Imperial College London

Examining the benefit of graduated compression stockings as an adjunct to low dose low molecular weight heparin in the prevention of venous thromboembolism in elective surgical inpatients identified as moderate or high risk for venous thromboembolism – a multi-centre randomised controlled trial

Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery - GAPS Trial

Version 3.0 03/12/2018

MAIN SPONSOR: Imperial College London, Sponsor Reference: 15HH3063

STUDY COORDINATING CENTRE: Imperial College London

ETHICS COMMITTEE: London City Road & Hampstead NHS Research Ethics Committee Ref: 16/LO/0015

This project is funded by the National Institute for Health Research HTA (project number 14/140/61)

PROTOCOL APPROVAL

Examining the benefit of graduated compression stockings as an adjunct to low dose low molecular weight heparin in the prevention of venous thromboembolism in elective surgical inpatients identified as moderate or high risk for venous thromboembolism – a multi-centre randomised controlled trial

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

Professor Alun H Davies		3rd Dec 2018
Chief Investigator		Date
Professor John Norrie		3rd Dec 2018
Individual Responsible for Statistical Review	Signature	Date

Revision History

Version	Date	Reason for update
V3.0	03/12//2018	Terminology has been made consistent throughout the document: the Study Coordination Centre referring to Imperial College London and Clinical Trials Unit referring to Centre for Randomised Trials Aberdeen. 'Moderate risk' has replaced all instances of 'medium or intermediate risk' throughout the document The flow chart has been updated to add secondary outcome text 'overall mortality' which was not included in the original flow diagram Section 7.4 has been updated to reflect changes to the statistical analysis based on the low number of events reported throughout the study Addition of wording to explain that a time only no cost extension of 12 months was approved by the Funder Tightening of the terminology- the word composite outcome has been removed to accurately reflect the outcome measure being used. A sentence has been added to say that data collected by the trial team for the duplex scan outside of the 14-21 day window will be recorded by the trial coordinating centre and analysed Addition of Appendix 3 summarising the rationale for the statistical changes made to the study
V2.1	17/03/2016	To change wording from 'post-randomisation' to 'post-surgery'
V2.0	04/02/2016	Changes made from v1.0 to submit to REC for approval.
V1.0		N/A- draft version of the protocol not submitted to REC

Study Management Group

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Clinical Queries

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Sponsor

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

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This project is funded by the National Institute for Health Research Health Technology Assessment (HTA) Programme (project number 14/140/61)

This protocol describes the **Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery (GAPS) trial**. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition, or subsequent). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
CTU	Clinical Trials Unit
DVT	Deep Vein Thrombosis
EQ-5D	EuroQuol 5 Domain
GAPS	Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery
GCP	Good Clinical Practice
GCS	Graduated Compression Stockings
LMWH	Low Molecular Weight Heparin
HTA	Health Technology Assessment
iDMC	Independent Data Monitoring Committee
IPC	Intermittent Pneumatic Compression
ISF	Investigator Site File
IT	Information Technology
ITT	Intention to Treat
IVC	Inferior Vena Cave
JCRO	Joint Compliance Research Office
LPLV	Last Patient Last Visit
NICE	The National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research

PI	Principal Investigator
PE	Pulmonary Embolism
PROM	Patient Reported Outcome Measure
RCT	Randomised Controlled Trial
R&D	Research & Development
REC	Research Ethics Committee
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
SCC	Study Coordinating Centre
TMF/SMF	Trial/Study Master File
TSC	Trial Steering Committee
VTE	Venous Thromboembolism

KEYWORDS

Surgery, Venous Thromboembolism, Deep Vein Thrombosis, Thromboprophylaxis, Graduated Compression Stockings, Pulmonary Embolism

TRIAL SUMMARY

TITLE **Graduated compression as an Adjunct to Pharmacoprophylaxis in Surgery (GAPS) Trial**

DESIGN Multicentre-centre, UK-wide, open, randomised controlled trial. Non-inferiority, group sequential trial design.

AIMS The aim is to determine whether low dose low molecular weight heparin (LMWH) alone is non-inferior to a combination of graduated compression stockings (GCS) and low dose LMWH for the prevention of venous thromboembolism (VTE) adult elective surgical inpatients identified as being at moderate and high risk for VTE. The primary clinical objective is to compare the VTE rate in elective surgical inpatients receiving GCS and LMWH, compared with LMWH alone.
Other objectives include:

- To profile the adverse effects of GCS and LMWH anticoagulation in this context.
- To support future guidance and policy in VTE prevention.

OUTCOME MEASURES

Primary
VTE within 90 days {duplex ultrasound-proven new lower-limb DVT up to 90 days post-surgery (symptomatic or asymptomatic) and symptomatic PE (imaging confirmed) up to 90 days post-surgery}
Secondary
• Quality of life – EQ5D
• Compliance with stockings and LMWH
• Overall mortality
Safety
• GCS-related complications
• Bleeding complications
• LMWH allergy

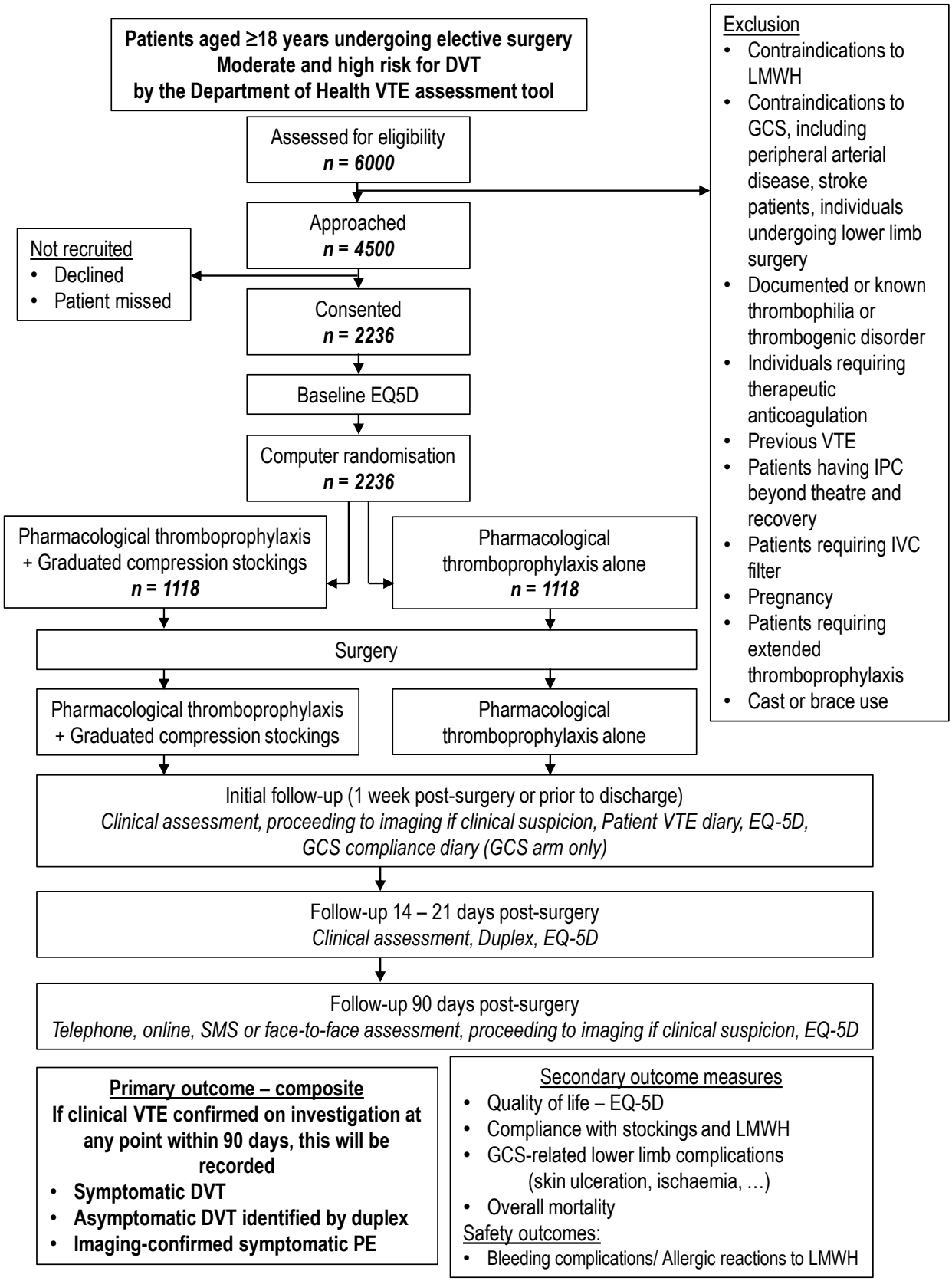
POPULATION Elective surgical inpatients assessed as being at moderate or high risk of VTE according to the widely-used UK Department of Health VTE Risk Assessment for Venous Thromboembolism (based upon the NICE recommendations).

