Compression Hosiery to Avoid Post-Thrombotic Syndrome

(CHAPS)

CLINICAL STUDY PROTOCOL

Sponsor:	Imperial College London
IRAS ID:	263041
REC Reference Number:	19/LO/1585
Indications:	Deep venous thrombosis (DVT)
Sponsor's Reference Number:	19CX5434
Funder's Reference Number:	NIHR HTA 17/147/47
Protocol Version:	4.0
Protocol Date:	25/06/2020

This study/project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme (project reference 17/147/47). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

REVISION HISTORY

Protocol Version	Date	Amendments
V 4.0	25/JUN/2020	- The Covid-19 pandemic has led to a long pause in study set up and recruitment which has enabled the authors to re-evaluate the protocol in detail. Although previous versions of the protocol were written with a pragmatic approach to the level of compression i.e. supplying UK Class II (18-24 mm Hg). The authors re-evaluated this decision and have amended the protocol to standardise the study intervention with other recently published trials. Stockings provided to trial patients randomised to the intervention arm should be the Class II European variety which have a slightly higher level of compression (23- 32 mm Hg). The stockings will be provided by a Medi UK. This change will allow the results of the trial to be more widely generalisable to the international community. - Addition of updated NICE guideline [NG158] (reference 21) which replaces NICE guideline [CG144] (reference 20). - New citation (reference) 1 to provide clarity on the definition of the exclusion criteria- contraindication to graduated compression stockings. - Update in the protocol to say the 2 week visit can be performed over the phone or via video call if restrictions prevent the participant attending in person. - The correct disclaimer for the funding body has been added to the title page.
V 3.0	02/JAN/2020	- Addition of information detailing the CHAPS Process Evaluation procedures.

v 2.0	21/NOV/2019	- Correction of typographical errors throughout the document to ensure that all stockings are Class II, 18-24mmHg - Correction of typographical errors to correct the name of the BMQ questionnaire to the BSQ questionnaire - Addition of a 'patient letter' to send to participants asking them to complete the health related quality of life questionnaires and a 'patient reminder letter' to send if the participant has not responded to the first letter. - Clarification of adverse event reporting procedures
v 1.0	02/SEP/2019	Protocol submitted to HRA/Ethics

CONTACT LIST

Chief Investigator

Professor Alun H Davies
Professor of Vascular Surgery & Consultant Surgeon
Department of Vascular Surgery
4th Floor, East Wing
Charing Cross Hospital
Fulham Palace Road
London, W6 8RF

Tel: +44 (0)203 311 7309
Fax: +44 (0)203 311 7362

Sponsor

Imperial College London
Contact: Head of Regulatory Compliance
Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2 Medical School Building
Norfolk Place
London, W2 1PG

Tel: +44 (0)207 594 1872

Funder

National Institute for Health Research (NIHR)
Health Technology Assessment (HTA) Programme (# 17/147/47)

University of Southampton
Alpha House
Enterprise Road
Southampton, SO16 7NS

Study Manager

Rebecca Lawton
Department of Vascular Surgery
Room 14, 4th Floor, East Wing
Charing Cross Hospital
Fulham Palace Road
London, W6 8RF

Tel: +44 (0)203 311 5204

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
Tel: +44 (0)131 651 7895

Study Statistician

Imad Adamestam
Clinical Trials Statistician
Edinburgh Clinical Trials Unit
Usher Institute- University of Edinburgh
9 Little France Road, Nine Edinburgh BioQuarter
Edinburgh, EH16 4UX
Email:
Tel:

Health Economist

Dr David Epstein
Department of Applied Economics
Faculty of Economics and Business Sciences
University of Granada
Email: davidepstein@ugr.es

Process Evaluation

Professor Robert Horne
Director, Centre for Behavioural Medicine
School of Pharmacy
University College London
Email: r.horne@ucl.ac.uk

Clinical Trial Unit

Edinburgh Clinical Trials Unit
Level 2, Nine Edinburgh BioQuarter
9 Little France Road
Edinburgh, EH16 4UX
Tel: +44 (0)131 651 7895
Fax: +44 (0)131 537 3581

ABBREVIATIONS

ABPI	Ankle Brachial Pressure Index
AE	Adverse Event
ATTRACT	Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis trial
B-IPQ	The Brief Illness Perception Questionnaire
BMI	Body Mass Index
BSQ	The Beliefs about Stocking Questionnaire
CACE	Complier Average Causal Estimation
CEAP	Clinical Etiological Anatomical Pathophysiological
CG	Clinical Guideline
CHAPS	Compression Hosiery to Avoid Post-Thrombotic Syndrome
CHEERS	Consolidated guidelines for economic evaluation
CI	Confidence Interval
CRF	Case Report Form
CTU	Clinical Trials Unit
DMC	Data Monitoring and Ethical Committee
DVT	Deep venous thrombosis
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
EQ-5D-5L	Euroqol 5D instrument for measuring generic health status
GCS	Graduated compression stocking
HRA	Health Research Authority
HTA	Health Technology Assessment
ICMJE	International Committee of Medical Journal Editors
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
ICTU	Imperial Clinical Trials Unit
MARS	Medication Adherence Report Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NNT	Number needed to treat
PPI	Patient and public involvement
PTS	Post-thrombotic syndrome
QA	Quality Assurance
QALY	Quality-adjusted life year
QC	Quality Control
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIMS	The Satisfaction with Information about Medicines Scale
SMS	Short Messaging Service
SOP	Standard Operating Procedure
SOX	Compression Stockings to Prevent the Post-Thrombotic Syndrome Trial
TIQ-A	Treatment Intrusiveness Questionnaire_Adapted (TIQ_A)
TMG	Trial Management Group
TSC	Trial Steering Committee
VEINES QoL/Sym	Instrument to measure quality of life in deep venous thrombosis
VTE	Venous thromboembolism

Table of Contents

CONTACT LIST **4**

ABBREVIATIONS **6**

TRIAL SUMMARY **10**

1. BACKGROUND 11
   - *1.1 Epidemiology of post-thrombotic syndrome 11*
   - *1.2 Impact of preventing post-thrombotic syndrome 11*
   - *1.3 Summary of current research 12*
   - *1.4 Rationale for the study 12*
   - *1.5 Risk / Benefit Assessment 12*
2. OBJECTIVES AND OUTCOMES 13
   - *2.1 Primary Objective 13*
   - *2.2 Secondary Objectives 13*
   - *2.3 Primary Endpoint 13*
   - *2.4 Secondary Endpoints 13*
3. STUDY DESIGN 14
   - *3.1 Design 14*
   - *3.2 Figure 1. Study Flowchart 15*
4. PARTICIPANT ENTRY 17
   - *4.1 Study setting and population 17*
5. DETAILS OF INTERVENTIONS 18
   - *5.1 Study Arms 18*
   - *5.2 Permanent Discontinuation of Study Intervention and Change of status 19*
6. PROCEDURES AND MEASUREMENTS 20
   - *6.1 Identification and recruitment of patients 20*
   - *6.2 Screening and pre-randomisation evaluations 20*
   - *6.3 Study Assessments 20*
   - *6.4 Randomisation and Blinding 21*
   - *6.5 Stocking ordering/re-ordering and fitting: 21*
   - *6.6 Follow up 21*
   - *6.7 Code-breaking/ Unblinding 22*
7. SAFETY REPORTING 27
   - *7.1 Adverse Event (AE) 27*
   - *7.2 Adverse Event recording 27*
   - *7.3 Serious Adverse Events (SAE) 28*
   - *7.4 Reporting of SAEs 29*
   - *7.5 Reporting urgent safety measures 29*
8. STATISTICS AND DATA ANALYSIS 31
   - *8.1 Sample Size and power considerations 31*
   - *8.2 Planned Data Analysis 31*
9. REGULATORY, ETHICAL AND LEGAL ISSUES 33
   - *9.1 Declaration of Helsinki 33*
   - *9.2 Good Clinical Practice 33*
   - *9.3 Independent Ethics Committee Approval 33*
   - *9.4 HRA approval 33*

