken within the NHS annually (11) and with full adherence to NICE guidelines this is estimated to rise to 68,800. Additionally, an estimated 30-40,000 procedures are undertaken annually in the private sector.

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), and endothermal heat-induced thrombosis (EHIT) are known thrombotic complications of endovenous treatment and occur at a rate of up to 3.4% (according to our evidence synthesis). VTE is a significant cause of disability with subsequent societal economic consequences (12). Concerningly, VTE is often related to hospital encounters with hospital-acquired thrombosis (HAT), defined as the development of VTE within 90 days of a hospital episode, accounting for significant morbidity and mortality totalling 57 deaths per 100,000 admissions within the NHS (13). Morbidity following a DVT is substantial, with as many as 50% of patients developing post thrombotic syndrome (PTS) (14), which is characterised by chronic leg pain, oedema and skin changes (15). Crucially, the rate of venous ulceration with PTS is as high as 29% (16). PE is also associated with lifelong functional and psychological harm (17, 18) and ultimately the risk of death during the index event. The term EHIT is used to describe any thrombus within 4 weeks of endovenous ablation originating from the treated vein and protruding towards or into a deep vein and is comprised of 4 categories (9). EHIT classes 3 - 4 involve significant thrombus extending into and encompassing the deep vein (10) with consensus that these should be considered and treated as DVT (10).

Varicose vein procedures represent a unique VTE risk in comparison to other short-stay surgical procedures as illustrated by development of varicose vein intervention-specific risk assessment models (12) and a VTE rate comparable with major joint surgery (13). To contextualise this, comparable day-case surgical procedures such as inguinal hernia repair or laparoscopic cholecystectomy are associated with a VTE rate of 0.3% (19). Furthermore, clinicians lack confidence in current risk assessment tools (RATs) for this patient group. Both the Department of Health Risk Assessment (DHRA) Tool, utilised in the UK, and the Caprini

RAT, predominantly used across Europe and the US, have not been validated for patients undergoing varicose vein procedures. As a result of this, varicose vein intervention-specific RATs have been developed – however, these also lack validation. There is currently no consensus on which risk factors provide clinical indication for pharmacological thromboprophylaxis (20) or confer high-risk for VTE. In attempting to reduce the risk of VTE, pharmacological thromboprophylaxis at the time of the procedure, or extended for a duration post-operatively, is prescribed. National survey of vascular surgeons in Ireland revealed that 73.3% of practitioners routinely prescribe pharmacological thromboprophylaxis for varicose vein procedures, 71.4% and 28.6% of whom use a single dose of LMWH and an extended course, respectively (21). The remaining 26.7% of practitioners do not prescribe any form of pharmacological practice (21). These findings are mirrored by our own UK survey of current practice which revealed 47.4%% of practitioners prescribe a single dose of LMWH, 15.8% prescribe extended pharmacological prophylaxis and 36.8% do not prescribe any pharmacological prophylaxis. Pharmacological thromboprophylaxis could have clinical and cost benefit in preventing VTE however requires grade A evidence to support or refute this practice.

1.2 Rationale for the study

1.2.1 Review of existing evidence

There is currently no high-quality evidence to support current pharmacological thromboprophylaxis strategies for those undergoing endovenous treatments for varicose veins. International and national guidelines reflect the paucity of evidence in this area, with the European Society of Vascular Surgery guidelines providing a (IIa B) recommendation for consideration of individualised thromboprophylaxis strategies (6). This is exacerbated by NICE NG89 recommending that “prophylaxis is generally not needed for people undergoing varicose vein surgery” if they are assessed to be low-risk for VTE (22).

To review existing evidence in this area, a systematic review and meta-analysis of all study arms, including participants undergoing varicose vein procedures in addition to reporting the rate of VTE, was undertaken (PROSPERO: CRD42021274963, accepted Annals of Surgery). MEDLINE, Embase, the Cochrane Controlled Trials Register, Clinicaltrials.gov, European Union Clinical Trials, International Standard Randomised Controlled Trial Number Registry were searched from their inception without constraints. All published articles with 30 patients or more, in which patients underwent an endovenous procedure to treat superficial venous incompetence and reported the rate of DVT and/or PE were included. Primary outcome was the rate of VTE in those treated with pharmacological thromboprophylaxis in addition to mechanical thromboprophylaxis versus mechanical thromboprophylaxis alone. There were 221 trial arms included in the review. In respects to randomised trial arms, the rate of DVT with pharmacological thromboprophylaxis was 0.52% (95% CI 0.23-1.19%) (9 studies; 1095 patients), compared to 2.26% (95% CI 1.81-2.82%) (37 studies; 6951 patients) with mechanical prophylaxis alone. The rate of PE in randomised trial arms for pharmacological

thromboprophylaxis was 0.45% (95% CI 0.09-2.35) (5 studies, 460 participants) versus 0.23% (95% CI 0.1-0.52%) (28 studies, 4834 participants) for mechanical prophylaxis alone. Rate of EHIT grade 3 - 4 for pharmacological thromboprophylaxis vs. mechanical prophylaxis alone was 0.35% (95% CI 0.09-1.40) (3 studies, 822 participants) and 0.88% (95% CI 0.28-2.70%) (11 studies, 48,177 participants) respectively. Review of the literature failed to identify any high-quality evidence to support current pharmacological thromboprophylaxis strategies in this group of patients. Analysis for pharmacological thromboprophylaxis versus compression stockings alone revealed the rate of thrombotic complications to be 1.09% and 3.20% respectively. Although the analysis is intrinsically biased by study design, confounding by indication, and poor-quality evidence, this suggests a possible treatment effect.

