Examining the benefit of graduated compression stockings in the Prevention of vEnous Thromboembolism in low-risk Surgical patients: a multicentre cluster randomised controlled trial (PETS Trial)

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Protocol authorised by:

Name & Role	Date	Signature
Professor Alun Davies Chief investigator	29/03/2022	
Professor John Norrie Lead Statistician and Co-Applicant	29/03/2022	
Ms Becky Ward Sponsor Representative	29/03/2022	

Study Management Group

Chief Investigator:
Professor Alun Davies
Imperial College London, Academic Section of Vascular Surgery
Room 3, 4th Floor East Wing, Charing Cross Hospital
Fulham Palace Road, London, W6 8RF
Email: a.h.davies@imperial.ac.uk

Senior Statistician:
Professor John Norrie
Chair of Medical Statistics and Trial Methodology
Director of Edinburgh Clinical Trials Unit
Usher Institute- University of Edinburgh
9 Little France Road
Nine Edinburgh BioQuarter
Edinburgh, EH16 4UX
Email: j.norrie@ed.ac.uk

Co-investigators:

Mr Joseph Shalhoub, Consultant Vascular Surgeon/Honorary Clinical Senior Lecturer

Professor John Norrie, Director of Edinburgh Clinical Trials Unit

Mr Matthew Machin, Academic Clinical Research Fellow

Miss Sasha Smith, Clinical Trial Manager

Professor Beverley Hunt, Professor of Thrombosis and Haemostasis

Dr Tamara Everington, Consultant in Haemostasis and Thrombosis

Dr David Epstein, Associate Professor

Mr Manjit Gohel, Consultant Vascular Surgeon

Professor David Warwick, Consultant Orthopaedic Surgeon

Dr Christopher Baker, Consultant Cardiologist

Mr Zaed Hamady, Consultant General Surgeon

Ms Layla Bolton, Clinical Nurse Specialist

Ms Annya Stephens-Boal, PPI representative

Ms Beverley Gray, PPI representative

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Mrs Sarrah Peerbux

Address:
Imperial College London
Section of Vascular Surgery
Room 3E, 4th Floor East Wing
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Tel: +44 (0)203 311 7371
E-mail: s.peerbux@imperial.ac.uk/petstrial@imperial.ac.uk

Clinical Queries

Clinical queries should be directed to the Trial Manager at petstrial@imperial.ac.uk who will direct the query to the appropriate person

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:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 1862**

Funder

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This protocol describes the PETS study and provides information about procedures for entering participants. 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 UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CTU	Clinical trials unit
DHRA tool	Department of health risk assessment tool
DVT	Deep venous thrombosis
EQ-5D	Euro-Qol 5D instrument for measuring generic health status
GAPS	Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients' study
GCS	Graduated compression stocking
HAT	Hospital-acquired thrombosis
ICC	Intraclass correlation
iDMC	Independent data monitoring committee
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
TEDS	Thromboembolic deterrent stockings
SAP	Statistical Analysis Plan
SMS	Short Messaging Service
SOP	Standard operating procedure
TSC	Trial Steering Committee
VTE	Venous thromboembolism
WHO	World Health Organisation

KEYWORDS

Venous Thromboembolism, graduated compression stockings, deep venous thrombosis, pulmonary embolism, cluster design

STUDY SUMMARY

TITLE Examining the benefit of graduated compression stockings in the Prevention of vEnous Thromboembolism in low-risk Surgical patients: a multicentre cluster randomised controlled trial (PETS Trial)

DESIGN Multicentre, cluster, randomised controlled trial

AIMS To evaluate the potential benefit of Graduated Compression Stockings (GCS) in the prevention of Venous Thromboembolism (VTE) in patients undergoing short-stay surgical procedures, assessed as being at low-risk for VTE.

OUTCOME MEASURES

Primary Outcome:
The rate of symptomatic VTE within 90 days for surgical patients undergoing short-stay procedures assessed as being at low-risk of VTE for those treated with GCS in comparison to those not given GCS.

