Compression Hosiery to avoid the Post Thrombotic Syndrome (CHAPS)

Statistical Analysis Plan

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List of Abbreviations

Abbreviation	Full name
DVT	Deep Venous Thrombosis
PTS	Post-thrombotic Syndrome
ICER	Incremental cost-effectiveness ratio
ABPI	Ankle brachial pressure index
CI	Chief Investigator
CACE	Complier average causal estimation
IQR	Interquartile range
SD	Standard deviation
MAR	Missing at random
MCAR	Missing completely at random

Changes to the Statistical Analysis Plan

The CHAPS study was terminated early on 20th May 2022 by the funder NIHR/HTA withdrawing funds on the basis of poor recruitment in the context of the NHS and the COVID-19 pandemic. The last patient last visit was 31 Dec 2022. At closure the study had recruited around 152 of the 864 target sample size. The original sample size calculation required 864 to have 90% power at a 5% level of significance to detect an absolute reduction in the incidence of PTS from 30% in the standard of care arm to 20% in the stockings plus standard of care arm, allowing for 10% loss to follow up. With just n=152 randomised, and 10% lost to follow up, the study would be powered at 90% to detect a reduction from 30% to 9%, or a 70% relative reduction (21% absolute reduction) which was considered clinically implausible.

The Statistical Analysis Plan was then changed throughout to remove any formal statistical comparisons, making the analysis purely descriptive.

1. Introduction

Deep venous thrombosis (DVT) occurs in approximately 1-2 per 1000 adults in the UK (1)and just under half will go on to develop lifelong disability from post-thrombotic syndrome (PTS) (2). 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 (3). The pathophysiology of post- thrombotic syndrome is sustained venous hypertension from venous outflow obstruction and valvular incompetence (4). Three clinical scales are widely used to diagnose PTS after objectively-diagnosed DVT, Brandjes scale (5), Ginsberg measure (6) and Villalta scale (7) with the Villalta considered the “gold standard” for the diagnosis and classification of post-thrombotic syndrome (8).

The average age of patients developing PTS is 55 years (9), 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 (2, 9). Severe PTS is characterised by leg ulceration. The incidence of DVT rises markedly with age (10) and the

severity of PTS increases with age and body mass index (2) . With an older, heavier UK population in the future, the burden of PTS is set to rise.

OBJECTIVES and OUTCOMES

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)). With the study terminated early, the follow up was determined by what was available at database lock, with no expectation anymore that the median would be 18 months as originally specified. The last patient last visit occurred on 31 Dec 2022.

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

Primary Endpoint

The primary outcome measure is any incidence of PTS using the validated Villalta's score. The original intention was with a 2 year recruitment period with a constant rate of recruitment the follow up would have a median of 18 months (with a range 6 to 30 months), and that 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). However, with the early closure and the non-constant, lower than anticipated recruitment rate, with interruptions for the COVID-19 pandemic, the anticipated median, range, and scheduled times for measuring PTS were not adhered to. The descriptive analysis will now instead summarise all data that was captured, with no formal statistical analysis.