9.5 Non-Compliance and Serious Breaches 34
9.6 Insurance and Indemnity 34
9.7 Trial Registration 34
9.8 Informed Consent 34
9.9 Contact with General Practitioner 35
9.10 Subject Confidentiality 35
9.11 Data Protection and Patient Confidentiality 35
9.12 End of Trial 35
9.13 Study Documentation and Data Storage 35
10. DATA MANAGEMENT 36
10.1 Source Data 36
10.2 Language 36
10.3 Database 36
10.4 Data Collection 36
10.5 Archiving 36
11. STUDY MANAGEMENT STRUCTURE 37
11.1 Trial Steering Committee 37
11.2 Trial Management Group 37
11.3 Data Monitoring Committee 37
11.4 Early Discontinuation of the Study 37
11.5 Risk Assessment 37
11.6 Monitoring 38
11.7 Quality Control and Quality Assurance 38
11.8 Peer review 38
11.9 Patient and Public Involvement 38
11.10 Publication and Dissemination policy 38
12. REFERENCES 40
SIGNATURE PAGE 1 (CHIEF INVESTIGATOR) 43
SIGNATURE PAGE 2 (SPONSOR) 44
SIGNATURE PAGE 3 (STATISTICIAN) 45
SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR) 46
APPENDIX 1- VILLALTA'S SCORE 47
APPENDIX 2- SCHEDULE OF ASSESSMENTS 1

TRIAL SUMMARY

TITLE
Compression Hosiery to Avoid Post-Thrombotic Syndrome (CHAPS)

OBJECTIVE
To measure the difference in incidence of post-thrombotic syndrome at a median of 18 months follow up after first, acute DVT between standard clinical care (anticoagulation) and the intervention arm (a graduated compression stocking and the standard clinical care (anticoagulation)).

DESIGN
Multi-centre, pragmatic, blinded outcome assessment, randomised controlled trial. The trial will follow patients up for a median of 18 months (range 6 – 30 months) and will be conducted in approximately 11 secondary care Trusts in the United Kingdom.

SAMPLE SIZE
A total of 864 patients will be recruited, in 1:1 allocation between the two randomised arms.

ELIGIBILITY CRITERIA

Inclusion Criteria

- Symptomatic presentation of first deep vein thrombosis, <2 weeks from diagnosis
- Imaging confirmed, lower limb deep vein thrombosis (popliteal, femoral, iliac or combination)
- Ability to give informed consent
- Age 18 or over

Exclusion Criteria

- Life expectancy < 2 years
- Contraindication to wearing graduated compression stockings (in line with International consensus statement(1))
- Previously intolerant of or already wearing graduated compression stockings for more than 1 month.
- Ankle brachial pressure index (ABPI) <0.8 or pedal pulses absent
- Bilateral deep vein thrombosis
- Previous chronic venous insufficiency (patients with existing chronic skin changes or ulceration, defined as C4,5,6 by CEAP classification)
- Pre-existing post thrombotic syndrome, significant leg pain (e.g. knee arthritis, spinal claudication) or oedema (e.g. lymphoedema).
- Newly diagnosed cancer, metastatic cancer, or cancer undergoing active treatment or palliation
- Contraindication to anticoagulation
- Known allergy to fabric in compression stockings

PRIMARY ENDPOINT

The primary outcome is any incidence of Post Thrombotic Syndrome (PTS) using the validated Villalta criteria (Appendix 1) over a median 18 month follow up (range 6 to 30 months). The primary outcome will be assessed on up to three occasions (6 and 12 months post randomisation, and at study end) depending on an individual participant's length of follow up (minimum 6 and maximum 30 months)

SECONDARY ENDPOINTS

- Venous ulceration incidence as measured by the validated Villalta criteria
- Employment status-(change in number of days working from baseline)
- Change in disease-specific and generic quality of life- VEINES-QoL and EuroQoL EQ5D scales from baseline over 6m, 12m and end of study visit
- Adherence to stockings and anticoagulants- patient self-report
- Cost-effectiveness of stocking prescription- Incremental cost-effectiveness ratio (ICER) from the EQ-5D questionnaire, with appropriate sensitivity analysis

1. BACKGROUND

1.1 Epidemiology of post-thrombotic syndrome

Deep venous thrombosis (DVT) occurs in approximately 1-2 per 1000 adults in the UK (2) and just under half will go on to develop lifelong disability from post-thrombotic syndrome (PTS) (3). PTS is defined as "chronic venous symptoms or signs secondary to deep vein thrombosis" e.g. lifelong leg pain, oedema and skin changes, progressing in 5% to venous ulceration (4). The pathophysiology of post- thrombotic syndrome is sustained venous hypertension from venous outflow obstruction and valvular incompetence (5). Three clinical scales are widely used to diagnose PTS after objectively-diagnosed DVT, Brandjes scale (6), Ginsberg measure (7) and Villalta scale (8) with the Villalta considered the "gold standard" for the diagnosis and classification of post-thrombotic syndrome (9).

The average age of patients developing PTS is 55 years (10), meaning that around half of patients work to support a family. Of patients having a lower limb DVT, around 30% of patients will develop mild PTS, 10% moderate and 5% severe PTS (3, 10). Severe PTS is characterised by leg ulceration. The incidence of DVT rises markedly with age (2) and the severity of PTS increases with age and body mass index (3) . With an older, heavier UK population in the future, the burden of PTS is set to rise.

1.2 Impact of preventing post-thrombotic syndrome

PTS is a lifelong condition that affects men and women of working age. On average, patients with PTS have difficulty walking and staying in active employment; and have levels of disability comparable to other chronic diseases such as chronic obstructive pulmonary disease (11). The 15-year direct healthcare costs of PTS have been estimated at £3000 per patient (12). Reducing the rates of venous ulceration are a key outcome as these increase costs from £3000 to £20,000 per patient (13, 14), due to the nursing time involved in twice-weekly compression bandaging and hospital admissions for management of infection. For those who work, there are personally incurred costs such as the use of taxis or the loss of earnings through days off sick and unemployment.

1.3 Summary of current research

Systematic reviews of the literature (15-17) highlight the need for a large definitive trial to settle the discrepancies between the earlier positive Brandjes (18) and Prandoni (19) RCTs and the later negative SOX trial (10). Furthermore, in the UK (20, 21) and USA (22) stockings are not recommended, however in Europe they are (23).

The ATTRACT trial evaluated the benefit of thrombolysis for acute DVT and showed no significant benefit in the prevention of post-thrombotic syndrome (47% v 48% at 2 years) (18). This has called into question the current DVT thrombolysis strategy recommended by NICE (15). Thrombolysis costs approximately £10,000 (19), requires an inpatient stay in a high dependency unit and has important safety risks such as intracranial haemorrhage. However, more importantly only 1 in 40 patients were actually eligible for thrombolysis in ATTRACT, meaning that 39/40 could not be offered thrombolysis (18). These issues are not encountered with stockings.

1.4 Rationale for the study

Until 2015, graduated compression stockings were recommended as standard of care by NICE. Key barriers to stocking use are evidence of effect, demonstration to Clinical Commissioning Groups that they are cost-effective and that adherence can be improved with low cost measures that are widely applicable. They also have to be seen as patient friendly and part of patient self-care for the condition.

Previous studies evaluating the effectiveness of graduated compression stockings (GCS) in preventing PTS have been inconsistent due to high heterogeneity. Further evidence is needed to determine the benefit of GCS in the incidence of PTS.

CHAPS includes an internal pilot study and process evaluation that acts as an adherence checkpoint at 1 year follow-up. In previous trials, 74% of patients allocated to stockings actually wore stockings for more than half of waking hours (24). Stockings are a medical device that are required to be used by patients regularly to exert a therapeutic effect on venous haemodynamics. As such, patients need to be trained and motivated in order for them to be used effectively. This was an important criticism of the SOX trial. Following recommendations from a previous study of the critical components to patient adherence (25), aids to adherence have also been incorporated into CHAPS.