Secondary outcomes:

- Mortality
- Incremental Cost-Effectiveness Ratio (ICER) up to 2 years
- Quality of life – EQ-5D administered at 7 and 90 days
- Adverse events with GCS (assessed at 7-days, in those enrolled in the intervention cluster only).

POPULATION Patients undergoing short-stay surgical procedures, assessed as being at low-risk of developing VTE by Department of Health Risk Assessment (DHRA) tool (equivalent to scoring 0, i.e. absence of all assessed thrombosis risk factors).

SAMPLE SIZE A total of 21,472 participants.

ELIGIBILITY

Inclusion criteria

- Adults (18-59 years of age) scheduled to undergo a surgical procedure with a hospital stay <48 hours
- Individuals assessed as being at low-risk of developing VTE as per the DHRA Tool (i.e. no assessed thrombosis risk factors / scoring 0)

Exclusion criteria

- Individuals with a contraindication to GCS
- Individuals assessed as being at moderate or high-risk of VTE as per the DHRA tool

- Individuals requiring therapeutic anticoagulation
- Individuals with thrombophilia/ thrombogenic disorder
- Individuals with a previous history of VTE
- Individuals requiring intermittent pneumatic compression therapy beyond theatre and recovery
- Individuals requiring extended thromboprophylaxis beyond discharge
- Female patients of childbearing age who have a positive pregnancy test
- Individuals with lower limb immobilisation
- Inability to provide informed consent

DURATION 45-months

1. INTRODUCTION

1.1. BACKGROUND

Hospital-acquired thrombosis (HAT) is defined as any venous thromboembolism (VTE) related event within 90 days of hospital admission (1), and is a term that encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). HAT accounts for significant morbidity and mortality with 57.1 VTE-related deaths per 100,000 hospital admissions reported in the year 2018-2019 within the NHS (1). The probability of untreated moderate-risk surgical inpatients developing HAT was previously estimated to be as high as 15%, this reducing to 4.1% with pharmacological and mechanical prophylaxis (2).

The UK annual VTE-related mortality is estimated to be 32,000 fatalities, with associated costs of £640 million per annum (3). After suffering from a DVT, around half of patients develop post-thrombotic syndrome (PTS) (4), characterised by leg pain, oedema, skin changes and leg ulceration (5). Surgery is an established risk factor for VTE (6). It is estimated that the untreated risk of VTE for patients undergoing most general surgical, urological or open gynaecological procedures is 10-40% (7). Furthermore, for those undergoing hip or knee arthroplasty this risk increases to 40-80% (7). Specific surgical factors such as abdominal and pelvic procedures, operations for cancer, and procedures with a greater duration are associated with a greater risk of VTE (8,9). Conversely, operations with a short anaesthetic and procedural time, that can be performed within a <48-hour hospital stay, and that permit early ambulation are associated with a low risk of VTE. An example of this is groin hernia repair - in a large consecutive cohort of 5649 patients, half of whom received low-molecular weight heparin (LMWH), the rate of DVT was just 0.12% (10).

Mechanical thromboprophylaxis is often utilised in the form of graduated compression stockings (GCS), also known by the brand name ThromboEmbolic Deterrent (TED) (7,11,12). GCS apply a level of graduated pressure at rest, i.e. not whilst ambulant - they are designed for immobile patients at-risk of VTE. However, it has recently been shown that GCS provide no added benefit in the reduction of VTE for moderate-high VTE risk surgical inpatients receiving LMWH (13). Additionally, the CLOTS 1 trial, which randomised acute stroke patients to either LMWH alone or the combination of GCS and LMWH, reported no difference in the rate of DVT (14). The findings of these studies have cast doubt on the use of GCS in prevention of VTE. Importantly, the patients in the aforementioned trials were at a higher risk from this distinct low VTE risk group to which this application refers.