1.2.2 Evidence justifying why this research is needed now

VTE is a serious preventable condition that has a significant impact on the lived experience of patients and has vast subsequent economic consequence for healthcare providers and society. Interventions for established acute DVT and preventing PTS are conflicting with little reassuring evidence to support their use (23), hence preventing VTE is a key priority (24). There are currently three thromboprophylaxis strategies used across the UK, with the trial arms of this application mirroring these practices (21). Our own aforementioned national survey of current practice reinforces these previous findings. Contradicting NICE guidelines, the routine use of pharmacological thromboprophylaxis for endovenous interventions has become prevailing practice, despite having no supportive evidence base. A recent survey of current practice suggests that clinicians are already prescribing Direct-acting Oral Anticoagulants (DOACs) for extended thromboprophylaxis which are associated with significant costs to the provider.

Research is needed now to guide this, potentially costly, unproven clinical indication. Furthermore, as current RATs have not been validated in this patient group, unbiased prospective evidence will help to guide risk-stratifying patients in the future. This research question also aligns with the James Lind Alliance priority setting for venous disease, further underlining the need for this trial.

2. STUDY OBJECTIVES

The aims of this study are to establish whether in patients undergoing endovenous varicose vein procedures:

1) A single dose of pharmacological thromboprophylaxis decreases the risk of VTE
2) An extended course of pharmacological thromboprophylaxis further decreases the risk of VTE
3) Pharmacological thromboprophylaxis is associated with an increased rate of bleeding events

4) Providing pharmacological prophylaxis is cost effective
5) There is a signal to suggest the pharmacological agent used affects the rate of VTE

2.1 Primary outcome

The primary outcome is imaging confirmed lower limb DVT with or without symptoms, or PE with symptoms within 90 days of varicose vein treatment.

2.2 Secondary outcomes

Secondary outcomes include:

- Individual components of the composite outcome
- Comparisons of quality of life at 7- and 90-days post-procedure using the EQ-5D
- Mortality rates in each group
- Cost-effectiveness of providing pharmacological thromboprophylaxis
- Sub-group analyses of the following risk assessment tools: DHRA tool, Caprini score

Table 1: Objectives and outcome measures

Objectives	Outcome measure	Measuring tool	Timepoint(s) of evaluation of this outcome
Primary objective	Lower limb DVT (with or without symptoms), or PE with symptoms	Duplex ultrasound, VTE outcome questionnaire (self-reported)	7 days post-procedure, 21 days post-procedure, 90 days post-procedure
Secondary objectives	Lower limb DVT with or without symptoms (individual component of the composite outcome)	Duplex ultrasound, VTE outcome questionnaire (self-reported)	7 days post-procedure, 21 days post-procedure, 90 days post-procedure
	PE with symptoms (individual component of the composite outcome)	VTE outcome questionnaire (self-reported)	7 days post-procedure, 90 days post-procedure
	Quality of life	EQ-5D	7 days post-procedure, 90 days post-procedure

	Mortality	Self-reported questionnaire, SAE reporting form (if applicable)	90 days post-procedure
	Cost-effectiveness of providing pharmacological thromboprophylaxis	ICER	90 days post-procedure
	VTE risk stratification using current risk assessment tools	DHRA tool, Caprini score	Baseline, Up to 90-days post-procedure

2.3 Safety outcomes

Safety monitoring includes any bleeding event. Major bleeding is defined as per the International Society on Thrombosis and Haemostasis standardised definition (25), which includes:

1. Bleeding into a critical organ
2. Bleeding into a surgical site requiring reoperation
3. Bleeding that leads to presentation to acute service

3. STUDY DESIGN

3.1 Type of study

This is a multi-centre, assessor-blind, randomised controlled trial with a superiority comparison using an intention-to-treat analysis. There will be an internal pilot of feasibility at 9 months and one interim analysis at the point of 50% mature primary outcome data. A total of 40 sites (6,660 participants) will be included in the study.

The duration of the study will be 39 months including 3 months completion of site setup, 27 months of recruitment, 3 months follow-up and 6 months for analysis and dissemination.

3.2 Blinding

Clinicians and participants will be aware of their treatment allocation. Assessors, being those who perform the duplex imaging and those responsible for collecting follow-up data at 7- and 90- days post-procedure, will be blinded to the treatment allocation.

3.3 Follow up

Participants will undergo a lower limb venous duplex ultrasound scan at 21 – 28 days post-intervention to identify asymptomatic DVT. This is timed to capture the peak onset of events which is at 3 weeks (26). Participants will be further followed up remotely by telephone or online at 7- and 90-days with an expected VTE capture >95% (26). Longer term follow-up may be considered with award from a subsequent project grant to assess long-term efficacy of the intervention, hence contact at a later point will be included in the consenting process.

3.4 Internal pilot

There will be an internal pilot to assess feasibility of recruitment over 9 months (beginning of month 7 to end of month 15) of recruitment to the trial, in which we will start recruiting from the (minimum) 40 centres. Site setup will be staggered over 9 months, i.e., 5 centres per month. The target number of participants by the end of the 9-month internal pilot is 1450 participants. For the internal pilot, we will use a stop-go criteria based on a Green-Amber-Red statistical approach, as follows:

Table 2: Internal pilot feasibility assessment at 9 months

Progression criteria	Red	Amber	Green
% Threshold	<10.9%	10.9 – 20.9%	≥21%
Trial recruitment (of eligible participants)	<15%	15 – 17.6%	≥17.6%
Recruitment rate / site / month	<5	5 – 7.1	≥7.2
Number of centres opened	<25	25 – 40	≥40
Total number of participants recruited	<725	725 – 1449	≥1450

4. PARTICIPANT ENTRY

4.1 Study setting and population

This trial will take place in hospitals/clinics, including both NHS and private providers, delivering endovenous varicose vein procedures under local anaesthesia. Recruitment centres will need to have a pre-existing practice prior to the trial to prevent any learning curve effects.