1.5 Risk / Benefit Assessment

Graduated compression stockings, when used in patients with an adequate arterial circulation (palpable foot pulse or ABPI≥0.8), have no major side effects. There is a small risk that if not worn properly, GCS can cause excess pressure on the skin. GCS must be worn smoothly on the skin with no folding. There is also a risk that GCS can cause skin irritation, itching, redness or rash. Therefore, it is important patients are examined by a trained health professional before use.

In terms of benefit, prevention of long-term disability that results in 50% of patients following DVT is being examined. The CHAPS study group feel this is an acceptable risk/benefit balance.

2. OBJECTIVES AND OUTCOMES

2.1 Primary Objective

To measure the difference in incidence of post-thrombotic syndrome at a median of 18 months follow up after first, acute DVT between standard clinical care (anticoagulation) and the intervention arm (a graduated compression stocking and the standard clinical care (anticoagulation)).

2.2 Secondary Objectives

- To compare specific and generic quality of life at the end of the trial
- To compare employment status at the end of the trial
- To evaluate whether the use of stockings to prevent PTS is cost effective
- To perform a detailed process evaluation to understand barriers to adherence
- To measure adherence in detail over the initial first year and at the end of the trial
- To capture off-label stocking use in the standard care arm

2.3 Primary Endpoint

The primary outcome measure is any incidence of PTS using the validated Villalta's score over a median 18 month follow up (range 6 to 30 months). The primary outcome will be recorded at fixed time points for all those randomised; at 6 and 12 months post randomisation and at study end (estimated to be a median of 18 months, range 6-30 months).

2.4 Secondary Endpoints

- Venous ulceration incidence as measured by the validated Villalta's score
- Employment status-(change in number of days working from baseline)
- Change in disease-specific and generic quality of life- VEINES-QoL and EuroQoL EQ5D scales from baseline over 6m, 12m and end of study visit
- Adherence to stockings and anticoagulants- patient self-report
- Cost-effectiveness of stocking prescription- Incremental cost-effectiveness ratio (ICER) from the EQ-5D questionnaire, with appropriate sensitivity analysis

3. STUDY DESIGN

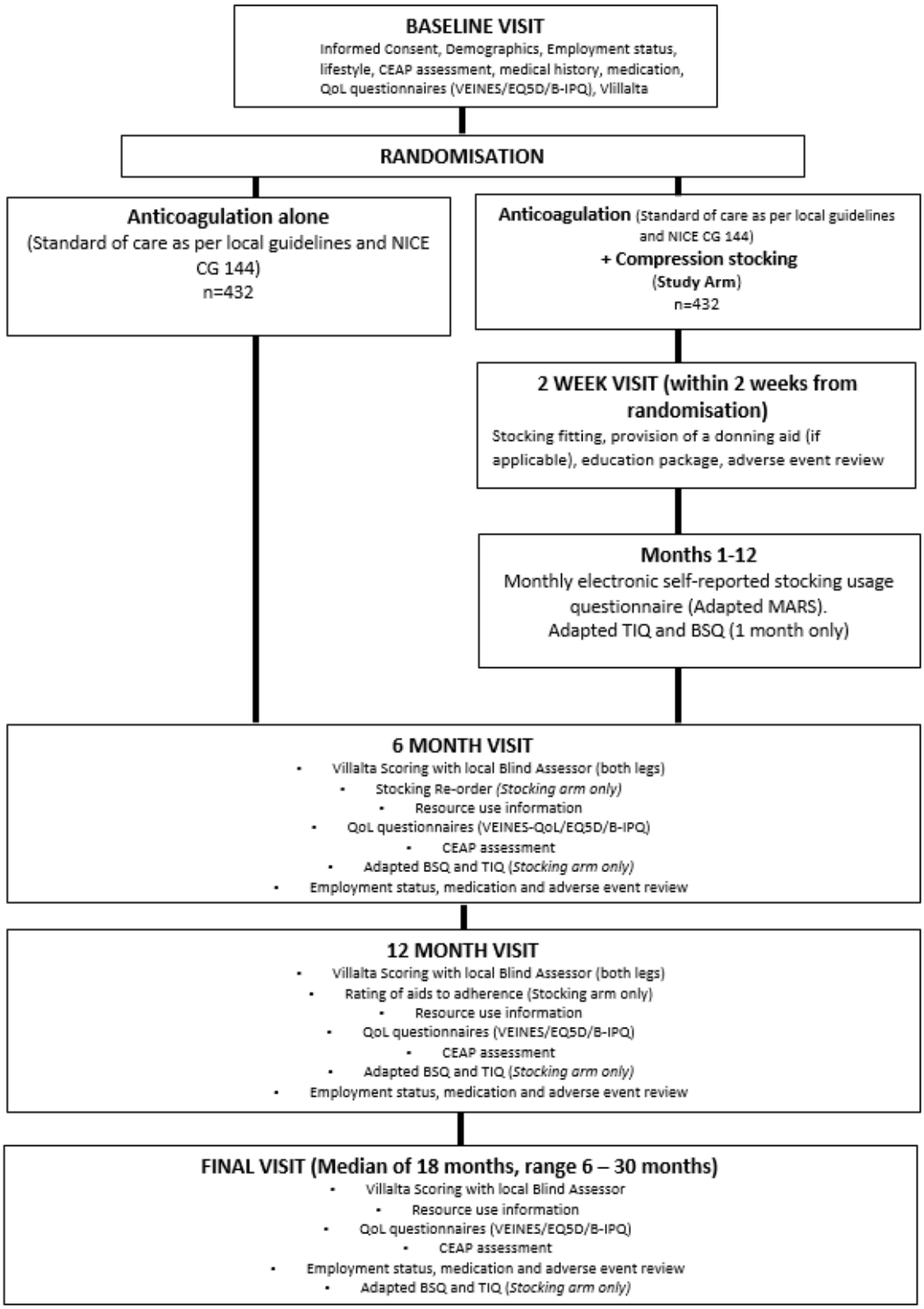
3.1 Design

CHAPS is a UK, multi-centre, pragmatic, blinded outcome assessment, randomised controlled trial. The 45-month trial will follow up patients with first, acute lower limb DVT for a median of 18 months (range 6 – 30 months) and will be conducted in approximately 11 secondary care Trusts in the United Kingdom.
Participants (n=864) will be randomised 1:1 to standard care (anticoagulation as per local hospital guidelines) or intervention (anticoagulation as per local hospital guidelines and regular use of a graduated compression stocking).

CHAPS has an internal pilot study which will follow the first 200 patients (100 intervention, 100 control) for one year and provide detailed information on stocking use in both arms. **At six months median follow up,** the criteria for continuing CHAPS is ≥70% of participants wearing stockings (self-reported patient adherence) for ≥4 days per week in the intervention arm, along with a documented reorder of stockings within the last 6 months.

A parallel process evaluation will complement the main CHAPS trial with the aim to better understand how and why the educational elements of the intervention were effective or ineffective. We will identify contextually relevant strategies for successful implementation through detailed descriptions of the participants' views and experiences of wearing graduated compression stockings. We will assess patients' perspectives of the stockings by applying a mixed-methods approach to identify the salient perceptions and practicalities influencing patients' motivation and ability to use the stockings as recommended..