Limited evidence is available on the rate of hospital-acquired VTE in low-risk surgical patients. NICE guidelines for the prevention of VTE published in 2007 previously recommended that all surgical patients should receive GCS to reduce the risk of VTE, irrespective of the absence of thrombosis risk factors (15). The subsequent updated NICE guidelines did not include this blanket recommendation, but instead provided specific recommendations for differing procedure types. The most contemporary NICE guidelines, published in 2018, recommend that all patients undergoing abdominal, thoracic, spinal, bariatric, head and neck, and elective joint surgery should be treated with GCS and to consider treatment with GCS for all those undergoing cardiac, vascular and ear, nose and throat surgery (16). The interpretation of these recommendations has meant that patients undergoing short-stay procedures, who are able to ambulate early and have no other thrombosis risk factors, are still treated with GCS. An

example of this interpretation is the provision of GCS for inguinal hernia repair procedures - an operation that fits into the recommendation of provision of GCS for an abdominal procedure, however, patients ambulate immediately and are discharged from hospital on the same day. This blanket provision of GCS is evidenced by our detailed feasibility analysis that demonstrated many NHS Trusts within the UK offer GCS to all surgical patients, even those at low-risk of VTE. Hence, it is now common practice for patients undergoing day case procedures, even those that have no other assessed risk factors, to be prescribed GCS in the absence of contraindications.

1.2. RATIONALE FOR CURRENT STUDY

The evidence to support GCS for short-stay ambulant patients is poor. A systematic review (17) examining the use of GCS in comparison to no prophylaxis in low VTE risk short stay surgical patients confirmed that there have been no RCTs to support this practice. Furthermore, a meta-analysis in the 2018 Cochrane Review for patients at moderate and high-risk of VTE revealed a significantly lower odds ratio of DVT in those treated with GCS in comparison to those that were not (18). However, this analysis is not relevant to the current research question which comprises of the use of GCS alone in low VTE risk surgical patients, i.e. not receiving low molecular weight heparin (LMWH) and undergoing short stay procedures. None of the included 18 surgical RCTs identified in the Cochrane Review consisted of low risk procedures, i.e. ambulatory day case procedures. The case mix consisted of the following types of procedures: neurosurgery, orthopaedic trauma, major lower limb arthroplasty and major abdominal surgery.

Moreover, the NIHR HTA-funded RCT (GAPS trial) assessing the use of GCS in addition to LMWH for the prevention of VTE in moderate and high-risk, i.e. not low risk, elective surgical patients demonstrating that LMWH alone was non-inferior to dual thromboprophylaxis with LMWH and GCS, has further drawn the role of GCS in the prevention of VTE in surgery into question (13). This is on the background of other RCTs, such as the CLOTS 1 trial which randomised acute stroke patients to either LMWH alone or the combination of GCS and LMWH and reported no difference in the rate of DVT (14). In the GAPS trial there was no adjuvant benefit of GCS in patients receiving LMWH, while the clinical community are adopting these findings into clinical practice, they cannot safely be extrapolated to this large cohort of low VTE risk patients.

Due to this lack of evidence to support the use of GCS in the prevention of VTE for low VTE risk surgical patients, an adequately powered trial is required to provide level-1A evidence in relation to this practice.

If this practice is demonstrated to not be beneficial then these valuable resources can be redistributed elsewhere, and the potential adverse effects of GCS avoided.

To summarise, this trial is necessary because:
a) There is no evidence to support clinicians in the prescription of GCS to prevent VTE in low VTE risk surgical patients
b) There is no information to counsel patients when informing them regarding the use of GCS
c) There is potential to save a significant financial resource
d) Evidence is required to guide future clinical practice policy

2. STUDY OBJECTIVES

The aim of this study is to evaluate the potential benefit of GCS in the prevention of VTE in patients undergoing short-stay surgical procedures, assessed as being at low-risk for VTE.

2.1 PRIMARY OUTCOME

The primary outcome is the rate of symptomatic VTE within 90 days for surgical patients undergoing short-stay procedures assessed as being at low-risk of VTE for those treated with GCS in comparison to those not given thromboprophylaxis.