4.1.1. Inclusion criteria

- Adults (>18 years)
- Scheduled to undergo endovenous intervention of truncal varicose veins under local anaesthesia
- Treatment technologies including radiofrequency, laser, mechanochemical, foam sclerotherapy and cyanoacrylate glue

4.1.2. Exclusion criteria

- Clinical indication for therapeutic anticoagulation e.g., atrial fibrillation
- Previous personal or first-degree relative history of VTE
- Thrombophilia
- Female patients of childbearing potential who have a positive pregnancy test
- A history of allergy to heparins or direct oral anticoagulants
- A history of heparin-induced thrombocytopenia
- Inherited and acquired bleeding disorders
- Evidence of active bleeding
- Concomitant major health problems such as active cancer and chronic renal and/or liver impairment
- Thrombocytopenia (platelets less than 50 x 10^9/l)
- Surgery or major trauma in the previous 90 days
- Recent ischemic stroke in the previous 90 days

4.2 Identification and recruitment of participants

Research nurses (or other appropriately trained individuals) will identify potentially eligible participants utilising the scheduling lists for local anaesthetic varicose vein procedures, which can be generated at each site. The direct healthcare team may also identify eligible patients and enquire if they are willing to speak to the research team, after which the direct healthcare team will notify the research nurse or delegated individual. The research nurse or delegated individual may then approach the participant in person, via email, post, or telephone to enquire if they would be interested in participating in the trial and providing the Participant Information Sheet (in person or else via post/email). If necessary, non-English speaking participants will be provided with translations of study information and assistance from local NHS translation services will be obtained as per standard clinical practice. Therefore, potential participants will have had the opportunity to review the Participant Information Sheet prior to attending their local anaesthetic varicose vein procedure.

4.3 Informed consent

Research nurses (or other appropriately trained and delegated staff) will obtain informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the trial. The person taking consent will be GCP trained, suitably qualified, and will have been delegated this duty by the PI on the delegation log.

Participants may provide their consent to participate in the trial by one of the following methods:

- Electronic: Participants will receive a link via email to complete their consent electronically. This data will be automatically populated into the eCRF and thus negating the need for paper consent forms for participants who provide electronic consent.
- Written (in person, most likely on the day of, but prior to, their procedure): Participants will initial each statement on the consent form to confirm agreement. A copy of the consent form will be provided to the participant and the original consent form will be kept at site as source documentation. Consent data will be transcribed into the eCRF by the research nurse (or other appropriately delegated individual).

There is no defined timeframe between initial consent and the baseline visit, however confirmation that the participant's consent is still valid prior to randomisation will be required in the baseline CRF.

4.4 Participant withdrawal

4.4.1. Permanent discontinuation of study intervention

Participants may discontinue study intervention for the following reasons:

- At the request of the participant
- Adverse event / Serious Adverse Event
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

Participants may withdraw from individual aspects of the study (e.g., EQ-5D questionnaires) and will continue to be followed up, unless they have asked to be withdrawn from the study.

The trial will be continually monitored for safety and stopped at any time on the recommendation of the data monitoring committee (DMC) if there is marked clinical harm resulting in a lack of equipoise and it being deemed unethical to continue the trial.

4.4.2. Change of status

A change of status refers to discontinuation of study intervention and study procedures and can occur for the following reasons:

- Subject decision to withdraw
- Loss to follow-up
- Death

4.4.3. Procedures for withdrawal from study

Participants who meet the above criteria will be free to withdraw from the study without any effect on their usual medical care. The reason for their withdrawal will be recorded in the CRF/eCRF and medical records if offered. All randomised patients will be followed up for 90 days unless they specifically ask to be withdrawn as per intention to treat. In line with this analysis, patients lost to follow up or withdrawn from the study will not be replaced.

5. ASSESSMENT AND FOLLOW-UP

5.1 Day of surgical procedure (Day 0)

The baseline assessment will take place in the local recruitment sites by a member of the clinical trial team prior to the surgical procedure taking place. The following data will be collected during the baseline visit:

- Baseline demographic data
- Quality of life – EQ-5D at baseline
- VTE risk scores for the DHRA tool and Caprini risk assessment models

5.1.1 Randomisation

Participants (n = 6,660) will undergo 1:1:1 web-based randomisation to one of three thromboprophylaxis strategies prior to undergoing endovenous treatment. Randomisation will be conducted through an automated system linked to the eCRF setup via the Study Data Centre at the Edinburgh Clinical Trials Unit (ECTU), University of Edinburgh (a fully registered UKCRC Clinical Trials Unit, registration number 15).

Participants will be individually randomised to one of three thromboprophylaxis strategies prior to undergoing endovenous treatment:

1. Compression therapy* alone
2. Compression therapy* + single dose of low-molecular weight heparin (LMWH) at time of procedure
3. Compression therapy* + single dose of LMWH at time of procedure + extended prophylactic dose of anticoagulation with LMWH or Direct-Acting Oral Anticoagulants (DOAC)**

*compression bandaging, compression stockings or compression wraps aligning with standard of care

**7, 10 or 14-day course of prophylactic dose LMWH or DOAC as per local preference

As placebo will not be administered, participants and the research/clinical teams will be unblinded to the treatment strategy. However, the primary outcome assessments (duplex ultrasound scan and VTE outcome questionnaires) will be conducted by members of staff who will have no previous involvement with, or knowledge of, the participant's treatment allocation and as such will be blind to the randomised treatment strategy.

Participants will be considered enrolled in the study at the point of randomisation. For all participants enrolled in the study, their General Practitioner (GP) will be notified by sending a localised GP Enrolment Letter after the baseline visit has been completed.