3.2 Figure 1. Study Flowchart


BASELINE VISIT
Informed Consent, Demographics, Employment status, lifestyle, CEAP assessment, medical history, medication, QoL questionnaires (VEINES/EQ5D/B-IPQ), Vlillalta
RANDOMISATION
Anticoagulation alone
(Standard of care as per local guidelines and NICE CG 144)
n=432
Anticoagulation (Standard of care as per local guidelines and NICE CG 144)
+ Compression stocking
(Study Arm)
n=432
2 WEEK VISIT (within 2 weeks from randomisation)
Stocking fitting, provision of a donning aid (if applicable), education package, adverse event review
Months 1-12
Monthly electronic self-reported stocking usage questionnaire (Adapted MARS).
Adapted TIQ and BSQ (1 month only)
6 MONTH VISIT
Villalta Scoring with local Blind Assessor (both legs)
Stocking Re-order (Stocking arm only)
Resource use information
QoL questionnaires (VEINES-QoL/EQ5D/B-IPQ)
CEAP assessment
Adapted BSQ and TIQ (Stocking arm only)
Employment status, medication and adverse event review
12 MONTH VISIT
Villalta Scoring with local Blind Assessor (both legs)
Rating of aids to adherence (Stocking arm only)
Resource use information
QoL questionnaires (VEINES/EQ5D/B-IPQ)
CEAP assessment
Adapted BSQ and TIQ (Stocking arm only)
Employment status, medication and adverse event review
FINAL VISIT (Median of 18 months, range 6 – 30 months)
Villalta Scoring with local Blind Assessor
Resource use information
QoL questionnaires (VEINES/EQ5D/B-IPQ)
CEAP assessment
Employment status, medication and adverse event review
Adapted BSQ and TIQ (Stocking arm only)

4. PARTICIPANT ENTRY

4.1 Study setting and population

This study is open to all patients who are 18 years or older at the participating NHS sites with a diagnosis of first, acute DVT meeting specific inclusion and exclusion criteria.

(i) Inclusion criteria

- Symptomatic presentation of first deep vein thrombosis, <2 weeks from diagnosis
- Imaging confirmed, lower limb deep vein thrombosis (popliteal, femoral, iliac or combination)
- Ability to give informed consent
- Age 18 or over

Exclusion Criteria

- Life expectancy < 2 years
- Contraindication to wearing graduated compression stockings
- Previously intolerant of or already wearing graduated compression stockings for more than 1 month.
- Ankle brachial pressure index (ABPI) <0.8 or pedal pulses absent
- Bilateral deep vein thrombosis
- Previous chronic venous insufficiency (patients with existing chronic skin changes or ulceration, defined as C4,5,6 by CEAP classification)
- Pre-existing post thrombotic syndrome, significant leg pain (e.g. knee arthritis, spinal claudication) or oedema (e.g. lymphoedema).
- Newly diagnosed cancer, metastatic cancer, or cancer undergoing active treatment or palliation
- Contraindication to anticoagulation
- Known allergy to fabric in compression stockings

5. DETAILS OF INTERVENTIONS

5.1 Study Arms

(i) ARM 1: STANDARD OF CARE

Anticoagulation as per standard care, usually for a minimum of 3 months (as per NICE CG 144). Anticoagulation is usually prescribed as standard of care for a minimum of 3 months, however is variable on an individual patient basis. During this study, participants' anticoagulation regime will be recorded, as will be the adherence to prescription. The type and duration of anticoagulation will be left to the discretion of the treating clinician.

(ii) ARM 2: INTERVENTION/STUDY ARM

Anticoagulation as per standard care, usually for a minimum of 3 months (as per NICE CG 144) and a fitted, below knee stocking providing 23- 32 mm Hg pressure (Class II) worn during waking hours. Stockings will be supplied by Medi UK.

Regularly wearing stockings requires behavioural change, therefore a number of low cost behavioural aids will be made available to patients in the intervention arm to aid adherence:

- A patient education video at their first or second visit, detailing what post-thrombotic syndrome is, how it can affect a patient's life and their beliefs regarding wearing stockings
- A patient and carer training session at recruitment of how to don stockings, reinforced by up to 2 follow up fitting appointments at 2 weeks and again if necessary
- Free provision of a donning aid at 2 weeks if the participant is struggling to wear the stockings regularly
- An SMS reminder to wear their stockings including a motivational SMS reminder to wear their stockings and fill out their adherence questionnaire. A number for stocking re-order will be provided
- An anonymous web forum to provide peer to peer support regarding the best types of stockings and tips and tricks for use
- A variety of below knee stockings including cotton stockings for the summer months to mitigate the effects of heat, and dress stockings for social occasions. Once a good fit has been established, patients will be provided with 2 pairs of stockings (one summer one winter pair) to minimise the number of times that washes are required. Every 6 months, patients will be asked to reorder stockings by telephone or text, as per their instructions for use (26)

5.2 Permanent Discontinuation of Study Intervention and Change of status

(i) Permanent discontinuation of study intervention

Subjects may discontinue study intervention for the following reasons:

- At the request of the subject.
- Adverse event/ Serious Adverse Event
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illness that develop after entering the study, e.g. development of peripheral arterial disease or leg amputation.

(ii) Change of status

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

- Subject decision to withdraw
- Loss to follow-up
- Death
- New diagnosis of metastatic cancer
- Venoplasty or venous stenting for post-thrombotic syndrome

(iii) Procedures for Withdrawal from Study

Participants who meet the above criteria will be free to withdraw from the study. Participants will be free to withdraw from the study without any effect on their usual medical care. The reason for their withdrawal will be recorded in the CRF/eCRF and medical records if offered. All randomised patients will be followed up for between 6 – 30 months (median 18 months) unless they specifically ask to be withdrawn as per intention to treat. In line with this analysis, patients lost to follow up or withdrawn from the study will not be replaced.

6. PROCEDURES AND MEASUREMENTS

6.1 Identification and recruitment of patients

Recruitment will primarily be from vascular or haematology clinics and A&E but in addition may be from inpatient and maternity wards in approximately 11 secondary care UK hospitals. The largest sites see around 240 proximal DVTs per year, whereas the smaller sites see around 120. Hence the total number of potential participants would be just under 3000 per year, across 11 sites. From this pool, recruitment of 864 participants is planned over 30 months. In summary, it is anticipated that 1 in 6 participants will be eligible and willing to join CHAPS.

6.2 Screening and pre-randomisation evaluations

Adults with first, acute DVT presenting to participating NHS organisations will be pre- screened by a member of the direct care team and invited to speak to a research nurse. With permission of the participant the reasons for non-inclusion will be logged anonymously along with a minimum data set of age, sex and reason for exclusion. The anonymised pre-screening logs will be transferred to the Trial Coordinating Centre for the purposes of monitoring recruitment.

Participants will have pedal pulses palpated by a trained health professional. If pedal pulses are absent (score=0) the participant will not be eligible to take part in the trial. If the research team are unable to assess the pedal pulses an ankle-brachial pressure measurement should be taken prior to entry into the study. An ABPI of <0.8 is an exclusion criteria.

Informed consent can be taken by research personnel if the patient is eligible at the baseline visit. If the patient requires more time to consider the study a baseline assessment can be arranged for another time but must be ≤ 2 weeks after imaging confirmed diagnosis of DVT.

6.3 Study Assessments

Baseline visit

Following consenting and screening procedures patients will undergo a series of baseline assessments or questionnaires to record the following:

- Demographic data- date of birth, gender and ethnicity
- Employment status
- Height, weight and Body Mass Index (BMI)
- Lifestyle data- smoking status, alcohol consumption, physical activity level
- Comprehensive Classification System for Chronic Venous Disorders (CEAP). A score between C4-C6 indicates that the patient is ineligible for the study.
- Villalta's score
- Medical history
- Concomitant medication

- Quality of life assessments- EQ-5D-DL, VEINES-QoL and B-IPQ

Details about the patients DVT including symptom onset, extent and location will be recorded at baseline. A copy of the anonymised imaging report confirming the DVT diagnosis will be securely transferred to the Trial Manager (Imperial College London) using the Imperial College File Exchange. For full details of the study assessments see Appendix 2.