2.2 SECONDARY OUTCOMES

- Mortality
- Incremental Cost-Effectiveness Ratio (ICER) at 90 days and, if relevant up to 2 years
- Quality of life – EQ-5D (19) administered at 7 and 90 days
- Adverse events with GCS (assessed at 7-days, in those enrolled in the intervention cluster only).

3. STUDY DESIGN

This is an assessor-blind multicentre, cluster randomised controlled trial. A total of 50 sites (21,472 participants) will be randomised to either GCS or no GCS. Inclusion criteria stipulates these participants are adult, undergoing short stay procedures, and assessed low-risk for VTE as per the Department of Health risk assessment tool (20).

The duration of the study will be 45 months including 6-months set up, 30 months of recruitment, 3 months follow-up and 6 months for analysis and dissemination. **Figure 1** is a flow diagram summarising the study design.

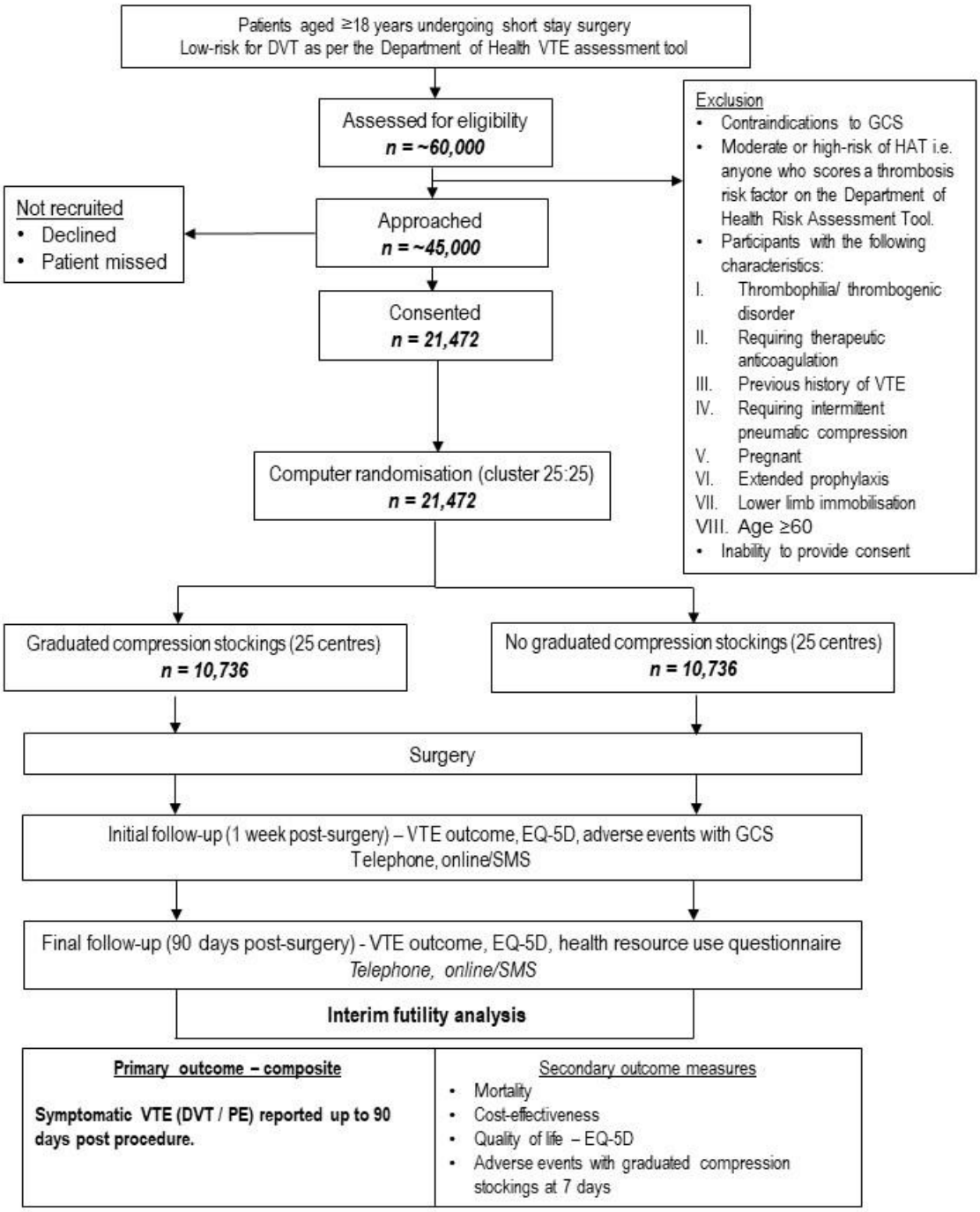
3.1. STUDY OUTCOME MEASURES

Primary outcome measure: The primary outcome is the rate of symptomatic VTE within 90 days. This will be assessed via patient self-report.

Secondary outcome measures:

- Cost-effectiveness of stocking provision- Incremental cost-effectiveness ratio (ICER) using the EQ-5D, with appropriate sensitivity analysis
- Change in generic QoL using the EQ-5D
- Adverse events associated with GCS use.

Figure 1: Study flow diagram



4. PARTICIPANT ENTRY

4.1. INCLUSION CRITERIA

- Adults (18-59 years of age) scheduled to undergo a surgical procedure with a hospital stay <48 hours.
- Individuals assessed as being at low-risk of developing VTE as per the DHRA tool (20) i.e. no assessed thrombosis risk factors / scoring 0.

Examples of procedures from which patients are at low-risk of VTE include (but not limited to): open general surgery (e.g. inguinal hernia repair), laparoscopic general surgery (e.g. laparoscopic cholecystectomy), ear, nose and throat (e.g. myringotomy), urology (e.g. cystoscopy), gynaecology (e.g. diathermy for endometriosis), and orthopaedics (e.g. joint arthroscopy).

4.2. EXCLUSION CRITERIA

- Individuals with a contraindication to GCS
- Individuals assessed as being at moderate or high-risk of VTE as per the DHRA tool
- Individuals requiring therapeutic anticoagulation
- Individuals with thrombophilia/ thrombogenic disorder
- Individuals with a previous history of VTE
- Individuals requiring intermittent pneumatic compression therapy beyond theatre and recovery
- Individuals requiring extended thromboprophylaxis beyond discharge
- Female patients of childbearing age who have a positive pregnancy test
- Individuals with lower limb immobilisation