5.2 Day 7 post-procedure (central follow-up)

Participants will be contacted by the coordinating centre at Imperial College London by telephone or online survey (link to survey sent via email or SMS) 7 days post-procedure. The following information will be collected and entered into the eCRF:

- VTE outcome
- Quality of life questions – EQ-5D
- Adverse events / safety outcomes

5.3 Day 21 post-procedure

Participants will undergo a lower limb venous duplex ultrasound scan at 21 – 28 days post-procedure. This scan is not routinely undertaken in the NHS at this time following intervention, however it is regularly used in the NHS to test for DVT. The intended purpose of this scan is to identify asymptomatic DVT. The ultrasound duplex scan will be conducted locally by an ultrasonographer, vascular scientist or other appropriately trained and delegated member of staff. The lower limb venous duplex ultrasound scan will be conducted as per standard practice for determining the presence or absence of DVT. Guidelines prepared by the Society for Vascular Technology (SVT) may be followed in conjunction with local protocols agreed between local sonography and vascular departments.

A standardised report of the duplex ultrasound scan will be supplied to the study research team for CRF/eCRF completion. The Trial Manager may follow up with the research team if these data have not been entered into the eCRF by day 28.

5.4 Day 90 post-procedure (central follow-up)

Participants will be further followed up centrally by the coordinating centre at Imperial College London by telephone or online survey (link to survey sent via email or SMS) at 90 days post-procedure. The following information will be collected and entered into the eCRF:

- VTE outcome
- Quality of life – EQ-5D
- Adverse events / safety outcomes
- Compliance with intervention
- Collection of resource use diary entries

- Mortality

5.5 End of trial

The end of the study is defined as the last participant's last visit.

6. DETAILS OF INTERVENTIONS

6.1 Interventions (IMPs)

6.1.1. Low-molecular-weight-heparins (LMWHs)

Single dose of LMWH

A single prophylactic dose of LMWH (e.g., dalteparin sodium, tinzaparin sodium, enoxaparin sodium) will be prescribed as per standard practice and administered in accordance with the relevant Summary of Product Characteristics (SmPC), manufacturer's recommendations and instructions for use.

Extended course of LMWH

The choice between LMWH or DOAC for the extended thromboprophylaxis arm will be site-specific and dependent on local preference. An extended duration of LMWH (e.g., dalteparin sodium, tinzaparin sodium, enoxaparin sodium) will be prescribed as per current local practice and administered in accordance with the relevant SmPC, manufacturer's recommendations and instructions for use. The duration of this must be at least 7 days, but can be in line with local practice i.e., between 7 and 14 days in duration.

6.1.2. Direct oral anticoagulants (DOACs)

The choice between LMWH or DOAC for the extended thromboprophylaxis arm will be site-specific and dependent on local preference. An extended duration of a DOAC (e.g., rivaroxaban, apixaban, dabigatran etexilate) will be prescribed as per current local practice and administered in accordance with the relevant SmPC, manufacturer's recommendations and instructions for use. The duration of this must be at least 7 days, but can be in line with local practice i.e., 7, 10 or 14 days.

6.2 Control

All participants will receive compression bandaging, compression stockings or compression wraps aligning with standard of care. Advice regarding wearing and removal of the stockings will be given to participants according to local practice.

6.3. Dispensing and accountability

Hospital stock will be used for all IMPs (LMWH/DOACs). Dispensing and handling of the investigation medicinal product (IMP) will be in accordance with the relevant SmPC and local SOPs.

6.4. Incidental findings

Incidental findings may be identified during study assessments, such as the duplex ultrasound scan. Such findings will be reported to the local clinical team and to the participant's GP.

7. STATISTICS AND DATA ANALYSIS

7.1 Sample size calculation

Best available evidence from 52 studies suggests that the rate of VTE (including DVT, PE, EHIT) after endovenous great saphenous vein interventions is 1.7% (1). However, this review did not investigate treatment effects. We conducted an analysis of 229 study arms, pooling 480,581 participants undergoing endovenous interventions, performing subgroup analyses for pharmacological thromboprophylaxis and compression therapy versus compression therapy alone, and asymptomatic screen detected versus symptomatic VTE (accepted with revisions, Annals of Surgery). Rates of DVT, PE, and EHIT 3 - 4 for those receiving pharmacological thromboprophylaxis (either single dose of LMWH or extended duration) were 0.521%, 0.216%, and 0.354%, respectively – giving a summary VTE rate of maximum 1.09%. Rates of DVT, PE and EHIT 3 - 4 for those receiving compression therapy alone were 2.264%, 0.058%, and 0.878%, respectively – giving a summary VTE rate of maximum 3.20%. Rates of EHIT and DVT are distinct in this calculation i.e., there is no overlap between groups, so double counting contributing events will be negligible. When analysing data from RCT arms alone, rates of DVT were similar. When interpreting these figures in the context of the wider literature, balancing this with confounding by indication and considering that the rate of VTE will be most likely lower in the compression therapy alone arm with exclusion of those at highest risk of VTE, we

anticipate that the true value lies closer to 1.0% in pharmacological thromboprophylaxis arm and 2.7% in compression therapy alone arm.

At 90% power and 2.5% alpha (to approximately control overall alpha to 5%, given each of two active drugs being compared with a common control) the study could detect a significant change of 1.7% in 90-day VTE. This base case would require 1554 participants per group. Allowing for 10% crossover (which can only be control patients, compression therapy only, receiving pharmacological thromboprophylaxis, since everyone receives compression therapy) increases this to 1919 per group.

Allowing for a single interim analysis at half time (50% randomised with 90 day follow up) for early stopping, for either futility or overwhelming evidence of efficacy analysis, inflates this to 1998 per group. If we then allow 10% for loss to follow up, the total sample, randomised 1:1:1 between all groups, becomes 6660 (or 2220 per group).