6.4 Randomisation and Blinding

Participants will undergo 1:1 web based randomisation to either standard care or the intervention via an automated system linked to the eCRF setup via the Study Data Centre at the Edinburgh Clinical Trials Unit (ECTU), University of Edinburgh (a fully registered UKCRC Clinical Trials Unit, registration number 15).

An independent researcher at each site will perform leg assessments blind to participant allocation. This researcher will not have been involved in recruitment, stocking provision, adherence monitoring or behavioural interventions. Participants will be encouraged to remove their stockings on the day prior to their clinic visit, they will be asked not to discuss the stockings with the independent assessor. Blinding will be assessed by asking the assessors whether the patient attended study visits wearing a stocking, and whether the patient made it known that they had been wearing a stocking or not.

6.5 Stocking ordering/re-ordering and fitting:

Participants randomised to the stocking arm will have their index leg measured for stockings at baseline by the local research nurse. Once the participant's legs have been measured the research nurse will contact Medi UK Ltd to request a pair of Class II stockings (23-32mmHg). The participant's leg measurements will be provided to the manufacturer, along with their study ID to ensure the stockings are supplied to the correct participant. No other information will be sent to the supplier. Medi UK will send the stockings to the local hospital site. The research nurse will then send the stockings to the participant in the post or the participant will be able to collect them in person. Thehe level of compression must be between 23- 32 mm Hg (Class II) and knee-length or thigh length depending on patient preference. They should be worn on the DVT-affected leg daily, applied upon waking and removed upon retiring to bed, beginning as early as possible within 14 days after DVT diagnosis and continued for the duration of the study. Patients will be reminded by the research nurse at each face to face follow up visit to wear their stockings daily in addition to receiving SMS reminders.

Medi UK Ltd will act as stocking supplier for the study. A proportion of the stockings will be donated free of charge for the use of participants randomised into the study. Medi UK Ltd will not have access to any data during the study or prior to publication of the anonymised results of the study.

6.6 Follow up

Participants in both arms will be followed up face to face at 6 months 12 months and at the final visit which may be between 18 and 30 months depending on when the patient was recruited into

the trial. Visits will be performed in clinic so that a blinded clinical assessment of both legs can be performed using the Villalta's score.

In addition, participants randomised to wear stockings will be seen in clinic at 2 weeks for a stocking training session. This can be performed over the phone or via video call if restrictions mean the participant cannot attend hospital. The research nurse will discuss any barriers to wearing the stockings, check the size and position and provide training in the use of a donning aid if required. The stocking video will be shown to the patient again to motivate them to adhere to the intervention. Participants randomised to the stocking arm will also receive a monthly online stocking usage questionnaire (adapted MARS) which will be completed remotely by the patient via the electronic database who will receive an email from ECTU with login details. Participants can opt to receive this via phone call or the post if they prefer.

At face to face clinic visits, patients randomised to wear stockings will also receive the Beliefs about Stockings Questionnaire (BSQ) which has been adapted to assess patients' beliefs and views about wearing stockings. They will also receive the Treatment Intrusiveness Questionnaire (TIQ) which has been adapted to assess how stockings may interfere with participants' daily lives as well as practical barriers to prevent daily wear.

Monthly online stocking usage questionnaire:

Participants in the intervention arm will receive a monthly web survey regarding their use of stockings, to assess adherence to the intervention. This can also be administered via the phone or post if the participant chooses.

The web survey has been adapted from the Medication Adherence Rating Scale (MARS). It is a commonly used questionnaire in which the patient himself/herself assesses how often he/she engages in nonadherent behaviour. This scale has been adapted for CHAPS to assess use of stockings rather than medication.

A visual analogue scale will assess since the last visit how much of the time the patient has worn stockings, whether this was a trial stocking, if not a trial stocking the make and class of the stocking (compression level), and if they have discontinued stocking use, why?

Further Follow-Up

- Face to face follow up at the end of the follow up period will be performed with an independent blind assessor who has been trained in the use of the Villalta's scoring system for PTS. Participants will be followed for between 6 – 30 months (median 18 months).
- If a patient develops a leg ulcer, they will be advised to attend their local vascular service for treatment according to standard care.

6.7 Code-breaking/ Unblinding

It is not possible to mask participants or the research to the intervention and a sham stocking was deemed impractical to administer. The primary outcome assessment (incidence of PTS) will be completed by an independent clinical assessor trained in the use of the Villalta's score, who will

have no previous involvement with, or knowledge of, the participant's treatment allocation and as such will be blind. Participants will be reminded to remove their stockings prior to any face to face clinic visit or assessment with the blinded clinician.

6.8 Process Evaluation

The aim of the process evaluation is to complement the main CHAPS trial, to better understand how and why the educational elements of the intervention were effective or ineffective. We will identify contextually relevant strategies for successful implementation through detailed descriptions of the participants' views and experiences of wearing graduated compression stockings. We will assess patients' perspectives of the stockings by applying a mixed-methods approach to identify the salient perceptions and practicalities influencing patients' motivation and ability to use the stockings as recommended.

6.8.1 Process evaluation design

The design of the process evaluation is a mixed-methods study using quantitative and qualitative data from interview data and purposively selected case study practices.

We will use a combination of:

Common quantitative methods including:

• Structured observations;

• Self-report questionnaires- adapted BSQ, TIQ, MARS

• Secondary analysis of routine data.

Common qualitative methods include:

• One-to-one telephone interviews with a post-doctoral qualitative researcher based at University College London (UCL)

Patients randomised to the intervention will receive an education 'package' containing a number of elements designed around a Perceptions and Practicalities Approach (PAPA™) (27) for supporting adherence. As non-adherence may be linked to ideas around patient beliefs about the development of PTS the necessity of wearing stockings and concerns about the potential side effects, confidence building and constructive feedback through interactions with the research nurse are designed to improve self-mastery and ultimately adherence to GCS throughout the study.

Adherence is considered to be a modifiable trait and the process evaluation aims to understand if adherence has been enhanced by the education package over the course of the trial. Definitions of adequate adherence will be described in detail in the CHAPS statistical analysis plan.

At the trial baseline visit patients will be randomised 1:1 to receive either: Standard care (anticoagulation alone), or Intervention (anticoagulation plus graduated compression stockings).

Patients randomised to the intervention will be told of their treatment allocation and then administered the educational package designed to increase understanding of PTS, the importance of wearing GCS regularly to avoid PTS and provided with supporting tools designed to motivate and encourage them to adhere to the intervention.

The overarching concept of the adherence-promoting package is that by targeting patients' motivation, enhancing the usual patient-provider interaction and improving the healthcare environment, adherence will reach a level of adequacy to provide a robust and conclusive answer to the main CHAPS research question.

The Perceptions and Practicalities framework (27) suggests that non adherence to recommended therapies is a complex human behaviour which can be broadly categorised as:

Unintentional non-adherence

Occurring when patients want to take the recommended treatment but are prevented in doing so by external barriers beyond their control. For example, patients may forget to apply GCS, they may not be physically able to get them on or the healthcare practitioner may not have communicated that they need to be worn everyday.

Intentional non-adherence

Occurs when the patient decides not to adhere. Intentional non-adherence is best explained in terms of the perceptions that shape the patient's motivation to start and continue with treatment. For example, patients may not display any symptoms of PTS for many months so could think compression therapy is unnecessary. As around 50% of people will go on to develop PTS after first acute DVT some patients may decide to take their chance.

6.9 Process evaluation methods

In-depth telephone interviews will take place on a sample of patients enrolled in the trial around 2 weeks after receiving the intervention. A further series of qualitative interviews will take place at around 6 months post randomisation to capture patients who have experienced wearing stockings during more than one season.

A sample of patients who are both at high and low risk of non-adherence will be identified based on responses to the online questionnaires. Subjects will be invited to attend a telephone interview with a qualitative researcher at UCL via their local research nurse. If the participant consents to take part in the process evaluation, their contact details and a copy of their consent form will be passed on to the qualitative researcher who will arrange a time to conduct the interview. Once the consent from has been checked by the qualitative researcher it will be destroyed in a confidential manner.