- Inability to provide informed consent

4.3. WITHDRAWAL CRITERIA

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.

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. A formal interim analysis, with the possibility of stopping early for futility (no prospect of a clinically meaningful treatment effect), will be performed at the point of 50% mature primary outcome data.

5. ADVERSE EVENTS

5.1. DEFINITIONS

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

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

- **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 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 subject 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

For the purposes of the study, only AEs related to the study intervention (graduated compression stockings) will be recorded. This information will be collected at 7-days only. Participants enrolled in the center which has been randomized to the stockings allocation are only required to wear the stockings for the duration of the short-stay surgery (donning the stockings just prior to undergoing the surgery and removing when ambulant), hence AEs associated with the stockings are only expected in the short-term and thus collected at 7-days. Participants who report a treatment related AE which requires further investigation/follow-up will be advised to consult with their GP/relevant clinical team where necessary. 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

Only AEs related to the study intervention (graduated compression stockings) will be recorded.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie 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 related and unexpected SAEs.

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

Contact details for reporting SAEs
RGIT@imperial.ac.uk
Please send SAE forms to: petstrial@imperial.ac.uk
Tel: +44 (0)203 311 7371 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

6.1 ELIGIBILITY AND ASSESSMENT

This is a "cluster study" i.e randomisation will be conducted at recruitment centre level rather than on an individual participant level. Recruiting centres will be randomised/allocated to either the intervention arm (where all participants who undergo short-stay surgery will receive GCS to wear during their short-stay procedure) or the control arm (where no GCS will be provided to those undergoing short-stay surgery). This treatment allocation will apply to ***all*** patients (cohorts in whom equipoise has been agreed) who undergo short-stay surgery within the Trust, i.e. the Trust will adopt this allocation as their standard of care.