ELIGIBILITY

Exclusions
• Contraindications to LMWH/GCS
• Documented or known thrombophilia/thrombogenic disorder
• Requiring therapeutic anticoagulation
• Previous VTE
• Having intermittent pneumatic compression beyond theatre and recovery
• Patients requiring IVC filter
• Pregnancy
• Need extended VTE prophylaxis
• Cast/brace use

DURATION 48 months

REFERENCE DIAGRAM (BASED ON ORIGINAL SAMPLE SIZE CALCULATION)



1. INTRODUCTION

1.1 BACKGROUND

At present, in the UK, NICE recommends that all surgical patients who are deemed at moderate or high risk for venous thromboembolism (VTE), in whom there are no contraindications, should receive both pharmacological thromboprophylaxis and mechanical thromboprophylaxis in the form of graduated compression stockings (GCS) (1). Are the risks and costs associated with GCS medically or health-economically justified for DVT prevention in moderate and high risk elective surgical inpatients receiving LMWH prophylaxis? VTE encompasses a range of clinical presentations, including pulmonary embolism, and is an important preventable cause of death in hospitalized patients (2). Furthermore, symptomatic venous thrombosis carries a considerable burden of morbidity, sometimes long-term due to chronic venous insufficiency. This in turn can cause venous ulceration and development of a post-thrombotic limb (characterised by chronic pain, swelling and skin changes), which impacts on quality of life and consumes 2% of the NHS budget (1). Treatment of non-fatal symptomatic VTE and related long-term morbidities is associated with a considerable cost to the health service (1). Reducing VTE is a clinical priority within the NHS (1), particularly amongst individuals undergoing surgery where the risks are significant. The risks need to be balanced against the risks of preventative measures, both mechanical and pharmacological. The evidence base supporting NICE's recommendations for the use of GCS for VTE prevention in the UK has recently been challenged (3,4). The main reasons include:

- The Cochrane Review (5) which showed a benefit for GCS included small trials (18-152 patients).
- Stocking manufacturer support of the included trials.
- Exclusion of two large trials from the Cochrane Review (in stroke (6) and orthopaedic patients (7)), one for being too specific a population, the other for being too pragmatic; neither of these studies supported the use of GCS (3).

Additionally, systematic review and meta-analysis data has highlighted the current lack of evidence for the additional benefit of GCS over and above the benefit of LMWH in surgical patients (8,9); further trials to address this matter have been called for (3).

If GCS were to offer a reduction in VTE risk over and above that afforded by LMWH, these benefits need to be weighed against a number of risks and disadvantages of GCS; these include (but are not limited to) discomfort, ischemia, rolling down and creating a constrictive band, blistering, cost, compliance issues, and the requirement for staff to assist patients in wearing. Indeed a large RCT in patients with stroke showed that routine care plus thigh-length GCS did not confer significantly more protection against VTE than routine care alone and was associated with significantly more harm (6). As a result, their use has already been limited in certain contexts. In addition to efficacy and risks, patients' experience may be impacted upon by the use of GCS. The annual cost of purchasing and applying GCS stockings to surgical inpatients assessed as being moderate or high risk for VTE in England is estimated at £63.1 million. This estimate does not include the further cost and time implications related to the identification and management of complications related to GCS. It is important that cost-effectiveness of this health technology is determined to ensure that NHS resources are correctly distributed. The results of this trial will support future guidance and policy in VTE prevention.

1.2 EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW

Recent meta-analysis considering VTE rates in surgical patients receiving pharmaco-prophylaxis and GCS compared with pharmaco-prophylaxis alone (8), while containing a number of methodological shortcomings, concluded that evidence concerning "adding compression to anticoagulation reduces VTE risk is of low quality." To address some of the shortcomings, a systematic review has been undertaken aiming to summarise and assess the quality of existing evidence concerning the benefits of GCS in addition to prophylactic dose pharmaco-prophylaxis in inpatients across all surgical specialties, including orthopaedics (9). Inclusion criteria were: RCTs published within the last 10 years, surgical inpatients, a study arm examining prophylactic dose pharmacological thromboprophylaxis alone (including low molecular weight heparin, fondaparinux, or unfractionated heparin), a study arm examining prophylactic dose pharmacological thromboprophylaxis in conjunction with GCS, and outcome of VTE. A heterogeneity analysis was conducted concerning rates of VTE in the included study arms. 1025 articles were screened of which 27 RCTs were included (7,11-33). Six RCT study arms included patients with GCS in conjunction with prophylactic dose pharmacological thromboprophylaxis, whilst 22 RCT study arms included patients treated with prophylactic dose pharmacological thromboprophylaxis alone. Only one RCT had both its' study arms included in the systematic review. Total number of patients that received prophylactic pharmacological thromboprophylaxis alone was 12,481. Of these patients, 1,292 (10.4%) suffered VTE. The total number of patients that received GCS in

conjunction with prophylactic pharmacological thromboprophylaxis was 1,283. Of these patients, 75 had VTE (5.8%). Heterogeneity analysis demonstrated that the results of included study arms were significantly heterogeneous, precluding calculation of the usual meta-analytic summary estimates. The additional benefit of GCS to pharmacological thromboprophylaxis in surgical inpatients is not clear based on existing data. There is sufficient uncertainty to conduct a trial to examine whether GCS further reduces VTE incidence in surgical patients receiving prophylactic dose LMWH. Overall, systematic review and meta-analysis data have highlighted the current lack of evidence for the additional benefit of GCS over and above the benefit of LMWH in surgical patients (8,9); further trials to address this matter have been advised (3).

The VTE risks need to be balanced against the risks of preventative measures, both mechanical and pharmacological. Patient experience of stockings in the 'real world' is poor. In particular, the use of GCS is known to be associated with a number of undesired effects for the patient, including discomfort, ischemia, rolling down and creating a constrictive band, blistering. Previously, national stroke guidelines on VTE prevention extrapolated from small trials showing that GCS reduce the risk of DVT (6). The large randomised CLOTS 1 trial found no significant difference in symptomatic or asymptomatic femoro-popliteal DVT in individuals admitted to hospital with acute stroke (6). Importantly, CLOTS 1 also identified that skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to GCS than in those allocated to avoid their use (6). The widespread use of GCS has already been challenged and (3,4) limited in certain contexts, for example stroke patients. In view of the efficacy of GCS as an adjunct to LMWH in VTE prevention in surgical patients being poorly defined, GCS being responsible for complications and the enormous healthcare costs associated with their use, sufficient uncertainty is achieved to conduct a trial to examine whether GCS further reduces VTE incidence in surgical patients receiving prophylactic dose LMWH. There remains (despite guidelines) some variation in practice across the UK. We are aware of one centre, Salisbury District Hospital, which over the past three years has adopted a pharmacological prophylaxis policy (without GCS) that has been used for high risk surgical patients (n=249). In Salisbury, the incidence of hospital-acquired thrombosis is 1.3-2.9 per 1000 admissions, which is comparable to centres elsewhere in the UK (Kings College Hospital 3.83 per 1000 admissions) (34). As such, both patients and the health service stand to benefit from evidence to support the safe rationalisation of the use of GCS as a health technology. In this trial, all participants will receive effective thromboprophylaxis in the form of low dose (prophylactic rather than therapeutic) LMWH. This pharmacological strategy is used exclusively for groups where GCS are already contraindicated (for example peripheral arterial disease) or where evidence-based guidelines do not recommend their use (for example stroke patients (6)). A