We will more accurately estimate the required sample size by simulation in a sample size re-estimation step at around 20% mature data, using Dunnett's 3-arm design with a common control, with correction, but for simplicity retaining the 1:1:1 equal randomisation; and inputting the observed missing data proportion at that stage.

7.2 Statistical analyses

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan (SAP), written by the study statistician and agreed by the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) before any unblinded data is seen. The main analysis will be according to the intention-to-treat principle and will compare the rates of VTE at 90 days, using a repeated measures analysis of variance (ANOVA), adjusting for any pre-specified strongly prognostic baseline covariates using a mixed effects logistic regression with study site as a random effect and pre-specified baseline covariates strongly related to outcome being used to adjust the estimated treatment effect. Repeated measures of the outcome will be measured at 7-14, 21 and 90 days.

The findings will be assessed for robustness against any missing data, first using multiple imputation assuming this data is missing at random and, if appropriate and the data permits, further sensitivity analyses will be attempted under any plausible missing data mechanisms not missing at random. Secondary outcomes will be analysed in a similar fashion with generalised linear models appropriate to the distribution of the outcome. Safety data will be summarised descriptively.

7.3 Sub-group analyses

Pre-defined sub-group analyses (primary outcome) include:

- Main treatment modality
- Sex
- Age
- BMI
- Smoking status

7.4 Interim analysis

We will also include a formal interim analysis with the possibility of stopping early for futility (no prospect of a clinically meaningful treatment effect), at the point of 50% mature primary outcome data. The data will be presented to the DMC to be assessed in the context of numbers needed to treat (NNT). Full details of the interim analysis and its statistical justification will be in the SAP and the DMC Charter.

7.5 Measurement of cost-effectiveness

Two health economic analyses will be conducted. The main analyses will be performed from the perspective of the NHS and Personal Social Services, with secondary analyses from a societal perspective.

1. A within-trial analysis will compare the two pharmacological thromboprophylaxis strategies to compression therapy (stockings or wraps) alone over the 90 days of the study. Resource use items associated with treatments in primary and secondary care will be collected using case notes and self-completed patient diaries, and costed using manufacturers list prices, previous literature, and national reference costs. Days off work and normal activities and other patient-related costs will be collected for a secondary analysis. EQ-5D will be collected at baseline and follow up, analysed using the NICE approved tariff.

2. If the trial indicates that pharmacological thromboprophylaxis could be an effective therapy a Markov (state–transition) decision model will be constructed to compare the cost-effectiveness of the two pharmacological thromboprophylaxis strategies and compression therapy alone over a longer time horizon. The time horizon of the model will be 2 years allowing extrapolation of sequalae of VTE events (such as PTS) over the longer term to quantify the impact of VTE on patient health via quality adjusted life years (QALYs) and resource use. A preliminary model has been constructed based on published literature to identify the key variables that would need to be collected during the clinical study, and to estimate the NNT to avoid one VTE, above which pharmacological thromboprophylaxis

would not be considered cost-effective at NICE thresholds. This model conservatively assumes 30% of patients with VTE develop PTS, with 3% of those having severe PTS.

The minimum cost of purchasing 10-days of thromboprophylaxis and providing allocated time for administration training equates to ~£63.13 (27, 28). Our model assumes cost of treatment of VTE, non-severe and severe PTS, as £451, £872 and £1,547 respectively and estimates of the respective utility decrement associated with symptomatic VTE and PTS are 0.8628, 0.7745 and 0.6752 respectively (29). Different durations of thromboprophylaxis will be modelled. These estimates will be reviewed at the time of the cost-effectiveness analysis, and any changes to these estimates will be updated.

Utilising a 2-year time horizon, incremental cost effectiveness ratio of pharmacological thromboprophylaxis in comparison to no pharmacological therapy would be £13,339 per QALY if the NNT were 59 participants (1/0.017). For pharmacological thromboprophylaxis to be cost-effective at a NICE willingness to pay threshold of £20,000 per QALY, the NNT would need to be below 80.

Main analyses will be undertaken from perspective of the NHS and Personal Social Services, with secondary analyses from a societal perspective. Health economic analysis will be conducted according to NICE reference case and CHEERS guidelines (30, 31), including sensitivity analyses and probabilistic sensitivity analyses. Results will be presented as estimates of mean incremental costs, effects, and incremental cost per QALY.

8. PHARMACOVIGILENCE

8.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not listed in the reference safety information (RSI) e.g., list of expected medical events within investigator's brochure for an unapproved investigational product or section 4.8 of the summary of product characteristics (SmPC) for an authorised product. When the outcome occurs, this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or **Serious Adverse Reaction:** any untoward medical occurrence or effect that at any dose:

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

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

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

8.2 Assessments of adverse events

Each adverse event will be assessed for severity, causality and expectedness by the local investigator, as described below.

8.2.1 Severity

All adverse events are assessed for severity by the delegated local investigator***.*** Please refer to the below table, along with the definitions provided in ***Section 8.1.*** when assessing and assigning severity of an adverse event.

Table 3: Severity definitions

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

8.2.2 Causality

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assessment of relationship of AE to the administration of IMP should be made by the responsible investigator based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Table 4: Causality definitions

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

If any doubt about the causality exists, the responsible investigator should inform the study coordination centre who will notify the Chief Investigators. Other clinicians may be asked to advise in some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

8.2.3 Expectedness

The reference document to be used to assess expectedness against the IMP is the SmPC. Please refer to the table below when assessing expectedness of adverse events.