Patients are only required to consent to be contacted for follow-up (7 and 90-days post procedure).

This trial will take place in at least 50 NHS Trusts offering day case and short stay surgical services. Patients from a variety of surgical specialties will be included in this pragmatic trial. Adults who are scheduled to undergo short-stay surgery will be pre-screened by a member of the direct care team and invited to speak to a member of the research team. Permission from the patient will be granted by the direct care team before any information is passed or approach made by the research team.

The reasons for non-inclusion will be logged anonymously along with a minimum data set of age, gender and reason for exclusion. The anonymised screening logs will be transferred to the Trial Coordinating Centre for the purposes of monitoring recruitment.

Intervention
Centres randomised to the intervention arm, which is the current standard of care, will consist of participants receiving GCS. Clinical staff (e.g. theatre support workers) will issue stockings to all patients who are scheduled to undergo short-stay surgery. Participants will be instructed to wear their stockings just before undergoing the surgical procedure and to remove the stockings as soon as they are ambulant (i.e. after the procedure).

Control
In those centres randomised to the control arm, participants will not receive GCS.

The intervention received at a given centre will therefore be guided by the cluster allocation.

6.2 INFORMED CONSENT

Participants will be consented to be contacted for follow-up (7 and 90-days post procedure).

Eligible patients will be provided with further information about the study. Formal informed consent to be contacted for follow-up (7 and 90-days) will be obtained prior to the day of procedure (e.g. at the preassessment visit) or at any point before the 7-day follow-up is due (including on the day of the surgical procedure). Informed consent can be collected in written, verbal or electronic form.

Prior to the surgical procedure, all participants will be provided with a leaflet which explains the signs and symptoms of developing a blood clot. Although VTE outcome will be assessed at 7 and 90-days post-procedure, participants will be advised to visit the emergency department if they suspect they have developed a blood clot (i.e. and not to wait for the study team to make contact).

Prior to the procedure, the following information will be collected from the patient and medical records:

- Baseline demographic information
- Name of surgical procedure
- Previous medical history and current medication

6.3 FOLLOW-UP

Participants will be followed-up by at 7 and 90-days post operation. This follow-up can be conducted via telephone or online questionnaire (the link to the questionnaire will be sent via email or SMS).

Data collection is summarised below:

Day 7 post procedure (assessed blindly)

- VTE outcome
- Mortality
- Quality of life questions – EQ-5D
- Adverse events with GCS (for participants enrolled in the intervention cluster only)

Day 90 post procedure (assessed blindly)

- VTE outcome
- Mortality
- Quality of life questions – EQ-5D
- Resource use questionnaire

The collection of follow-up data will be performed by blinded assessors based at the coordinating centre (Imperial College London).

Although the grant application stated that the EQ-5D would be collected at baseline (i.e. on the day of procedure), we have amended procedures so that the EQ-5D no longer needs to be collected at baseline. The collection of the EQ-5D at baseline would have made recruitment difficult from an operational/logistical perspective as patients would need to have been approached on the day of procedure to obtain this data. As the EQ-5D is no longer required at baseline, patients do not need to be approached on the day of procedure.

6.4 END OF STUDY

The end of the study is defined as the last patient last visit.

7. STATISTICS AND DATA ANALYSIS

7.1 Sample size calculation

Good quality data for the incidence of VTE in low VTE risk surgical patients not receiving VTE prophylaxis is lacking. The symptomatic VTE rate at 90 days for day-case cholecystectomy and inguinal hernia repair is approximately 0.3-0.5% (21). These patients are given GCS as standard practice. We are unable to determine how many of these patients received additional LMWH which would not be in line with NICE guidelines. Data from the recently published GAPS RCT on moderate and high risk patients reported 29/1858 VTE events at 90 days (1.6%) (13).