number of major international guidelines currently recommend mechanical thromboprophylaxis as an alternative to pharmacological thromboprophylaxis for patients at moderate risk of VTE (35,36), stating that pharmacological thromboprophylaxis 'may be combined with mechanical methods ... particularly in the presence of multiple risk factors' (35). The Caprini scoring system, used in the United States, currently recommends that in higher risk group patients mechanical thromboprophylaxis is optional (37). At all times, the decision as to whether to randomise participants will be guided by the "uncertainty principle", whereby the managing clinician should be substantially uncertain as to whether a patient will benefit from either the prescription or non-prescription of GCS.

1.3 RATIONALE FOR CURRENT TRIAL

The aim is to determine whether low dose low molecular weight heparin (LMWH) alone is non-inferior to a combination of graduated compression stockings (GCS) and low dose LMWH for the prevention of venous thromboembolism (VTE) adult elective surgical inpatients identified as being at moderate and high risk for VTE. The primary clinical objective is to compare the VTE rate in elective surgical inpatients receiving GCS and LMWH, compared with LMWH alone.

The primary health economic objective is to calculate the cost-effectiveness with regards the use of GCS in addition to prophylactic dose LMWH in elective surgical patients identified as being at moderate and high risk for VTE. Other objectives include:

- To determine the experience of surgical patients receiving LMWH and those receiving both GCS and LMWH.
- To profile the adverse effects of GCS and LMWH anticoagulation in this context.
- To support future guidance and policy in VTE prevention.

1. IMPACT

The impact of this trial will include:

- Determination whether, in moderate and high risk surgical inpatients, low dose LMWH alone is non-inferior to low dose LMWH in combination with GCS.

- Determination of the cost-effectiveness with regards the use of GCS in addition to prophylactic dose LMWH in moderate and high-risk surgical patients.
- Refining our understanding of the current VTE risk in moderate and high risk surgical patients in the era of modern preventative treatment.
- Profiling of the experience of surgical patients receiving LMWH and those receiving both GCS and LMWH.
- To profile the adverse effects of GCS and LMWH anticoagulation in this context.
- The opportunity to re-examine the VTE guidelines considering these findings. The Briefing Papers and other outputs directed at the NHS, professional bodies and professionals are expected to influence both future policy and practice. If GCS were found not to offer additional reductions in VTE risk in individuals given prophylactic dose LMWH, this would negate the need for GCS in this patient group, namely moderate and high risk surgical patients receiving LMWH. This would eliminate the side effects of this treatment in these patients and reduce the cost burden of GCS in surgical NHS patients; this has been estimated to be approximately £63.1 million per annum in England.

2. TRIAL OBJECTIVES

2.1 PRINCIPAL RESEARCH QUESTION

In surgical inpatients determined to be at moderate or high risk for VTE, is low dose LMWH alone non-inferior to low dose LMWH in combination with GCS?

The trial is a pragmatic, multicentre randomised clinical trial with adult surgical inpatients assessed by the ubiquitous Department of Health VTE assessment tool (38) as being at moderate or high risk randomised 1:1 to either:

- Current ‘standard’ combined low dose LMWH with GCS mechanical thromboprophylaxis, or
- Low dose LMWH pharmacoprophylaxis alone

3. TRIAL DESIGN

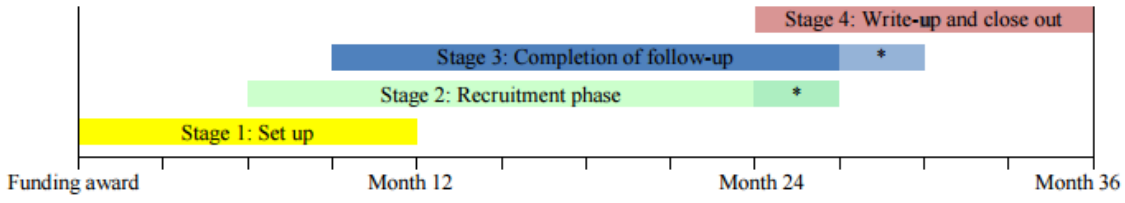
A multicentre, prospective, non-inferiority, group sequential randomised clinical trial to compare VTE outcomes in surgical inpatients assessed as being at moderate or high risk who are prescribed GCS in addition to low dose LMWH and those prescribed low dose LMWH alone.

Eligible and consenting moderate and high risk surgical patients will be computer randomised 1:1 to receive either prophylactic dose LMWH and GCS (or prophylactic dose LMWH alone (from point of admission. Each trial centre will be encouraged to use the LMWH+/-GCS regimen that has been adopted and established locally. Either below-knee or above-knee compression stockings may be used; and the inclusion of obese patients or those undergoing bariatric surgery will be allowed. We recommend that LMWH be given at 1800hrs daily, including the evening before surgery (if admitted the night before surgery) except those undergoing regional anaesthesia. Post-operatively, LMWH, and GCS when randomised, should be continued until discharge as this is less subjective than until 'ambulant'.

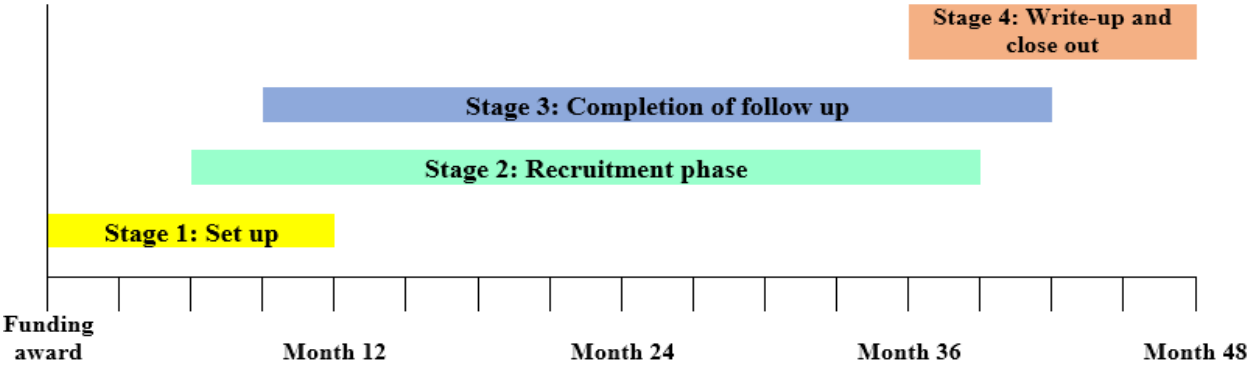
3.1 HEALTH TECHNOLOGIES BEING ASSESSED

Graduated elastic compression stockings (GCS) for thromboprophylaxis in elective surgical patients receiving prophylactic dose LMWH. These GCS are standard, widely available, and the optimal gradient of pressure has previously been shown to be 18mmHg at the ankle, 14mmHg at the calf, and 10mmHg at the knee (39). This technology is not subject to rapid change.

The trial was originally scheduled to take 36 months



In April 2018 the HTA approved a 12 month time only extension (at no additional cost) to enable sites to recruit to target.