Table 5: Expectedness definitions

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in section 4.8 of the SmPC
Unexpected	An adverse event which is not consistent with the information about the IMP listed in section 4.8 of the SmPC

8.3 Management of Adverse Events

8.3.1 Dose modifications

Renal function (creatinine clearance [CrCL]) should be assessed, as per standard practice, by conducting a blood test prior to (preferably within 7-days of) initiation of treatment with dabigatran etexilate, rivaroxaban, apixaban, and enoxaparin:

Dabigatran etexilate

- In patients with mild renal impairment (CrCL 50-≤80 mL/min), no dose adjustment is necessary.
- In patients with moderate renal impairment (CrCL 30-50 mL/min), the recommended dose of dabigatran etexilate is 300 mg taken as one 150 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment.
- In patients with severe renal impairment (CrCL 15-29 mL/min), treatment with dabigatran etexilate is contraindicated.

For further information, investigators should refer to the SmPC.

Rivaroxaban

- In patients with mild (CrCL 50-≤80 mL/min) or moderate (CrCL 30-50 mL/min) renal impairment, no dose adjustment is necessary.
- In patients with severe renal impairment (CrCL 15-29 mL/min), rivaroxaban should be used with caution. Use is not recommended in patients with creatinine clearance < 15 mL/min.
  Use is not recommended in patients with creatinine clearance < 15 mL/min.

For further information, investigators should refer to the SmPC.

Apixaban

- In patients with mild (CrCL 50-≤80 mL/min) or moderate (CrCL 30-50 mL/min) renal impairment, no dose adjustment is necessary.
- In patients with severe renal impairment (CrCL 15-29 mL/min), apixaban should be used with caution.

For further information, investigators should refer to the SmPC.

Enoxaparin sodium

- In patients with mild (CrCL 50-≤80 mL/min) and moderate (CrCL 30-50 mL/min) renal impairment, no dose adjustment is recommended. However, careful clinical monitoring is advised.
- In patients with severe renal impairment (CrCL 15-29 mL/min), the recommended dose of enoxaparin sodium is 2,000 IU (20 mg) SC once daily. Enoxaparin sodium is not recommended for patients with end stage renal disease (creatinine clearance <15 mL/min).

For further information, investigators should refer to the SmPC.

Individuals with known renal impairment should have their dosage adjusted as needed for the relevant IMP chosen. Alternatively, if renal impairment arises due to dehydration, a re-

evaluation may be re-assessed within 3-days of initiation of treatment. Local standard practice and clinician discretion is recommended in these instances.

8.3.2 Dose discontinuations

In the event of related serious adverse events (SAEs), the IMP should be withheld and only restarted if remedial action has been taken to mitigate risk to the participant and is in the participant's best interest in the investigator's judgment. This should be undertaken in discussion with the participant.

8.4 Reporting Procedures

All adverse events should be recorded and reported from the time of informed consent to study completion at 90-days. This includes AEs related to the endovenous procedure. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

8.4.1 Non serious AR/AEs

All such events, whether expected or not, should be recorded in the relevant CRF/eCRF within one month of the form being due.

8.4.2 Serious AR/AEs

Fatal or life-threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e., unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

8.4.3 SAEs

An SAE form should be completed within the eCRF within 24 hours of knowledge of the event. If the eCRF is unavailable at the time of reporting, a paper CRF should be completed and emailed to the study coordination centre within 24 hours of knowledge of the event. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

8.4.4 SUSARs

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

- Complete the SAE case report form & send it immediately (within 24 hours), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

OR

- Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

8.4.5 PREGNANCY

A woman is considered of childbearing potential while they are following menarche and until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

There is limited data on the use of apixaban, rivaroxaban, and dabigatran etexilate in pregnant women. It is therefore recommended that WOCBP should avoid becoming pregnant during treatment with a DOAC (rivaroxaban, apixaban, and dabigatran etexilate). WOCBP receiving

extended treatment of up to 14 days with a DOAC should use effective contraception (hormonal or barrier method of birth control; true abstinence) until treatment with the DOAC has ceased.

There is no evidence to suggest fetotoxicity or teratogenicity with enoxaparin, tinzaparin or dalteparin sodium. It is therefore not a requirement for WOCBP to use effective contraception during treatment with LMWH. It is at the discretion of the Clinician as to whether WOCBP should use an effective method of contraception while undergoing treatment with LMWH. Investigators should refer to the specific SmPC for further information regarding LMWH treatment during pregnancy.

If a female participant becomes pregnant at any point during the trial, a completed trial specific Pregnancy Reporting Form will be completed by the investigator at the site and emailed to thrivetrial@imperial.ac.uk (cc'ing in s.whittley@imperial.ac.uk). The study coordination centre should be notified immediately, but no longer than 24 hours after the investigator becoming aware of the pregnancy.

Participants will be given a copy of the THRIVE Pregnancy Monitoring Information Sheet and will be asked to sign the THRIVE Pregnancy Monitoring Consent Form agreeing for data on the pregnancy to be collected. With consent, additional information and any new developments regarding the pregnancy will be collected and reported to the Sponsor. Pregnancy should be followed to termination or term, at which point an updated form should be completed and forwarded to the study coordination centre. The study coordination centre will forward the form to RGIT. Any congenital malformations and/or birth defects are reportable as an SAE.