The VTE rate for short stay procedures in individuals formally assessed as being at low risk of VTE would be expected to be lower than this, however, as these short stay patients are not receiving LMWH we have conservatively assumed an overall control (no stockings nor drugs) of 1.0%.

The sample size calculation is for a superiority comparison based on symptomatic VTE (DVT or PE) at 90 days(Y/N) at 90% power with a significance level of 5%, assuming 1.0% in the no stocking (control) and 0.5% in the stocking (active) groups. That is, we expect that the stockings would need to achieve an absolute 0.5% reduction (50% relative reduction from 1%) to be clinically and cost-effective.

For an individually randomised trial, 6254 participants per group are required (equalling a total of 12,508). We will instead use a parallel groups cluster design in at least 50 hospitals. If we assume an ICC on the VTE at 90 days outcome of 0.001 (consistent with the control outcome rate varying uniformly between 0.5% and 1.5%) (22) and a coefficient of variation of site size of 0.25 (consistent with sites varying according to a Normal distribution mean=350 and SD=88 i.e. 95% of the sites would be between 174 and 526 participants), with 25 sites randomised to active and 25 sites to control, we would need to recruit 17,500 patients. Allowing for 15% loss to follow, but no sites lost to follow up, and adjusting for the group sequential design with one formal interim analysis at 50% with 90-day follow up, 21,472 participants are required. We do not believe there will be any meaningful crossover. We will incorporate a check on the sample size assumptions when there are 10 sites across both arms that have recruited at least 100 patients each (checking on variability in the control outcome for interclass correlation coefficient, ICC, and checking zero crossover). At this stage, as well as confirming the overall maximum sample size, we will include the schedule for a single efficacy or futility analysis at around 50% of the target recruitment with mature 90-day follow-up.

7.2 Statistical analyses

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan (SAP), authored by the study statistician(s) and agreed by the independent Trial Steering Committee (TSC).

The main analysis will be according to the intention-to-treat principle and will compare the rates of VTE at 90 days (Y/N), measured at an individual level, using a hierarchical (multilevel) logistic regression, adjusting for any other pre-specified strongly prognostic individual baseline covariates and site level baseline covariates, with site itself as a random effect. 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.

An early stopping rule based on numbers needed to treat (NNT) will be used. 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 independent Data Monitoring Committee (iDMC) to be assessed in the context of numbers needed to treat. Full details of the interim analysis and its statistical justification will be in the SAP and the iDMC Charter.

7.3 Internal pilot of feasibility and progression criteria

There will be an internal pilot of feasibility at 6 months, (beginning of month 7 to end of month 12) in which we will start recruiting the (minimum) 50 sites at 4 sites per month. The 100% recruitment rate to meet the sample size is 20 participants per centre month (accounting for the staggered site set-up). This equates to a target of 1440 participants at the end of the 6-month internal pilot. To clarify, although 1440 is equivalent to 7% of the overall 21,472 participants, it is the marker that the trial is on track to meet 100% recruitment by 30 months. Furthermore, criteria for crossover and follow-up have also been set for green progression. A stringent criterion of <5% failure to receive allocated intervention is set as a marker of crossover between trial arms. Regarding follow-up, a marker of <15% lost to follow-up would be indicative of green progression. The amber criteria is set at 75 – 99% of recruitment. This equates to a minimum of 1,080 participants across the 6-month internal pilot period and an associated mean recruitment rate of 15 participants per centre-month. We have set an amber criterion for site set-up independent of total recruitment number, hence, even if the total participant number is at 100%, if the number of sites set-up is <24 then this would stimulate a review of the site set-up strategy. Furthermore, amber criteria would be met if either of the crossover or follow-up criteria were not met. Any amber criteria would prompt a review of the trial methodology and recruitment strategy. The red criteria, i.e. consideration of stopping the trial early, is set at <75% recruitment and is equivalent to achieving fewer than 1,080 participants across the 6-month internal pilot period. An independent threshold for site set-up has been set at <18 sites. The Trial Steering Committee will meet at the end of month 13 (allowing 1 month of processing time after the 6 months of recruitment) with blinded estimation of the rate of VTE for each arm. This will confirm the sample size or lead to a sample size re-estimation.