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

Secondary endpoints removed due to funder terminating study early

- 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

Study Design

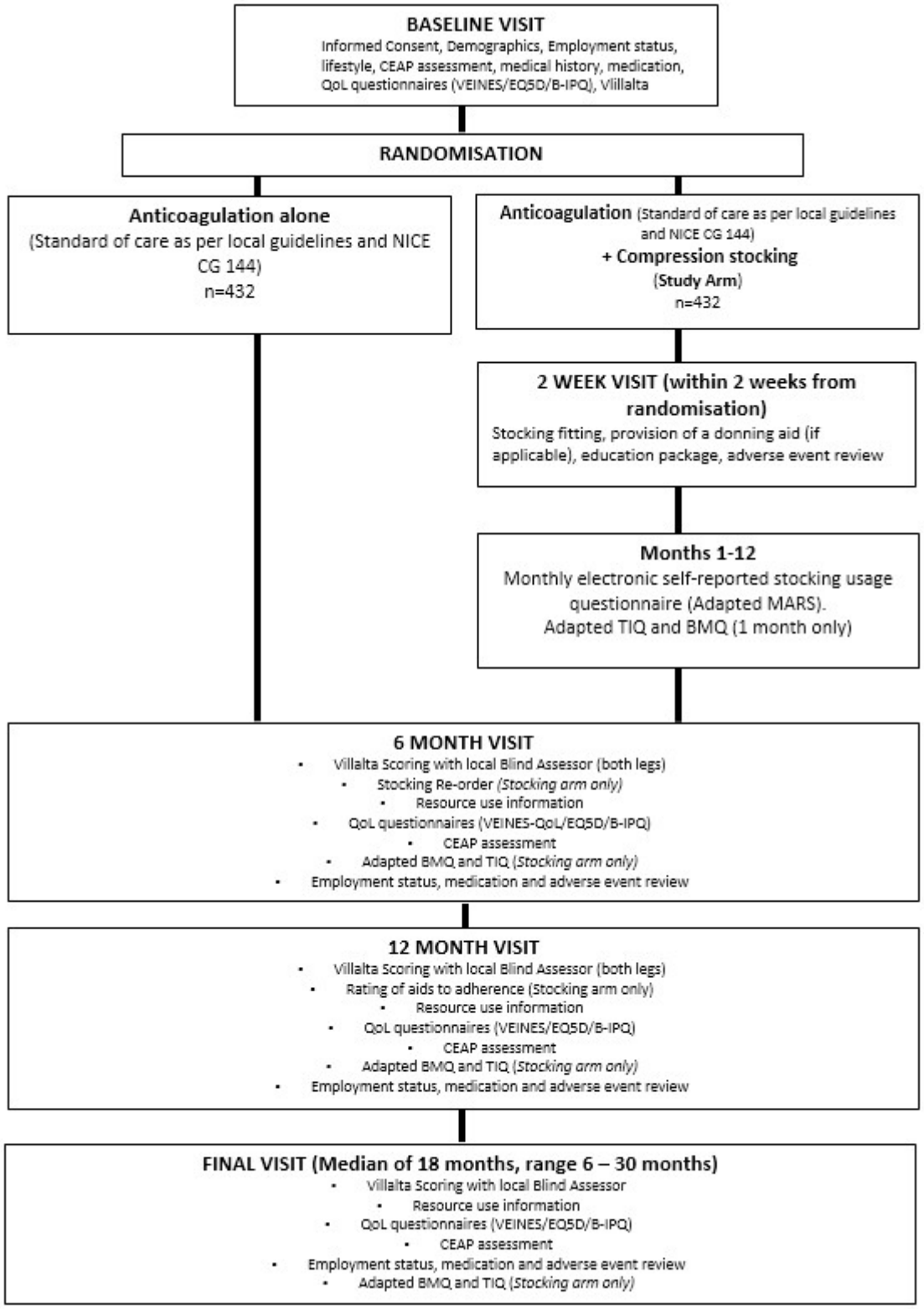
CHAPS is a UK, multi-centre, pragmatic, blinded outcome assessment, randomised controlled trial. The original 45-month trial was intended to follow up patients with first, acute lower limb DVT for a median of 18 months (range 6 – 30 months) and be conducted in approximately 11 secondary care Trusts in the United Kingdom.
The original sample size was n=864 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 had an internal pilot study which was designed to 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 would have been ≥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 was included to complement the main CHAPS trial with the aim to better understand how and why the educational elements of the intervention were effective or ineffective. This would have identified contextually relevant strategies for successful implementation through detailed descriptions of the participants' views and experiences of wearing graduated compression stockings and assessed 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.

The study was terminated before the 200 patient threshold was achieved and the sub study on adherence and the process evaluation were abandoned, along with the health economic evaluation.

Figure 1. Study Flowchart



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
- 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

2. Statistical Methods section from the protocol

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. These analyses will now be purely descriptive given the early termination of the study.

(i) Primary Endpoint Analysis

The intention was that 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 median of 18 months is no longer achievable given the slow recruitment, impact of the pandemic, and early closure of the study at 152 participants.

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. These analyses will be purely descriptive. Confidence intervals will be reported, but no P-values for statistical tests of hypothesis.

(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. These analyses will be purely descriptive. Confidence intervals will be reported, but no P-values for statistical tests of hypothesis.

The original intention was 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.

These causal models will not be undertaken, given the achieved sample size of 152 before early termination.

3. Overall Statistical Principles

Descriptive analysis will be conducted to present the variables (base line demographic data, working status, baseline vital signs, baseline lifestyle information, Villalta scores, past medical history) split by the two study arms (medicine and stocking or only medicine). We will present dichotomous and categorical variables as counts (percentages) in each category. Furthermore, we will present continuous variables as mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum.