Contact details for reporting SAEs and SUSARs

RGIT.ctimp.team@imperial.ac.uk

Please send completed SAE forms to the following:

thrivetrial@imperial.ac.uk

s.whittley@imperial.ac.uk

a.h.davies@imperial.ac.uk

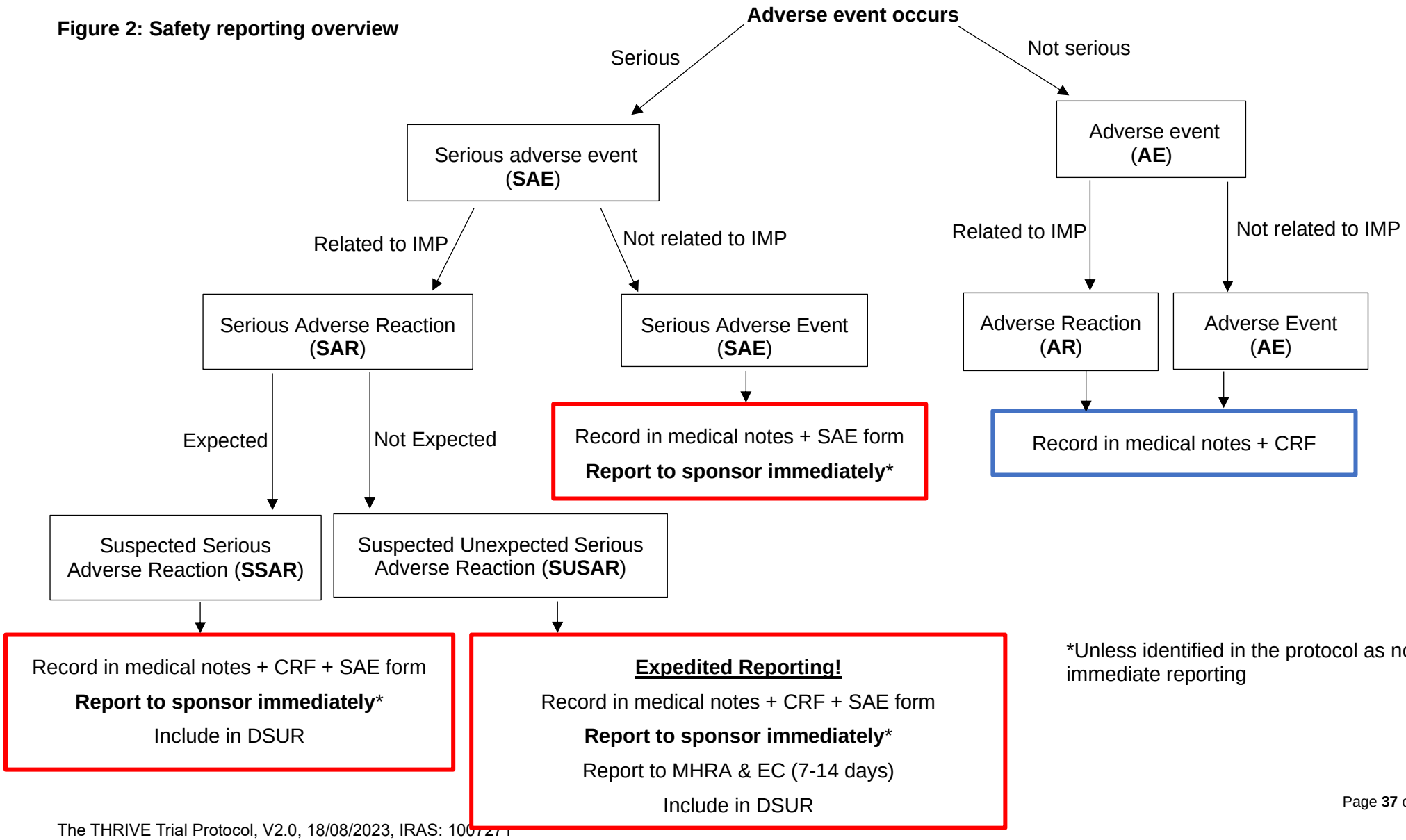
daniel.carradice1@nhs.net

Tel: +44 (0)203 311 7371 (Mon to Fri 09.00 – 17.00)

Completed Pregnancy Reporting Forms must be sent **within 24 hours** of becoming aware of the event to the sponsor

Email forms to: s.whittley@imperial.ac.uk and thrivetrial@imperial.ac.uk

Figure 2: Safety reporting overview



*Unless identified in the protocol as not requiring immediate reporting

9. REGULATORY ISSUES

9.1. CTA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: CTA 19174/0437/001-0001

9.2. Ethics approval

The Study Coordination Centre has obtained approval from the Brent Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

9.3. Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained (unless electronic consent has been obtained). The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.4. Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

As follow-ups will be performed by the coordinating centre (Imperial College London), patient identifiable data (name, address, email address and contact telephone number[s]) will be

stored on the REDCap database. This identifiable data will only be accessible by researchers at the local site (who will enter the data onto REDCap in the first place) and by the blinded assessors based at the coordinating centre who are responsible for conducting the follow-ups.

Data will be shared under the terms of the consent forms and will only be available to users under a data-sharing request. The Trial Manager will only have access to pseudonymised data on REDCap. Pseudonymised data will be transferred to the University of Granada for the purposes of conducting the cost-effectiveness analysis.

The investigator shall permit direct access to subjects' records and source documentation for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and RECs.

9.5. Indemnity

Imperial College London holds negligent and non-negligent harm cover for design and management of this study. Participating sites should provide insurance for the conduct of the study at the research site.

9.6. Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the trusts taking part in this study.

9.7. Funding

The National Institute for Health Research (NIHR) Health Technologies Assessment (HTA) are funding this study.

9.8. Audits and Inspections

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

10.DATA MANAGEMENT

10.1. Source data

Trial data will be generated from completion of clinical assessments, procedures, scans, patient questionnaires and diaries. Source data can be in the form of, but not limited to, patient medical records and study specific CRFs. This will be stored locally at the study centres in a secure space accessed only by authorised personnel. Data will be manually entered into the database by dedicated staff at the study centres (except for in the event of electronic consent, of which data will be directly populated in the eCRF by the participant). Follow up data will be entered directly into the eCRF either by the participant (electronic follow up) or the Trial Coordinator (telephone follow up). Quality of life surveys can be securely sent directly to patients for online completion to minimise burden to recruiting centres.