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.

7.4 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 GCS to no thromboprophylaxis over the 90 days of the study. Resource use items associated with treatments in hospital and community care will be collected using case notes and self-completed patient resource use diaries over the 90-day follow-up, 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. Appropriate methods will be used to handle missing data and any relevant subgroups in line with the SAP.

2) If there are clinically relevant and measurable differences in VTE or quality of life between the study arms at 90 days, a Markov (state–transition) decision model will be constructed to compare the ICER up to 2 years for GCS versus no thromboprophylaxis. 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 (quality adjusted life years) 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 number needed to treat (NNT) to avoid 1 VTE, above which GCS would not be considered cost-effective at NICE thresholds. The 2-year time point was chosen as we know from previous research that the incidence of PTS after acute DVT levels out after the first year.

   This preliminary model assumes 30% of patients with VTE develop PTS, with 3% of those patients having severe PTS. The cost of purchasing and applying GCS stockings are approximately £22.46 (23). The model assumes the cost of treatment of VTE, non-severe and severe PTS, are £451, £872 and £1547 respectively, and estimates of the utility decrement associated with symptomatic VTE and PTS which are 0.8628, 0.7745 and 0.6752 respectively (24). Using a 2-year time horizon, the ICER of GCS versus no prophylaxis would be £20,603 per quality-adjusted life year (QALY) if the NNT were 200 participants. Hence, for GCS to be cost-effective at a NICE willingness to pay threshold, the NNT would need to be below 200 (see sample size).

   The health economic analyses will be conducted and reported according to NICE reference case and CHEERS guidelines (25,26), including sensitivity analyses and probabilistic sensitivity analyses. The results will be presented as estimates of mean incremental costs, effects, and incremental cost per QALY.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx 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.

8.2. CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Consent will be obtained in written, verbal or electronic form. The right of the participant to refuse to participate without providing any reason will be respected. After the participant has entered the study, 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.

8.3. 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.

The trial manager will only have access to pseudonymised data on REDCap.

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

Anonymised data will be transferred to the University of Granada for the purposes of conducting the cost-effectiveness analysis.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

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

8.6. FUNDING

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

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Imperial College London.

10. PUBLICATION POLICY

The following outputs are anticipated to arise from the PETS trial:

- Publications in peer reviewed journals (including the protocol paper, main trial analysis and cost-effectiveness analysis)
- The NICE guidelines aiming to prevent VTE "Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism [NG89]" will be subsequently updated
- Cost-effectiveness information to guide clinical commissioning groups and NICE
- Updated systematic review of literature and meta-analysis
- An understanding of the safety of GCS and subsequent quality of life
- Presentation at international academic conferences including European and American vascular, venous, general surgery and haematology societies
- Dissemination of results to the wider public through social media streams
- If GCS are found to ineffective, this could prompt a wider effect on the design and application of graduated compression stocking devices within the healthcare setting

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Appendix 1. Summary of investigations, treatment and assessments

Assessment	Week of assessment			
	Pre-surgical procedure	**0 (Day of procedure)**	**1**	**12**
Inclusion/Exclusion	X	X		
Informed consent[1]	X			
Screening assessments	X			
Demographics[1]		X		
Medical history (including concurrent medications)[1]		X	X	X
Provision of leaflet explaining the signs and symptoms of developing a blood clot	X			
Provision of stockings*		X		
EQ-5D			X	X
VTE outcome (self-reported)			X	X
Adverse Events Assessment*			X	
Resource use information				X

*Sites randomised to the intervention arm only

[1]Can be collected at any point up to the 7-day follow-up, including prior to the day of procedure (i.e. at the preassessment stage) or on the day of procedure