In a guided conversation with the researcher, participants will be asked to describe their experience of taking part in the CHAPS trial, their perceptions of things they valued and found of particular benefit in the trial (in terms of wearing stockings), as well as any negative aspects. The interviewer

will also discuss any factors that encouraged or hindered their ability to wear GCS, and whether and in what ways they have continued to make use of the educational package received.

The interviews will be audio-recorded, transcribed and textual coding undertaken by a researcher at University College London. The lower level codes will be grouped into themes and analysis undertaken through a process of constant comparison. Two members of the process evaluation team will participate in data analysis to reduce bias in the identification and interpretation of themes.

6.10 Early interviews

Once recruitment has commenced approximately 20 patients enrolled into the study will be contacted by a research nurse and invited to take part in an in depth interview with a qualitative researcher. If the participant agrees, the qualitative researcher will make contact with the patient and explain the purpose of the interviews. The patient will receive a gift voucher for taking part.

The 1:1 interviews with the researcher will take place via telephone after the patient has read the information sheet and signed a consent form. Interviews will be semi structured and conducted in a conversational manner with probes, facilitation, and clarification of responses as required by the interviewer.

The topics covered will include participants' experiences of wearing GCS, their perceptions of things they found helpful in aiding their adherence and any negative aspects or things that hindered their use of GCS on a daily basis. The content of the educational video and coaching received from the research nurse will also be discussed and its usefulness in preparing them to wear GCS after DVT.

Interviews are planned to be conducted at this time point as feedback will give the coordination team the opportunity to adapt the intervention if themes emerge that may be relevant to future patients enrolled in the trial.

6.11 Late interviews

Late interviews will coincide with the main CHAPS trial at around the 6 month follow up visit. A purposive sample of 10 highly adherent patients and 10 poorly adherent patients will be identified at random by the study statistician based upon patient responses to the monthly questionnaires from the intervention arm only.

The rationale behind the late interviews is that patients will have been wearing GCS for 6 months and will have experienced wearing them through different seasons. A seasonal effect is something that was considered to be important in previous trials and anecdotally from interviews conducted with lay patients at the grant application stage.

Interviews will follow the same structure as the early interviews, 1:1 with a researcher via telephone. Interviews will be semi structured and conducted in a conversational manner with probes, facilitation, and clarification of responses as required by the interviewer.

The topics covered will include participants' experiences of wearing GCS over the previous six months, and for the poorly adherent what barriers have prevented them from wearing them regularly. Patient perceptions of things they found helpful in aiding their adherence and any negative aspects or things that hindered their use of GCS will be explored. The content of the educational video and the coaching from the research nurse will also be discussed and its usefulness in their decisions to continue to wear or not wear the GCS.

6.12 Quantitative Measures

Adapted questionnaires [BSQ, TIQ, MARS(28-30)] will be used to assess the key perceptions and practicalities likely to influence patients' motivation and ability to adhere to the stockings.
The BSQ and the TIQ will be assessed at months 1-6, month 12 and at the final study assessment visit. The MARS will be assessed monthly until the end of the participation. The questionnaires will be completed by the patient either at scheduled study visits or online in accordance with the CHAPS study protocol.

6.13 Process Evaluation Analysis

The interviews conducted with the researcher will be audio-recorded (with consent) and transcribed. The analysis will proceed alongside data collection and will be based on a framework approach (31). This is suitable for small numbers of cases and ensures that each case is fully taken into account in the analysis. Initial themes will be identified that are then grouped into main and subthemes. This is applied to the raw transcript data for each interview, and a thematic "chart" is created that summarises information for each theme and allows cross-case and within-case analysis through a process of comparison.

6.14 Data Storage

Investigators at each recruiting centre will retain the original consent form for the process evaluation until notified by the Sponsor, and for at least ten years after study completion. A copy of the consent form will be securely transferred to the researcher at UCL which will be destroyed after it has been checked.

Documents will be stored in such a way that they can be accessed/data retrieved at a later date. No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

Study data gathered by UCL during the process evaluation will be kept in a secure location and in accordance with the terms of the Data Protection Act 2018. Participant confidentiality will be maintained at all times and all study records will be kept in pseudonymised form identifying participants by a pseudonym rather than name, or hospital number.

Any paper interview transcripts or notes made by the UCL researcher during the interview will be kept in locked filing cabinets in locked rooms at UCL, only accessible by authorised personnel and destroyed at the end of the study. The key to the participant code list will be kept separately to these documents and destroyed at the end of the study.

Electronic data of pseudonymised interview transcripts, the final coding frame and coding tables may be transferred via the Imperial College File Exchange, password protected and encrypted where possible. Any data that is stored on Imperial College London networked computers will be stored in an anonymised form with no identifiable information. The electronic pseudonymised transcript will be retained by UCL until the end of the study, it will then be archived for up to 10 years in line with Imperial College Sponsor requirements.

7. SAFETY REPORTING

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the trial protocol.

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

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

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

7.2 Adverse Event recording

For the purposes of the study, all AEs will be followed up according to local practice until the event has stabilised or resolved, whichever the sooner is. It is essential that all AEs that occur during the course of the study are appropriately reported in order to ensure the participants continuing safety. Of particular importance is the assessment of any event for *causality* and *expectedness* in relation to the stockings. All adverse events whether expected or not should be recorded. 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.

(i) Severity of Adverse Events

Definitions for assessment of severity:

Mild: Awareness of event but easily tolerated
Moderate: Discomfort enough to cause some interference with usual activity
Severe: Inability to carry out usual activity

(ii) Causality of Adverse Events

Definitions for assessment of causality:

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.3 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" 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.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

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

7.4 Reporting of SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF).

All SAEs will be reported to the JRCO as soon as possible after becoming aware of the event.

(i) Related SAEs

Related: resulted from administration of any of the research procedures

(ii) Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

(iii) Reporting of SAEs that are related and unexpected

SAEs that are related and unexpected should be notified to the relevant REC and the Sponsor in accordance with local requirements.

Follow up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised.

(iv) Annual reporting of Serious Adverse Events

Annual Safety reports will be submitted to the Sponsor and the Ethics Committee in accordance with local requirements.

7.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICS AND DATA ANALYSIS

8.1 Sample Size and power considerations

The sample size calculation for this study was based on the primary endpoint of incidence of PTS. With improvements in anticoagulation since the previously mentioned SOX trial, it is anticipated that 30% of the control arm will develop PTS at some point during the follow up (median 18 months, range 6 to 30 months), rather than the 40% observed in SOX. In smaller trials, the number needed to treat varied from 1 in 2 (18), to 1 in 4 (19), however SOX demonstrated no benefit. As smaller trials tend to overestimate treatment effect and because the use of a stocking means investment into a behavioural change for each patient, the number needed to treat (NNT) for CHAPS has been set at 1 in 10.

With 864 participants, the study will have 90% power at a 5% level of significance using a test of binomial proportions to detect an absolute reduction in the incidence of PTS of 10% (from 30% in the standard care arm to 20% in the stockings plus standard care arm), allowing for 10% loss to follow up.

8.2 Planned Data Analysis

Quantitative analysis and oversight will be performed in conjunction with the Edinburgh Clinical Trials Unit (ECTU). ECTU will work closely with the CI and trial manager on the delivery of the data management and statistical aspects of the study, in compliance with the applicable regulations.

(i) Primary Endpoint Analysis

At a median of 18 months (range 6-30 months) patients will be seen by an independent, blinded observer to assess their degree of post-thrombotic syndrome using the validated semi-quantitative Villalta scoring system.
The primary analysis will be an intention-to-treat analysis that does not adjust for adherence to stockings. This will tell us the treatment effect given the observed adherence, which is appropriate to gauge real-world performance.
We will use a time-to-first-event approach since it is possible that the treatment effect may be a combination of averting PTS, but also in those that develop PTS the onset may be delayed.