10.2. Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3. Database

The software model for the data entry processes and monitoring will be Research Electronic Data Capture (REDCap). Data will be entered into the REDCap database by site personnel. All data recorded in the eCRF will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a signature and date. Specific instructions and further details will be outlined in the CRF completion guidelines. A record of all access to data will be maintained by Data Management on the Data Sharing Log. The study database will be locked before the final analysis. After analysis, all study data will be stored and archived in accordance with the RGIT SOPs. Source data stored at study sites will be archived locally as per local SOPs. Edinburgh Clinical Trials Unit will be responsible for the database build and system validation.

During the running of the trial, Reporting Data Extracts (RDE) will be provided for safety reporting, DMC meetings, interim and final analyses, and other reporting periods as outlined in the SAP.

10.4. Data collection

Details of procedures for CRF/eCRF completion will be provided in a separate study manual. A formal Data Management Plan will be constructed to describe the procedures involved in the data management activities and processes for the study so that it is managed and maintained in accordance with the ICH-GCP guidelines, local Research and Governance Integrity Team (RGIT) standard operating procedures (SOPs), appropriate regulatory requirements and the study protocol.

10.5. Archiving

Source data stored at study centres will be archived locally as per local SOPs. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

11.STUDY MANAGEMENT

11.1. Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including the chief investigator, co-chief investigator, trial manager, trial statistician, two patient representatives, an independent chair and at least one other independent member. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter. A TSC meeting will be held at the start of the trial prior to commencement of recruitment and then on a 6-monthly basis.

11.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be convened including at least an independent Chair, independent clinician, and independent statistician. The role of the DMC is to oversee the safety of the trial participants, and the DMC will be the only oversight committee that sees unblinded data as the trial progresses, which they will keep in strict confidence. A DMC meeting will be held prior to first patient visit, following completion of the pilot study, and will then be held one month prior to each TSC meeting. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.3. Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and Trial Manager. The TMG will be responsible for day-to-day conduct of the trial, operational issues and reaching major landmarks for centre set-up and trial recruitment.

11.4. Trial monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

11.4.1 Data monitoring at local site

The trial coordinating centre will centrally review eCRF data for errors and missing key data points on an ongoing basis. Monitoring visits will be organised with the study sites to review the CRFs/eCRFs and source data. The frequency, type and intensity of monitoring visits will be detailed in a separate Data Monitoring Plan (DMP). The DMP will also detail the procedures for completion and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, the study coordinating team must be notified as soon as possible. Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

11.4.2 Risk assessment

A study-specific risk assessment will be performed prior to the start of the study by the study sponsor. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.5. Quality control and quality assurance

Quality Control will be performed according to Imperial College internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

12.PUBLICATION POLICY

Results will be published in high-impact journals alongside presentation at European and American vascular and haematology societies. This trial is supported by the following organisations who will play a key role in dissemination: Imperial College London, Hull York Medical School, NIHR, Thrombosis UK, Vascular Research UK, Circulation Foundation, Lindsay Leg Club, Vascular All Party Parliamentary Group, Vascular Society of Great Britain and Ireland, and Royal Society of Medicine. Dissemination of the trial results to the wider public will be through the Imperial College London website, Vascular Research UK YouTube Channel, the Department of Vascular Surgery Twitter page and other social media pages.

This trial will lead to publications in peer reviewed journals (protocol, main trial analysis, cost-effectiveness analysis, long-term efficacy analysis) alongside presentations at international academic conferences including European and American vascular, venous, general surgery and haematology societies. The results may influence recommendations for NICE guidelines in reference to endovenous procedures in the treatment for varicose veins and also VTE prevention in addition to recommendations European Society for Vascular Surgery guidelines on chronic venous disease. Furthermore, the cost-effectiveness information may guide clinical commissioning groups and NICE in the provision of thromboprophylaxis strategies. From a wider scientific perspective, the trial will lead to a greater understanding of the role of VTE prevention strategies in patients undergoing endovenous treatment of truncal varicose veins and will likely stimulate updates to systematic review of literature, meta-analyses and guidelines.

Through collaboration with the following organisations: Circulation Foundation, Legs Matter, Thrombosis UK, Lindsay Leg Club Foundation and Vascular Research UK patient educational resources will be developed, and the results will disseminate to patients and the wider public. For patients undergoing varicose vein procedures, by improving our understanding of the risks of VTE, it will facilitate the creation of improved education resources allowing practitioners to better communicate with patients.

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14.APPENDICES

14.1. Appendix 1: Summary of investigations, treatment and assessments

Assessment	Day of assessment				
	Pre-surgical procedure	0	7*	21	90*
Screening	X				
Informed consent	X				
Inclusion/exclusion criteria	X				
Demography	X				
Medical history	X				
Concomitant medications	X	X			
Vital signs		X			
Dispense resource use diary		X			
EQ-5D		X	X		X
Randomisation		X			
Compression stockings provided		X			
LMWH administered[1,3]		X			
Extended pharmacological thromboprophylaxis provided[2,3]		X			
GP letter sent		X			
Endovenous surgery for varicose veins		X			
Duplex ultrasound scan				X	
VTE outcome (self-reported questionnaire)			X		X
Collect resource use diary					X
Adverse events / safety outcomes			X		X

*Conducted centrally

[1]Participants randomised to single dose of LMWH and extended duration of anticoagulation (+ single dose LMWH at time of procedure) arms

[2]Participants randomised to extended course of anticoagulation (+ single dose LMWH at time of procedure) only

[3]As per standard practice, renal function should be assessed prior to initiation of treatment with dabigatran etexilate, rivaroxaban, apixaban, and enoxaparin sodium. Investigators should refer to the relevant SmPC for dose modifications requirements, if required.