Originally, all performed statistical tests would have been two-sided with a significance level of 5%. Given the early termination of the study, no formal statistical tests will now be performed.

Two-sided 95% confidence interval will be presented.

Proportion of missing data will be recorded for all variables. The original intention of conducting sensitivity analyses to explore the robustness of the reported findings to observed patterns of missing data have been abandoned due to the early termination leading to a final sample size of 152.

Univariable analysis

The normality of the continuous variables was to be examined visually by constructing histograms and Q-Q plot. The difference between the two study arms was to be examined using a t-test for continuous variables that are normally distributed and Mann-Whitney U-test if the normality assumption is violated. Furthermore, Chi-square test will be employed to examine the difference between the two study groups for dichotomous and categorical variables.

Due to the early termination of the study, these between randomised groups comparisons will be calculated descriptively and 95% confidence intervals reported, but now no formal statistical test of hypothesis will be undertaken, and no P-values reported.

Multiplicity

There was to be no adjustment for multiplicity in any of the conducted analyses because they address the pre-specified objectives and there is only one primary outcome. Secondary outcomes are for explanatory purposes and they are pre-specified. Furthermore, the number of performed analyses will be clearly recorded in any publications resulting from this trial. This is no longer relevant as no formal statistical tests of hypothesis are being undertaken.

4. List of Analyses

Primary outcome (Binary)

Multivariable analysis

Given the limited sample size, no multivariable model to adjust the treatment effect for known strongly prognostic baseline factors will now be fitted.

We had intended to construct a multivariable logistic regression model. Categorical variables will be analysed using chi-square. Continuous variables that are normally distributed will be analysed using t-test while those that are not meet the normality assumption will be analysed using Mann-Whitney U-test. Covariates with a P-value < 0.2 will be considered for inclusion in the final model (11). The likelihood ratio test will be employed to select the variables for the best model fit. Furthermore, to allow for clustering on care trusts, we will use mixed effect logistic regression model by including the care trusts as a random effect. Furthermore, we will consider performing a Poisson or negative binomial regression (if the assumptions of the Poisson regression do not hold) with including the duration of follow up as an offset variable. None of this multivariable modelling will now be considered.

Binary secondary outcomes

A generalised linear mixed model with a logit link function will be constructed. Care trusts will be included as a random effect in the final model. We will present the results in odds ratio (OR) with the corresponding 95% CI and P-value. Again, given the early termination of the study, none of this modelling will be undertaken.

Continuous secondary outcome

Again, due to the small sample size given the early termination of the study, this proposed modelling will now not take place. A normal linear mixed model would have been constructed to analyse these outcomes. Care trusts will be included as a random effect in the final model. The adjusted mean difference with the corresponding 95% CI and P-value will be reported. The normality assumption will be tested using the normal probability plot. If the normality assumption does not hold, the outcome will be transform. In the event that the normality assumption is not met after transforming the outcome, alternative methods including categorising the outcome will be considered. We will adopt the same method if the residual versus fitted values show non-constant variance for the outcome.

Score derivation

The questionnaires used to produce the scores employed in this study are included in the case report forms (CRFs). The scores are derived as follows

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 (12). (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.

VEINES-QOL

The VEINES-QOL questionnaire is a disease-specific quality of life tool for the venous disorder of the leg (CVDL) (13). It covers 26 items; ten questions about manifestations due to CVDL, nine items about constraints in daily activities due to CVDL and five items on psychological influence (14). Besides, it contains one item on the difference in the patient's leg problem over one year and one item on the time of day that the leg problem is most intense (14). The derivation of the VEINES-QOL scores and dealing with missing elements in the questionnaire will be based on the method published by Bland et al (13).

EQ-5D-5L

The EQ-5D-5L health scale and EQ-5D-5L health index will be included in the analysis. EQ-5D-5L health scale is based on the EuroQOL group 5-dimension 5-level questionnaire health scale which is a visual analogue ranging from 0 to 100 (the higher the score, the better the health is) (15). Furthermore, the EQ-5D-5L health index is calculated using the value set for England (16). It ranges from 0 to 1 with the higher score showing better health (15).

5. Validation and QC

A second statistician will do the following to validate the main statistician's work

1. Performing the analysis and checking the results and conclusions of the primary analysis.
2. Reading the statistical report to ensure it is correct and understandable by clinicians.

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