(ii) Secondary Endpoints Analysis

Secondary analysis will determine how much the behavioural components affect adherence; firstly whether behavioural components change participants knowledge, beliefs and intentions regarding stocking usage. Secondly, to determine what extent compliance has indeed mediated outcome using Complier Average Causal Estimation (CACE) causal modelling through instrumental variable regression i.e. does better compliance improve outcomes; and looking ahead, whether future development of behavioural components is likely to be beneficial.

Full rationale and methodological details of the intention to treat compliance-unadjusted, supplementary compliance based analyses and secondary endpoint analyses will be detailed in the comprehensive Statistical Analysis Plan.

(iv) Adjusted Analysis (missing, unused and spurious data)

(v) Health Economic Analysis

A within-trial analysis and a decision model will be constructed. In both cases, the main analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary analyses will be performed from a societal perspective. The price year will be 2018. Discounting will be applied according to UK Government guidelines. The study will be reported according to consolidated guidelines for economic evaluation (CHEERS).

The within-trial analysis will compare the treatment strategies within the 18-month time horizon of the clinical trial. Data will be collected by case note review and questionnaires completed at baseline and follow-ups. Resource use items in hospital and community care, adverse events or complications will be recorded for each patient at each follow-up. Resource use will be multiplied by UK unit costs obtained from published literature, Healthcare Resource Groups, and manufacturers' list prices to calculate overall costs. Utilities (QALYs) will be calculated from the EQ-5D questionnaire. The extent of missing data will be assessed and appropriate methods to handle missing data will be applied. The incremental cost-effectiveness ratio will be calculated and compared to current UK decision making thresholds. Sensitivity analysis will be carried out to test the robustness of results to alternative assumptions (for example, about missing data, or using per-protocol estimates of treatment effect). Probabilistic sensitivity analysis will be carried out using bootstrapping. Subgroup analyses consistent with the protocol of the clinical trial will be considered.

The decision model provides a framework to incorporate evidence from other relevant studies and to extrapolate outcomes beyond the trial reporting period. The Markov model will include the key health states and events that may occur during the lifetime of the patient (PTS, venous leg ulcer, deep venous stenting, etc.) A literature review will be conducted to identify other economic studies and other trials in comparable populations. The data to support extrapolation may be taken from the trial (e.g. fitting parametric time-to-event functions to the trial data) or may come from external sources (such as observational data).

The results of the analyses will be presented as estimates of mean incremental costs, effects, and, incremental cost per QALY. Sensitivity analysis will be conducted to test the robustness of the results to alternative assumptions about model structure, assumptions and input data. Probabilistic sensitivity analysis will be conducted using Monte-Carlo simulation.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in the spirit of the 1964 Declaration of Helsinki, adopted by the 18th World Medical Assembly, and all later revisions.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Independent Ethics Committee Approval

(i) Initial Approval

Prior to the enrolment of subjects, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

(iii) Annual Progress Reports and End of Trial Notification

The REC will be sent annual progress reports in accordance with national requirements and will also be informed about the end of the trial, within the required timelines.

9.4 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.5 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

9.6 Insurance and 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.

9.7 Trial Registration

The study is registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

The study will be registered on ISCTRN.

9.8 Informed Consent

Consent will be through standard GCP measures including a patient information sheet and signed informed consent form. No minors are eligible to join CHAPS.
Consent to enter the study will be sought from each participant only after a full verbal explanation has been given, and an information leaflet offered. The consent will be informed, voluntary and participants will be given an appropriate amount of time to consider participation and to ask questions. There will be no set minimum time to consider the trial as this will be determined on a case by case basis, this is usually 24 hours but could be less if there is agreement from both the researcher and participant that the consent is fully informed.

Signed participant consent will be obtained and participants will be asked to consent for their data to be linked with appropriate databases including Hospital Episode Statistics (HES), and the National Vascular Database as well as for longer term follow-up in the event the trial is extended. A copy of the signed Participant Information Sheet/Informed Consent Form document will be provided to the patient and the original Informed Consent Form should be retained with the source documents.

The right of the participant to refuse to participate without giving reasons will be respected, although if the participate is willing a reason for declining will be recorded. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. Participants will be asked to consent to long term follow up to allow for linkage to routine datasets including Hospital Episode Statistics (HES) and the National Vascular Database.

9.9 Contact with General Practitioner

The investigator will inform the subject's General Practitioner by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter will be filed in the Investigator Site File. It is possible that the GP will be contacted to obtain trial information in the event that the patient cannot be contacted.

9.10 Subject Confidentiality

The investigator will ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) will be kept in a strictly confidential file by the investigator.

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.

9.11 Data Protection and Patient Confidentiality

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with the Data Protection Act

9.12 End of Trial

The end of trial is defined as the last subject, last visit.

9.13 Study Documentation and Data Storage

The investigator will retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) will be retained. Documents will be stored in such a way that they can be accessed/data retrieved at a later date. Consideration will be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

Data will be written directly into the CRF (source data) and then transcribed into the eCRF. Source documents include original documents related to the trial, to medical treatment and to the history of the participant, and adequate source documentation must be maintained to allow reliable verification and validation of the trial data.

10.2 Language

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

10.3 Database

The principal means of data collection from participant visits will be Electronic Data Capture (EDC) in the bespoke database system via the internet. Data is entered into the EDC system via site personnel. All source data recorded in the CRF will be signed by the Investigator or his/her appropriate designee. All changes made following the electronic signing will have an electronic audit trail with a username and date. Specific instructions and further details will be outlined in SOPs and/or manuals.

10.4 Data Collection

Details of procedures for CRF/eCRF completion will be provided in a study manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years *(amend as per Sponsor requirements)* following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

The study will be coordinated by a trial manager who will report to the Chief Investigator. The trial manager will liaise with local principal investigators to ensure that the trial is conducted locally according to protocol and in an expeditious manner. The organisational structure and responsibilities are outlined below.

11.1 Trial Steering Committee

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

A trial steering committee meeting will be held at the start of CHAPS prior to commencement of recruitment and at least annually as per NIHR guidelines, with the lay applicant invited to attend each convening.

11.2 Trial Management Group

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

11.3 Data Monitoring Committee

A data monitoring committee meeting will be held prior to first patient first visit, following completion of the pilot study, and will then be held one month prior to each TSC meeting. Further details will be defined in the separate DMC Charter.

After the results of the 100-patient adherence pilot are available in June 2020, the data monitoring committee will submit the pilot study adherence results to NIHR.

11.4 Early Discontinuation of the Study

If one year adherence is <70% of participants in the intervention arm wearing the stocking for <4 days per week the trial will stop after the 1 year adherence pilot phase. There will be no further follow up.

11.5 Risk Assessment

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

11.6 Monitoring

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

Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

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

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

11.8 Peer review

CHAPS has been peer reviewed by NIHR and international experts.

11.9 Patient and Public Involvement

Patients, their carers' and relatives were involved in a 3-stage consultation process during the trial development stage, incorporating the INVOLVE methodology. This consisted of a series of semi-structured interviews, a survey run via Thrombosis UK, and review of the CHAPS research plan and lay summary. Responses and feedback were incorporated into the design and budget of CHAPS.

The Imperial Vascular PPI group has contributed 4 patients and 2 members of the public who are available for the duration of CHAPS. These individuals had the opportunity to review the detailed research plan and will be available to review patient information sheets, newsletters and informed consent forms for CHAPS. The expert patients will help select appropriate brands and types of stockings for use in summer and winter months, along with donning aids that they have found to be beneficial. A patient applicant will be invited to join the TSC and attend trial meetings.
The patient applicant will moderate and feedback from the patient Facebook group, for example, if there are technical or scientific queries, or problems with reordering stockings.