3.2 TRIAL OUTCOME MEASURES

3.2.1 Primary Endpoint

VTE within 90 days { duplex ultrasound-proven new lower-limb DVT up to 90 days post-surgery (symptomatic or asymptomatic) + symptomatic PE (imaging confirmed) up to 90 days post-surgery} The 90 day endpoint is in line with the NHS Standard Contract for Acute Services which specifies that root cause analysis should be performed for all cases of hospital-associated VTE – defined as cases arising within 90 days of a hospital stay (40).

3.2.2 Secondary Endpoints

- Quality of life – EQ5D (a validated generic quality of life tool) over 90 days
- Compliance with stockings during admission
- Compliance with LMWH during admission

3.2.3 Measurement of outcomes

3.2.3.1 Primary outcome measure

Telephone, online or face-to-face (according to participant preference) at one week post-surgery or at discharge, and at 90 days. Proceeding to imaging at these points if there is clinical suspicion of a DVT or PE. Routine bilateral full lower limb duplex ultrasonography at between 14 days and 21 days post-operatively to capture peak VTE incidence (41,42). We expect to capture >95% of VTE since the average time-point for DVT is 7 days and PE is 21 days, with vast majority events being DVT. However, data from duplex scans outside this window will be collected and subsequently analysed.

The range of dates is to prevent restricting scanning to a single date. Routinely scanning participants only once reduces cost, and limits the time and inconvenience to the enrolled trial subjects (ethical consideration, improve recruitment and reducing dropouts and loss to follow-up). No pre-operative duplex for these same reasons and also because asymptomatic pre-operative DVTs should be accounted for by equal distribution in the two trial arms by the randomisation process. If participants are inpatients at the time of their routine bilateral full lower limb duplex ultrasonography at between 14 days and 21 days postoperatively, or if any inpatient duplex imaging is prompted by clinical suspicion, GCS will be removed prior to imaging to ensure optimum blinding of those undertaking the imaging (6). If clinical VTE is confirmed on investigation at any point within 90 days, this will be recorded. The 90 day endpoint is in line with the NHS Standard Contract for Acute Services which specifies that root cause analysis should be performed for all cases of hospital-associated VTE – defined as cases arising within 90 days of a hospital stay (40).

3.2.3.2 Secondary outcome measures

Generic quality of life will be assessed at baseline, upon discharge and at follow-up (both 14-21 days and 90 days) using the EQ-5D. EQ-5D is widely used and well validated, and is currently employed as part of the routine collection of Patient Reported Outcome Measures (PROMs) for the NHS in England (43).

Compliance with stockings will be addressed; participants will be issued with a VTE diary where they can document their GCS use, as well as any adverse outcomes related to GCS or LMWH use.

Compliance with LMWH will be assessed by review of the participant's medication chart by the local research nurse or study coordinator.
Mortality will be recorded however, it is anticipated that this will be very low.

3.2.3.3 Safety outcome measures

GCS-related complications, bleeding complications and adverse reactions to LMWH will be determined by review of medical notes and participant-reported comments in their VTE diary.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

The target population is adult (aged ≥18 years) elective surgical inpatients in secondary and tertiary NHS hospitals in the UK assessed as being at moderate or high risk of VTE. This target population is described based on their risk of VTE. There is an established VTE risk assessment tool which has been produced by the Department of Health (38), based on the NICE guidelines (1), and is mandated and in widespread use (44).

4.1.1 Screening and Participant identification

Adult patients presenting to the surgical wards related to a number of surgical specialties for elective surgery at the recruiting centres will be screened for eligibility. The trial will be pragmatic and include ‘all comers’ in terms of surgical specialty and operation type, which would allow the results of the trial to be maximally generalizable and externally valid, in addition to facilitating recruitment.

Patients will be admitted to hospital for their elective surgery, and are VTE risk assessed by the doctor or nurse during the admission process in accordance with NICE guidelines and the Department of Health. Risk assessment will identify patients as ‘low risk’ or ‘not low risk’ for a VTE.

If a patient is identified as ‘not low risk’ for VTE and ‘not at high risk’ for bleeding (i.e. can safely receive LMWH) the clinical team will flag patient to research nurse who will approach patient and will offer them an information leaflet about the trial. Participants will only be approached by the research team when they have given permission for this to happen via a member of their direct care team. Patients will be given an appropriate time period to consider participation. Written consent will be obtained from those patients who agree to participate..

Information about the study may be sent by post or given (for example in the outpatient clinic) potential participants by the direct care team prior to admission. This will allow potential participants to consider being involved in the study prior to their admission for surgery. This information will highlight that eligibility for the trial would be assessed following VTE risk assessment and not all patients would be eligible for the trial.

At each recruiting centre, a log of all screened patients will be kept. Basic demographic data and reasons for non-eligibility will be recorded.

Those who consent will be registered on the web-based data entry system which is maintained by CHaRT (The Centre for Healthcare Randomised Trials, NIHR registered Clinical Trials Unit #7, University of Aberdeen), and their eligibility for the trial confirmed. The randomisation will be web-based hosted at CHaRT, using a minimisation algorithm incorporating centre, moderate or high risk of VTE and gender, and in addition incorporate a random element. Although the trial is open (unblinded) every effort will be made to manage the patients and assess the study outcomes without any knowledge of the randomly assigned treatment being allowed to create any bias.

The VTE risk assessment tool (or the Trust equivalent based on this form) will be used for all patients (Appendix 2). The moderate and high-risk populations for inclusion in this trial are clearly defined according to this risk assessment tool. As patients will already be assessed as part of their admission process (with a target of >95% compliance under the NHS Contract), no additional VTE risk assessment will need to be undertaken for recruitment as part of the trial. Furthermore, no additional training is required for the individual who is undertaking the risk scoring.

4.2 INCLUSION CRITERIA

- Elective surgical inpatients assessed as being at moderate or high risk of VTE according to the widely-used UK Department of Health VTE Risk Assessment for Venous Thromboembolism (or the Trust equivalent based on this form) (38) (Appendix 2, based upon the NICE recommendations (1).*
- Able to give informed consent to participate in the trial after reading the patient information documentation
- Age ≥18 years*

Patients who cannot speak / understand English will be eligible for inclusion and informed consent will be obtained with assistance from translation services as per standard clinical practice. In view of the lack of cross-cultural validation for quality of life tools, only VTE outcome data will be collected.

Patients involved in current or recent research may be included provided that the research does not impact (either positively or negatively) on their risk of VTE, or a contraindication or interaction with LMWH or GCS. Any queries should be directed to the Chief Investigator.

*Following confirmation from the REC and the Sponsor from 20th December 2018, sites will continue to recruit only patients assessed as being at high risk of VTE and aged ≥ 65 years. Recruitment of those <65 and at moderate or high VTE risk is considered closed. Further details can be found in Appendix 3.

4.3 EXCLUSION CRITERIA

- Contraindications to low molecular weight heparin (LMWH)
- Contraindications to GCS, including peripheral arterial disease, stroke patients, individuals undergoing lower limb surgery
- Documented or known thrombophilia or thrombogenic disorder
- Individuals requiring therapeutic anticoagulation
- Previous venous thromboembolism (VTE)
- Patients having intermittent pneumatic compression (IPC) beyond theatre and recovery
- Patients requiring inferior vena cava (IVC) filter
- Pregnancy (female participants of reproductive age will be eligible for inclusion in the trial, subject to a negative pregnancy test prior to randomisation, and again on the day of surgery if there is a possibility of pregnancy since the last test)
- Patients requiring thromboprophylaxis to be extended beyond discharge
- Application of a cast or brace in theatre

4.4 CHANGE OF STATUS / WITHDRAWAL PROCEDURES

Participants will remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status with the exception of complete withdrawal of consent will mean the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis.

5. ADVERSE EVENTS

The GAPS trial involves procedures for the management of patients at moderate and high risk of VTE which are well established in clinical practice. Adverse effects may occur during or after any type of surgery.

5.1 DEFINITIONS

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

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

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

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

5.2 REPORTING PROCEDURES

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 Chief Investigator in the first instance.