11.10 Publication and Dissemination policy

The final results of CHAPS, the process evaluation and the cost-effectiveness analysis will be published in a high impact journal and presented at international and national vascular and haematology conferences. The results will be presented to the National Institute for Health and Care Excellence, and at UK, European and American vascular, venous and haematology societies. This will lead to the generation of altmetric data.
Dissemination will be via the Thrombosis UK Facebook group to patients, Imperial College London website to the public, via peer reviewed publication for health professionals, and an email summary will be sent to all trial participants.

All information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

12. REFERENCES

1. Rabe E, Partsch H, Morrison N, Meissner MH, Mosti G, Lattimer CR, et al. Risks and contraindications of medical compression treatment – A critical reappraisal. An international consensus statement. Phlebology. 2020:0268355520909066.

2. Raskob GE AP, Blanco AN, Buller H, Gallus A, Hunt BJ, Hylek EM, Kakkar A, Konstantinides SV, McCumber M, Ozaki Y, Wendelboe A, Weitz JI. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014;12(10):1580-90.

3. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Annals of internal medicine. 2008;149(10):698-707.

4. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. Journal of thrombosis and haemostasis : JTH. 2009;7(5):879-83.

5. Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood reviews. 2002;16(3):155-65.

6. Brandjes DPM, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. The Lancet. 1997;349(9054):759-62.

7. Ginsberg JS, Turkstra F, Buller HR, MacKinnon B, Magier D, Hirsh J. Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. Archives of internal medicine. 2000;160(5):669-72.

8. Villalta S BP, Piccioli A, Lensing A, Prins MH. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. Haemostasis. 1994.

9. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. Journal of Vascular Surgery. 2013;57(1):254-61.

10. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet (London, England). 2014;383(9920):880-8.

11. Kahn SR, Shbaklo H, Lamping DL, Holcroft CA, Shrier I, Miron MJ, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. Journal of thrombosis and haemostasis : JTH. 2008;6(7):1105-12.

12. Caprini JA, Botteman MF, Stephens JM, Nadipelli V, Ewing MM, Brandt S, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2003;6(1):59-74.

13. Epstein D, Gohel M, Heatley F, Davies AH. Cost-effectiveness of treatments for superficial venous reflux in patients with chronic venous ulceration. BJS open. 2018;2(4):203-12.

14. Olin JW, Beusterien KM, Childs MB, Seavey C, McHugh L, Griffiths RI. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. Vascular medicine (London, England). 1999;4(1):1-7.

15. Berntsen CF, Kristiansen A, Akl EA, Sandset PM, Jacobsen EM, Guyatt G, et al. Compression Stockings for Preventing the Postthrombotic Syndrome in Patients with Deep Vein Thrombosis. The American journal of medicine. 2016;129(4):447.e1-.e20.

16. Skervin AL, Thapar A, Franchini AJ, Prandoni P, Shalhoub J, Davies AH. Systematic Review and Meta-Analysis of Utility of Graduated Compression Stockings in Prevention of Post-Thrombotic Syndrome. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2016;51(6):838-45.

17. Subbiah R, Aggarwal V, Zhao H, Kolluri R, Chatterjee S, Bashir R. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. The Lancet Haematology. 2016;3(6):e293-300.

18. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet (London, England). 1997;349(9054):759-62.

19. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med. 2004;141(4):249-56.

20. Excellence. NIfHaC. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing CG144. NICE. 2015.

21. Excellence NIfHaC. National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing [NG158]

NICE; 2020.

22. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.

23. Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. Phlebology. 2018;33(3):163-84.

24. Soosainathan A, Moore HM, Gohel MS, Davies AH. Scoring systems for the post-thrombotic syndrome. J Vasc Surg. 2013;57(1):254-61.

25. Bouman AC, Ten Cate-Hoek AJ, Dirksen CD, Joore MA. Eliciting patients' preferences for elastic compression stocking therapy after deep vein thrombosis: potential for improving compliance. J Thromb Haemost. 2016;14(3):510-7.

26. SIGVARIS Compression Stockings IFU [Internet]. Available from: https://wwwsigvariscom/sites/default/files/95503_anziehanleitung_en_0pdf. 2018.

27. Mahler C, Hermann K, Horne R, Ludt S, Haefeli WE, Szecsenyi J, et al. Assessing reported adherence to pharmacological treatment recommendations. Translation and evaluation of the Medication Adherence Report Scale (MARS) in Germany. Journal of evaluation in clinical practice. 2010;16(3):574-9.

28. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. Journal of psychosomatic research. 2006;60(6):631-7.

29. Horne R, Hankins M, Jenkins R. The Satisfaction with Information about Medicines Scale (SIMS): a new measurement tool for audit and research. Quality in health care : QHC. 2001;10(3):135-40.

30. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication AU - Horne, Robert. Psychology & health. 1999;14(1):1-24.

31. Ritchie J SL, O'Connor W Carrying out qualitative analysis. Ritchie J LJ, editor. New York: Sage; 2003.

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Compression Hosiery to Avoid Post-Thrombotic Syndrome

Protocol Version Number: 2.0

Signed: _____

Professor Alun Huw Davies

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Compression Hosiery to Avoid Post-Thrombotic Syndrome

Protocol Version Number: 2.0

Sponsor Reference Number: 19CX5434

Signed: _____

Becky Ward
Research Governance Manager
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Compression Hosiery to Avoid Post-Thrombotic Syndrome

Protocol Number: 2.0

Signed: _____

Name of Statistician
Title
Organisation/Company

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Compression Hosiery to Avoid Post-Thrombotic Syndrome

Protocol Number: 2.0

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDIX 1- VILLALTA'S SCORE

Villalta's score is a disease specific clinical measure that can be used to both diagnose and categorise the severity of PTS (8). (Five patient-rated symptoms (pain, cramps, heaviness, pins and needles, itching) and six physical signs (pretibial edema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, redness)are graded for intensity (0 points=absent, 1 point=mild, 2 points=moderate, 3 points=severe). The points are summed into a total score. The range of scores for symptoms is 0-15, for signs is 0-18, and for total score is 0-33. The presence of a venous leg ulcer is also documented and classified as severe regardless of the presence or absence of other signs or symptoms. The patient is diagnosed as having PTS if the Vilallta score is ≥5 or if a venous ulcer was present. A score of 5-9 signifies mild disease, 10-14 moderate disease, and ≥15 severe disease. The Villalta's scale can be administered at any time during follow up if there is clinical suspicion of PTS or the patient reports symptoms outside the face to face follow up visits.

Villalta Score

Symptoms/clinical signs	None	Mild	Moderate	Severe
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent			Present

Total Score: _____

APPENDIX 2- SCHEDULE OF ASSESSMENTS

	Baseline Visit	Follow up visits					
Assessment	**Day 0**	**2 weeks**	**Months 1-5**	**Month 6**	**Months 7-11**	**Month 12**	**Final visit (18 or 30 months)**
Informed Consent	X						
Inclusion/exclusion Criteria	X						
Screening assessments	X						
Demography	X						
Working status	X			X		X	X
Height/weight	X						
Lifestyle	X						
CEAP clinical examination	X			X		X	X
Medical History	X						
EQ-5D-DL, VEINES-QoL and B-IPQ	X			X		X	X
Villalta's Score#	X			X		X	X
Concomitant medication	X			X		X	X
Randomisation	X						
GP letter issued	X						
SMS reminder set up*	X						
Stocking fitting*	X						
Education package: educational video, nurse led training*	X	X					
Online self-report stocking questionnaire (Adapted MARS)*			X	X	X	X	X
Stocking re-fitting/ provision of donning aid*		X					
Adapted BSQ, Adapted TIQ*			X[¥]	X		X	X
Resource Use Information				X		X	X
Adverse Event Assessment		X		X		X	X

*Stocking arm only, [¥] measured at month 1 only , #can be measured at any time if the patient reports symptoms of PTS or there is clinical suspicion

(Approved by REC: London - Bloomsbury Research Ethics Committee on 04 /08/2020)