5.3.1 Non-Serious AEs

The adverse events listed below are expected to be related and should be reported:

- GCS-related complications during admission (e.g. discomfort, skin breaks, skin ulcers, skin necrosis, blistering of the skin, rash, limb ischaemia)

- Bleeding complications during admission or within 24 hours of discharge

- Adverse reaction to LMWH during admission (e.g. rash or skin change, allergic reaction, thrombocytopenia, abnormal liver enzyme tests)

Please note this is not an exhaustive list, if you suspect an event is related to treatment please contact the Trials Unit.

5.3.2 Serious AEs

All SAEs should be reported. An SAE form should be completed and entered into the trial website within 24 hours. However, hospitalisations for elective or urgent treatment of a pre-existing condition do not need reporting as SAEs. In the event that the trial website is not available the Trial Manager should be notified by telephone, fax or email.

5.3.3 Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified and will notify the Sponsor within 24 hours of receiving the signed SAE notification. The Sponsor will review all reported SAEs. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

All SAEs should be reported to the research ethics committee where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and

- ‘unexpected’, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by the, Sponsor and/or Research and Development Office.

6. ASSESSMENT AND FOLLOW-UP

Please refer to Appendix 1 for a summary of the trial-related visits.

6.1 BASELINE VISIT

Once consented, participants will undergo detailed clinical assessment by the research nurse as part of the baseline evaluation. Recorded assessments will include:

- Demographic details (age, sex, ethnicity)
- Pregnancy test for woman of child bearing age
- General clinical details (body mass index, comorbidities, medication history)

Additional assessments will include:

- EuroQuol 5D (EQ5D) generic quality of life assessment

At this point, eligible participants will be randomised 1:1 via the trial website to either:

- Current 'standard' combined low dose LMWH with GCS mechanical thromboprophylaxis, or
- Low dose LMWH pharmacoprophylaxis alone

The participant will be given further materials including:

- Participant VTE diary
- GCS compliance diary (GCS trial arm only)
- Participant contact and reminder card
- LMWH reminder card

And will proceed to their elective surgery as planned. Women of child bearing age will have another pregnancy test on the day of surgery if there is a possibility of pregnancy since the last test.

Post operatively the participant will be reviewed clinically as per standard care. This will include vigilance for the VTE.

6.2 FOLLOW-UP VISIT 1

The participant will be either seen in person at 1 week after surgery or at discharge (whichever is earlier). Recorded assessments will include:

- Any diagnosis of VTE (Anonymised copies of any duplexes will be forwarded to the Study Coordinating Centre at Imperial College London)
- Any symptoms or signs of VTE (if there is clinical suspicion identified by the research nurse which has not been identified by the clinical team, the research nurse will inform the clinical team who will proceed to imaging if appropriate).
- EuroQuol 5D (EQ5D) generic quality of life assessment
- Review of participant diary (completed until discharge)
- Collection of stocking compliance diary
- Collection of Adverse or Serious Adverse Events

If participant have been discharged without being assessed they will be contacted at either 1 week or as soon as possible.

6.3 FOLLOW-UP VISIT 2

All randomised participants will undergo a routine bilateral full lower limb duplex ultrasonography between 14 and 21 days post operatively to identify VTE. An anonymised copy of the duplex will be collected and forwarded to the Study Coordinating Centre, Imperial College London. We expect to capture >95% of VTE since the average time-point for DVT is seven days and PE is 21 days, with vast majority events being DVT. The range of dates is to prevent restricting scanning to a single date. EuroQuol 5D (EQ5D) generic quality of life assessment will also be administered at this visit.

6.4 FOLLOW-UP VISIT 3

Participants will be seen in person or contacted by telephone or online (according to participant preference) at 90 days post surgery.

Recorded assessments will include:

- Any diagnosis of VTE (Anonymised copies of any duplexes will be forwarded to the Study Coordinating Centre, Imperial College London)

- Any symptoms or signs of VTE (if there is clinical suspicion identified by the research nurse which has not been identified by the clinical team, the research nurse will inform the clinical team who will proceed to imaging if appropriate).
- EuroQuol 5D (EQ5D) generic quality of life assessment
- Review of participant VTE diary (completed until 90 days)
- Collection of Adverse or Serious Adverse Events

If clinical VTE confirmed on investigation at any point within 90 days, this will be recorded

- Symptomatic DVT
- Asymptomatic DVT identified by duplex
- Imaging-confirmed symptomatic PE

Any participant with asymptomatic (or symptomatic) DVTs identified by duplex ultrasound will proceed to being treated as per local guidelines for the management of DVT.

6.5 BILATERAL FULL LOWER LIMB DUPLEX ULTRASONOGRAPHY – BLINDING

If participants are inpatients at the time of their routine bilateral full lower limb duplex ultrasonography at between 14 days and 21 days postoperatively, or if any inpatient duplex imaging is prompted by clinical suspicion, the research team will ensure that the GCS will be removed prior to imaging to ensure optimum blinding of those undertaking the imaging (9). The participant contact / reminder cards will also include a statement to remind participants to do this.

Maintaining the integrity of the blinding is a key consideration for all those involved in the trial, as compromising the blinding may have a significant impact on the interpretation of the results. We will ensure that measures are put into place that prevent deliberate or accidental unblinding. The blinding is particularly important in relation to the undertaking of imaging for the components of the primary endpoint. Clearly defined and communicated procedures for the prevention of unblinding will be implemented, which will target (i) imaging professionals, (ii) other healthcare professionals and (iii) the participant. Healthcare professionals caring for enrolled patients on the surgical wards will be requested to ensure that participants who have been randomised to receive GCS have these removed prior to leaving the ward for imaging. The healthcare professionals and the participants will be requested not to disclose which trial arm the participant is enrolled into to the imaging professionals. The imaging professionals – who are not part of the usual clinical team caring for the participants – will be instructed not to ask the participant or any accompanying

healthcare professional which trial arm the participant has been randomised to. The iDMC will be given information on any unintentional unblindings as the trial progresses, to assess whether there are training issues generally or at specific sites that need addressed. With these procedures in place, unintentional unblinding of the imaging staff should be minimised, and hopefully lowered to zero. We will explicitly ask the imaging staff for each individual randomised whether they were aware of the randomised treatment allocation, or thought that they were aware,

6.6 DEFINITION OF END OF PARTICIPANTS PARTICIPATION

The end of the participants participation is defined as 90 days from the date of the index elective operation.

7. STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE

7.1.1 ORIGINAL SAMPLE SIZE- APPLICABLE UP TO JANUARY 2018

With a one-sided test at 2.5% level of significance (equivalent to a 2-sided test at 5%) the trial has 90% power to conclude that the single pharmacological intervention is non-inferior to the combined intervention (pharmacology and stockings) assuming an event rate of 6% of VTE at 90 days in the combined group and a non-inferiority margin of 3.5%, and a conservative loss to follow up (i.e. non-evaluable for the primary outcome) rate of 10%. The maximum sample size required under this group sequential design, including allowance for loss to follow up, is a total of 2236.

We assume that the standard of care gives a VTE at 90 days proportion of 6%. Historically, we believe the systematic review supports an untreated rate of at least 15%. We have set the non-inferiority margin at 3.5% (i.e. a pharmacological alone rate under the null hypothesis of not more than 9.5%). We think this is justifiable on the grounds that clinicians would not tolerate more than a 3.5% absolute deterioration in VTE event rate over combination therapy, and that it preserves (9-3.5)/(15-6) or 5.5/9 i.e. 61% of the established treatment effect over no intervention (greater than the 50% minimum usually required by regulatory authorities for non-inferiority studies). At 90% power and using a one-sided 2.5% level of significance (equivalent to a two-sided 5%) level we would need to randomise 1936 participants in a fixed sample approach. We prefer to adopt a group sequential approach, giving 4 equally spaced formal interim analyses for efficacy (at 25%, 50%, 75% and a final analysis at 100% of the information) and one formal interim analysis for futility at 50% information. This flexibility to stop early on either efficacy or futility only marginally increases the maximum sample size to 2012 (4% increase, using East 6.3, Cytel Corporation 2014), a flexibility which is useful given the quality, relevance and uncertainty of the evidence base informing the sample size assumptions. If we conservatively allow for 10% loss to follow up, we would need to randomise no more than 2236 in total.

7.1.2 REVISED SAMPLE SIZE (APPLICABLE AFTER JANUARY 2018)

Due to the observed low event rate it was decided to abandon the group sequential design. It was clear from the blinded (aggregate) data that the overall population, subdivided by risk of primary outcome into 4 subpopulations by VTE risk crossed with age. i.e. Subpopulation #1 <65 years,

moderate risk of VTE; subpopulation #2 <65 years, high risk of VTE; subpopulation #3 ≥ 65 years at moderate VTE risk; subpopulation #4 ≥ 65 years at high VTE risk. (With around 250 randomised overall in subpopulation 1 (<65, moderate VTE risk) with zero expected events (0 events observed in the first 180 randomised to Dec 2017), very few events in subpopulation 2 (<65, high VTE risk; around 750 randomised to Dec 2017, observed event 3/510 or 0.6% in the first 510 randomised); virtually no-one randomised into subpopulation 3 (≥65, moderate VTE risk); only 12 randomised to Dec 2017 (this subpopulation will be reported descriptively with no further consideration of formal sample size or inference), and for subpopulation 4 (≥65, and high VTE risk) 750 in subpopulation 4 (306 randomised to Dec 2017 with 11 events observed), the study will not observe sufficient events in total or specifically in subpopulation 4 (the only subpopulation still open to recruitment) to make a re-application of the sequential design sensible.

We have considered (as at Dec 2017) the implications for the sample sizes for the 4 subpopulations, and the Table below gives the detectable non-inferiority margins for indicative sample sizes (at 90% power and a 1-sided level of significance of 2.5%):

Subpopulation	Subpopulation #	Expected number randomised	Assumed event rate	Detectable non-inferiority margin
<65, Moderate	1	258	0.1%	1.30%
<65, High	2	733	0.6%	1.85%
≥65, Moderate	3	12	N/A	N/A
≥65, High	4	912	3.6%	4.0%

Note that these revised sample size calculations do not adjust for multiple comparisons; nor do they adjust for the original group sequential alpha spending (since no interim analyses took place). See Appendix 3- Rationale for Statistical Changes to the Protocol for further details.

The funder agreed to the revised sample size of 912 in subpopulation 4 in April 2018. The other 3 subpopulations (1-3) were closed to any further recruitment at this time, and we will analyse all available data in these 3 subpopulations.

7.2 DATA ANALYSIS

7.2.1 ORIGINAL PLANNED DATA ANALYSIS

All statistical aspects of the trial will be governed by a comprehensive Statistical Analysis Plan (SAP), which will be authored by the trial statistician and approved by both the Trial Steering Committee (TSC) and Independent Data Monitoring Committee (iDMC). The final sample size will be determined by the pre-specified group sequential design, and there will be a single final analysis and reporting of the trial at that point. As a non-inferiority design, both an Intention to Treat (ITT) and a suitably specified Per Protocol analysis will be presented, with primacy given to the ITT approach (albeit it can be that for a non-inferiority design the Per Protocol approach is the more conservative under the null hypothesis). Missing data will be kept to a minimum by good design and conduct, including evidence based processes to maximise retention. It is expected that those missing primary outcomes will be <10% but nonetheless the robustness of the findings under the ITT approach will be assessed by adjusting for these missing data using Rubin's multiple imputation approach under an assumption of missing at random. The primary outcome (VTE at 90 days, Yes/No) will be analysed using a mixed effects logistic regression, with centre as a random effect, VTE risk (moderate vs high) and other to be pre-specified baseline factors as covariates. Secondary outcomes will be assessed in a similar fashion with generalised linear models appropriate to the distribution of the outcome. The level of statistical significance will be taken to be a nominal 0.05. We will undertake for the record the analysis of cohorts 1, 2 and 3 on those recruited prior to 20th December 2017 in line with the original data analysis plan v1.0. Under the new analysis, cohorts 1-4 will be analysed separately. The group sequential analysis is abandoned.

7.2.2 REVISED DATA ANALYSIS (APPLICABLE AFTER JAN 2018)

A single final analysis and reporting of the trial will occur in line with V2.0 of the Statistical Analysis Plan which was revised from version 1.0 (March 2016) in December 2018.

Under the revised analysis, subpopulations 1-4 as described in Appendix 3 will be analysed separately. Due to simplification it is no longer necessary to consider a group sequential design.

7.3 SUBGROUP ANALYSES

7.3.1 PLANNED SUBGROUP ANALYSES

There will be a subgroup analysis of moderate versus high baseline VTE risk, using a formal treatment VTE risk interaction term in the proposed model above for the primary outcome.

7.3.2 REVISED SUBGROUP ANALYSES

The original planned subgroup analyses have been abandoned as they are redundant given the change to statistical analysis of subpopulations 1-4.

7.4 PROPOSED FREQUENCY OF ANALYSES

There will be a single analysis at the final sample size for analysis and reporting of the main results. Confidential analyses will be presented to the iDMC at the agreed milestones under the group sequential design.

7.5 DATA MONITORING

7.5.1 ORIGINAL PLANNED DATA MONITORING

A group sequential design is proposed. The independent Data Monitoring Committee (iDMC) will formally examine data at 25%, 50%, 75% and at a final look at 100% of the information for effectiveness using a Lan-DeMets alpha spending function (<0.001, 0.002, 0.010, and 0.025 cumulative alpha spent) and at 50% for futility (0.02 of the 0.10 total cumulative beta spent). The trial at full size expects to observe around 156 VTE episodes at 90 days under the null hypothesis (that the single intervention is not non-inferior to the combined) and around 121 events under the alternative hypothesis (that the single intervention is non-inferior to the combined) so that in information time the interim looks will be scheduled to around 40 (25%), 80 (50%, including the single futility look as well) and 120 (75%) events recorded. The full details of the iDMC's remit (including the stopping rules for effectiveness and futility) will be agreed at the first meeting of the iDMC before any unblinded data are available or seen. The iDMC will meet to examine data at approximately 200 participants with outcome data at 90 days for the purpose of checking on the assumed underlying pooled event rate for the primary outcome at 90 days. The expected sample

size under the null hypothesis is 1546 and under the alternative hypothesis 1673 (having allowed for the 10% assumed to be missing primary outcome data).

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the trial, including the follow-up period.

7.5.2 REVISED DATA MONITORING

The iDMCwill meet regularly in line with the iDMC Charter V2.0 without any formal interim analyses due to the abandonment of the group sequential analysis and the closure of recruitment to subpopulations 1-3. The rationale for abandonment is described in Appendix 3.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The trial will be conducted in accordance with the principles of good clinical practice (GCP).

The Chief Investigator (CI) has obtained approval from the Research Ethics Committee. The trial must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the trial. The trial 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.

8.2 CONSENT

Consent to enter the trial 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. 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 trial 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.

8.3 CONFIDENTIALITY AND DATA PROTECTION

The CI and trial staff involved with this trial will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and trial staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Participant Confidentiality. Access to collated participant data will be restricted to the CI and appropriate trial staff.
Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

All evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to trial staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and trial staff involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this trial. Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial.

8.5 SPONSOR

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

8.6 FUNDING

This project is funded by the National Institute for Health Research Health Technology Assessment Programme (Number 14/140/61). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

The local sites will be reimbursed for:

- Clinical research nurses (one allocated to each of the participating centres) for a total of 24 months (for three months prior to recruitment, for the 18-month recruitment period and for

three months after to complete follow-up) to identify potentially eligible participants, approaching patients and discussing the trial. They will ensure the trial outcome data are collected, collated and returned to the Study Coordinating Centreat the baseline assessment point and follow-up. They will ensure accuracy and completeness of data collection, including assisting participants in completing questionnaires. The clinical research nurses will also work with the local PI and be responsible for local organisation, maintaining a positive local trial profile, liaising with local centre staff and dealing with all first line enquiries

- Bilateral lower limb venous duplex scanning costs.

Participant travel to attend trial follow-up or scan visits will be reimbursed.

8.7 AUDITS

The trial may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. TRIAL MANAGEMENT

9.1 PROJECT MANAGEMENT

The trial will be coordinated by a Trial Manager based at Imperial College London (with some senior trial management support from CHaRT) reporting to the Clinical Coordinator (JS) and the Chief Investigator (AHD). The clinical coordinator will liaise with local Principal Investigators (PIs) to ensure that the trial is conducted locally according to protocol and in an expeditious manner.

The organisational structure and responsibilities are outlined below:

9.2 CHIEF INVESTIGATOR

The Chief Investigator has overall responsibility for:

- Design and conduct of the trial
- Preparation of the Protocol and subsequent revisions
- Managing the Study Coordinating Centre
- Development of Standard Operating Procedures

9.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be formed and will meet on a regular basis decided by the Chair to discuss trial progress.

The TSC will have an independent chair and a minimum of 75% majority of independent voting members. Only appointed members will be entitled to vote and the chair will have a casting vote. The minimum quoracy for a meeting to conduct business is 67% of appointed members with attendance of non-members at discretion of the Chair. The Chair will maintain a log of potential conflicts and/or interests signed by the Chair and members and the primary TSC reporting line is via the chair to the NIHR HTA Programme Director

The role of the TSC/SSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards

set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main features of the TSC are as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To concentrate on progress of the trial, adherence to the protocol, participant safety and the consideration of new information of relevance to the research question
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the trial

9.3.1 Composition of the TSC

- An independent chair (UK based and/or holding a substantive UK based appointment)
- Independent clinicians with relevant expertise
- Independent statisticians/epidemiologists/diagnosticians with relevant expertise
- At least one individual who is able to contribute a patient and/or wider public perspective
- Ideally, the TSC should invite observers, including a representative of the sponsor and a representative from the research network to meetings
- Although there may be periods when more frequent meetings are necessary, the TSC should meet at least annually
- Meetings should be scheduled to follow shortly after iDMC meetings so that reports from that group can be considered
- Minutes of meetings should be sent to all members, the sponsor, the funder and the trial master file
- The responsibility for calling and organising TSC meetings lies with the Chief Investigator, in association with the Chair of the TSC

- There may be occasions when the Trial Sponsor or the Trial Funder will wish to organise and administer these meetings for particular trials. In the NIHR HTA programme's case this is unlikely, but it reserves the right to attend any meeting and the right to convene a meeting of the TSC in exceptional circumstances

9.3.2 The Role of the Chair of TSC/

The Chair of the TSC is directly answerable to the NIHR HTA programme, as funder.

The Chair's responsibilities include:

- Arranging an inaugural meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan
- Establishing clear reporting lines – to the Funder, Sponsor, and any other relevant stakeholders
- Being familiar with relevant guidance documents and with the role of the iDMC
- Providing an independent, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies
- Leading the TSC/SSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems
- Ensuring that changes to the protocol are debated and endorsed by the TSC/SSC; letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol
- Being available to provide independent advice as required, not just when TSC/SSC meetings are scheduled
- Commenting on any extension requests and, where appropriate, providing a letter of recommendation to accompany such a request
- Commenting in detail (when appropriate) regarding the continuation or termination of the project

9.4 DATA MONITORING COMMITTEE

The independent Data Monitoring Committee (iDMC) will focus on the rights, safety and well-being of trial participants. iDMC responsibilities are:

- It is the only body involved in a trial that has access to the unblinded comparative data
- The role of its members is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue
- The safety, rights and well-being of the trial participants are paramount
- The iDMC considers the need for any interim analysis advising the TSC regarding the release of data and/or information
- The iDMC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies
- If funding is required above the level originally requested, the iDMC maybe asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial
- Membership of the iDMC should be completely independent, small (3- 4members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician
- Responsibility for calling and organising iDMC meetings lies with the Chief Investigator, in association with the Chair of the iDMC. The project team should provide the iDMC with a comprehensive report, the content of which should be agreed in advance by the Chair of the iDMC.
- The iDMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the TSC
- Minutes of open meeting should be sent from the Chair of the iDMC to all members, the sponsor, the funder, the Chair of TSC and a copy stored in the trial master file. Minutes of the closed meeting should be circulated to all iDMC members and held securely in confidence by the trial statistician at the CHaRT until the end of the study.

9.4.1 Standard Constitution iDMC

The following list identifies the minimum constitution requirements, a set of outline terms of reference and the primary reporting line for iDMC:

- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members
- All iDMC members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment)
- Only appointed members will be entitled to vote and the chair will have a casting vote
- The minimum quoracy for a meeting to conduct business is 67% of appointed members
- The chair and members to sign and maintain a log of potential conflicts and/or Attendance at iDMC meetings by non-members is at the discretion of the chair
- The primary iDMC reporting line is via the chair to the TSC

9.5 STUDY COORDINATING CENTRE

The Study Coordinating Centre (SCC) is responsible for the overall coordination of the trial, including:

- Trial planning and organisation of Steering Committee meetings
- Agreement of each local recruitment plan
- Contractual issues with local trial sites
- Ethics Committee applications and amendments
- Design, implementation and maintenance of IT systems for the trial
- Auditing and monitoring of overall progress of the trial
- Clinical safety monitoring (including the reporting of all “related” SAEs to the Chair of the iDMC and Ethics Committee)
- Liaison with the iDMC and (where appropriate) with regulatory authorities and other outside agencies
- Responding to technical and administrative queries from local trial sites

9.6 LOCAL TRIAL SITES

The local Principal Investigator (PI) and clinical staff at the local trial sites are responsible for:

- Obtaining local NHS Research and Development and management approval (aided by the Study Coordinating Centre)
- Provision of adequate space and the identification of potentially eligible participants
- Conducting trial procedures and follow-up according to trial protocol
- Dealing with routine enquiries from participants and their families
- Obtaining appropriate information to confirm potential primary and secondary trial endpoints
- Attend annual trial collaborator meetings to discuss trial progress

9.7 PATIENT AND PUBLIC INVOLVEMENT

In keeping with the briefing notes for researchers published by INVOLVE (48), we are committed to active patient and public involvement in this research proposal. We have had continued input and support from Thrombosis UK (formerly known as Lifeblood: The Thrombosis Charity) who have advised on lay perspectives. Annya Stephens-Boal, an expert patient and executive officer of Thrombosis UK, has offered patient and public views on the research participants, the research question and the content of this application. Ms Stephens-Boal is a co-applicant and contributed to a number of relevant areas within this submission, including the wording of all patient information documentation. Other patient members of Thrombosis UK have offered their constructive opinion on the research participants, the research question and the patient experience questionnaire and these have been taken into account throughout and appropriate modifications been made accordingly. Additionally, surgical inpatients were approached for their views in relation to the research participants and the planned trial. Of the 11 individuals in the group, seven gave positive views of research planned, nine felt it a worthwhile trial to undertake, and seven felt hypothetically that they would consent to participate in the trial if approached. Key patient opinions with regards the trial included ensuring that the results were relevant to all patients, regardless of gender or age, and ensuring minimisation of patient inconvenience. Based on the latter point, routine bilateral lower limb duplex ultrasonography has been planned for a single time-point at patient follow-up. Patients and public members will be part of the trial steering committee (TSC). It is important to involve patients, major beneficiaries of the research, in the trial so major trial decisions (e.g. on trial continuation) take into account patient perspectives. There will be a lay

member of the TSC, representing patient and public views, with full voting rights. Patient groups, thrombosis and vascular charities will be informed of research and of results through presentations. These groups will further cascade research details to other groups and wider public, increasing knowledge and awareness of VTE prevention; it is hoped this will encourage trial recruitment.

To summarise, patients and the public will be actively involved in:

- Design of the research
- Developing participant information resources
- Analysing and interpreting the research as a member of the research team
- Dissemination of research findings
- Management of the research, including as part of the Trial Steering Committee

10. PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other trial documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other trial documents will not be implemented without these approvals.
In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor and then to the appropriate REC and lead NHS R&D Office for review and approval.
In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately.

10.1 TRIAL RECORD RETENTION

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the trial, including the follow-up period in accordance with the Imperial College JCRO Archiving Trial Documents SOP.

10.2 END OF TRIAL

The end of trial is defined as the time of the database lock which will occur following the last participant last visit (LPLV). The Sponsor, CI and/or the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the trial will be provided to the Sponsor and REC within 1 year of the end of the trial.

11. PUBLICATION & DISSEMINATION PLAN

11.1 TRIAL TEAM

11.1.1 Chief Investigator

Professor Alun H Davies

11.1.2 Co-Investigators

Mr Joseph Shalhoub
Professor Beverley Hunt
Professor Gerard Stansby
Dr Tamara Everington
Dr Christopher Baker
Professor Andrew Bradbury
Mr Manjit Gohel
Professor John Norrie
Sister Karen Dhillon
Ms Annya Stephens-Boal
Professor David Warwick

11.2 AUTHORSHIP POLICY

Ownership of the data arising from this trial resides with the Chief Investigator and Sponsor. On completion of the trial, the trial data will be analyzed and tabulated, and a clinical trial report will be prepared.

11.3 PUBLICATION POLICY

The clinical trial report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the trial. Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

11.4 DISSEMINATION PLAN

There will also be an online dissemination plan, with participants and healthcare professionals able to access results on a trial website, and appropriate use of social media (Twitter, Facebook, LinkedIn). Trial participants will also be offered a mailed summary of the trial findings.

12. REFERENCES

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APPENDIX 1 SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

Timepoint	Estimated Duration (mins)	Computer Randomisation	Clinical Evaluation [a]	Duplex Imaging	Participant VTE Diary	EQ-5D	Stocking Compliance	Safety / Complications Monitoring [b]
Baseline (at the time of admission for elective surgery)	60							
During admission				If suspicion				
7 days post surgery OR At discharge [c]	60			If suspicion				
14 to 21 days post surgery	60						If not previously collected	
90 days post surgery	60			If suspicion				

a. Demographic details (age, sex, ethnicity), Pregnancy test for woman of childbearing age . General clinical details (body mass index, comorbidities, medication history, VTE symptoms and signs).

b. GCS- related lower limb complications / Bleeding complications / Allergic reactions to LMWH

c. Whichever occurs first

APPENDIX 2 UK DEPARTMENT OF HEALTH VTE RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM

RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

All patients should be risk assessed on admission to hospital. Patients should be reassessed within 24 hours of admission and whenever the clinical situation changes.

STEP ONE

Assess all patients admitted to hospital for level of mobility (tick one box). All surgical patients, and all medical patients with significantly reduced mobility, should be considered for further risk assessment.

STEP TWO

Review the patient-related factors shown on the assessment sheet against **thrombosis** risk, ticking each box that applies (more than one box can be ticked).

Any tick for thrombosis risk should prompt thromboprophylaxis according to NICE guidance.

The risk factors identified are not exhaustive. Clinicians may consider additional risks in individual patients and offer thromboprophylaxis as appropriate.

STEP THREE

Review the patient-related factors shown against **bleeding risk** and tick each box that applies (more than one box can be ticked).

Any tick should prompt clinical staff to consider if bleeding risk is sufficient to preclude pharmacological intervention.

Guidance on thromboprophylaxis is available at:

National Institute for Health and Clinical Excellence (2010) Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. NICE clinical guideline 92. London: National Institute for Health and Clinical Excellence.

http://www.nice.org.uk/guidance/CG92

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1

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RISK ASSESSMENT FOR VENOUS THROMBOEMBOLISM (VTE)

Mobility – all patients (tick one box)	**Tick**		**Tick**		**Tick**
Surgical patient		Medical patient expected to have ongoing reduced mobility relative to normal state		Medical patient NOT expected to have significantly reduced mobility relative to normal state	
Assess for thrombosis and bleeding risk below				**Risk assessment now complete**	

Thrombosis risk			
Patient related	**Tick**	**Admission related**	**Tick**
Active cancer or cancer treatment		Significantly reduced mobility for 3 days or more	
Age > 60		Hip or knee replacement	
Dehydration		Hip fracture	
Known thrombophilias		Total anaesthetic + surgical time > 90 minutes	
Obesity (BMI >30 kg/m²)		Surgery involving pelvis or lower limb with a total anaesthetic + surgical time > 60 minutes	
One or more significant medical comorbidities (eg heart disease;metabolic,endocrine or respiratory pathologies;acute infectious diseases; inflammatory conditions)		Acute surgical admission with inflammatory or intra-abdominal condition	
Personal history or first-degree relative with a history of VTE		Critical care admission	
Use of hormone replacement therapy		Surgery with significant reduction in mobility	
Use of oestrogen-containing contraceptive therapy			
Varicose veins with phlebitis			
Pregnancy or < 6 weeks post partum (see NICE guidance for specific risk factors)			

Bleeding risk			
Patient related	**Tick**	**Admission related**	**Tick**
Active bleeding		Neurosurgery, spinal surgery or eye surgery	
Acquired bleeding disorders (such as acute liver failure)		Other procedure with high bleeding risk	
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with INR >2)		Lumbar puncture/epidural/spinal anaesthesia expected within the next 12 hours	
Acute stroke		Lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours	
Thrombocytopaenia (platelets< $75x10^9$/l)			
Uncontrolled systolic hypertension (230/120 mmHg or higher)			
Untreated inherited bleeding disorders (such as haemophilia and von Willebrand's disease)			

2

APPENDIX 3 RATIONALE FOR STATSTICAL CHANGES TO THE PROTOCOL

This appendix describes the impact of emerging blinded data on the study and explains the rationale for changes made to the protocol and statistical analysis plan.

The original sample size was determined by the pre-specified group sequential design, with a final analysis and reporting of the trial at that point. The formal interim analyses in the group sequential design (version 1.0 of the SAP) were specified in event time (i.e. after a number of events had accumulated), rather than participant time (i.e. after a certain number of participants had been randomised) or in calendar time (i.e. after a certain number of months of recruitment had accumulated).

Under the null hypothesis it was expected 134 events would be recorded in a maximum sample size of 2,236 participants. The first interim analysis was scheduled at 25% of these events i.e. 34 events. The iDMC were unable to meet according to the schedule as the number of events was substantially fewer than expected. This prompted investigation by the senior statistician which resulted in a report based on blinded interim data. This report presented to the TSC, DMC and study funders. In December 2017 four distinct subpopulations of risk recruited to the study were identified.

1. Participants aged <65 years at moderate risk of VTE
2. Participants aged <65 years at high risk of VTE
3. Participants aged ≥ 65 years at moderate risk of VTE
4. Participants aged ≥ 65 years at high risk of VTE

The TMG proposed to immediately stop recruitment of subpopulations 1-3 and on 20th December 2017, following agreement from the REC, Sponsor, TSC and DMC a letter was issued to all 7 sites requesting immediate cessation of the recruitment of participants to subpopulations 1-3 and for continuation of recruitment to subpopulation 4 only.

In April 2018 the HTA approved a 12 month time only extension (no additional funds) enabling sites to continue to exclusively recruit and follow up participants to subpopulation 4 until April 2019.

