A prospective randomized-controlled trial of custom-manufactured vs. off-the-rack (OTR) compression hosiery for initial management of venous disease

NCT03630185

Version Date: 03/02/2017

UTHealth The University of Texas Health Science Center at Houston IRB APPROVAL DATE: 03/02/2017

Study Protocol

Table of Contents

IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

I. LIST OF ABBREVIATIONS

AE Adverse Effects

CEAP **C**linical, **E**tiology, **A**natomy, **P**hysiology disease severity classification

FDA Food and Drug Administration

PI Principal Investigator

II. PRINCIPAL INVESTIGATOR & RESEARCH TEAM

Principal investigator: *Stuart A. Harlin, MD* (Vascular Surgeon)

Co-Investigators: Charles C. Miller, PhD (Biostatistician)

Research Team: Susan Pouliot, RN (Research Nurse)

III. STUDY SITES

1. *UT Physicians Cardiothoracic and Vascular Surgery at Katy*

   Katy, Texas

2. *Bayshore UTP Clinic*

   Houston, Texas

3. UT Physicians EP Heart- Sugarland

   Sugarland, Texas

4. Department of Cardiothoracic and Vascular Surgery

   University of Texas Medical School at Houston

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

IV. CONTACT INFORMATION

1. ***Stuart A. Harlin, MD***

   Principal Investigator

   6400 Fannin Street, Suite 2850, Houston, TX, 77030

   Phone (713) 486 – VEIN (8346)

   Stuart.A.Harlin@uth.tmc.edu

2. ***Susan Pouliot, RN***

   Research Nurse

   6400 Fannin Street, Suite 2850, Houston, TX, 77030

   Phone (713) 486 – 5131 Fax (713) 512 – 7200

   Susan.M.Pouliot@uth.tmc.edu

V. RESEARCH SYNOPSIS

A. Study Title

Study Full Title

A prospective randomized-controlled trial of custom-manufactured vs. off-the-rack (OTR) compression hosiery for initial management of venous disease

Study Short Title

Custom vs OTR compression hosiery for venous disease

B. Clinical Phase

Phase IV

C. Study Population

IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

The study will include patients aged 18 and over who have CEAP classification 2-5 venous disease and require compression as definitive therapy or in preparation for ablation therapy.

D. Study Design

Prospective double-blinded, controlled randomized clinical trial with 2-armed parallel-group sequential design

E. Sample Size

200

F. Study Duration

2 years

G. Study device and Intervention Description

Subjects will be randomized into two groups: group A will receive custom-manufactured compression hosiery (Isobar compression garment), and group B will receive off-the-rack stockings (Sigvaris).

H. Primary Objective

To assess the efficacy of custom-manufactured compression hosiery compared to off-the-rack compression hosiery for improving patient satisfaction, health-related quality of life and compliance with prescribed compression therapy

I. Secondary Objectives

- *To identify subgroups that may benefit more from custom hosiery.*
- *To determine whether improved fit affects likelihood to progress to invasive treatment.*

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

VI. BACKGROUND AND SIGNIFICANCE

Currently available off-the-rack compression hosiery are manufactured in eight fixed sizes (S-XLFC) that cannot be varied in size over their length to accommodate unusual anatomic patterns (eg., small ankle with large calf or vice versa) and may not achieve a comfortable fit that meets the compression goal over a uniform distribution of the limb. The custom-fitted garment is manufactured specifically for each patient based on measurements taken with a 3-dimensional volumetric laser scan of the extremity, and can be sized individually to each limb. In addition to providing data to computer assisted design-enabled manufacturing equipment, the scan data can be downloaded for analysis and may be useful for identifying patients for whom custom stockings are most beneficial and may ultimately be useful for prediction compliance and patient satisfaction. We propose to scan all trial participants prior to randomization so we can assess this in a control group as well.

VII. PRIMARY OBJECTIVES

To assess the efficacy of custom-manufactured compression hosiery compared to off-the-rack compression hosiery for improving patient satisfaction and compliance with prescribed compression therapy.

1) Health-Related Quality of Life (HRQoL): We will use the short-form 12-item (SF12) HRQoL instrument for measuring HRQoL. It has been used widely and validated in many health conditions, and can be administered to patients in less than 5 minutes. It produces overall HRQoL estimates and subscale scores that assess both mental / emotional and physical functioning related to health.

2) Five-point satisfaction scale: This scale is used to assess the patient's pain management experience during their postoperative care. It consists of patients rating their overall postoperative pain management experience using a 5-point rating system. The scale ranges from 1 to 5, with 1 being "extremely dissatisfied", 2 "somewhat dissatisfied", 3 "Neutral/Neither satisfied nor dissatisfied", 4 "somewhat satisfied" and 5 "extremely satisfied" with their postoperative pain care. This rating has been used in other clinical trials and has been shown to be a reproducible assessment tool.

3) Brief Pain Inventory: The Brief Pain Inventory is a medical questionnaire used to measure pain, developed by the Pain Research Group of the WHO Collaborating Centre for Symptom Evaluation in Cancer Care.[1,2]

Primary outcome measures

HRQoL, BPI and 5-point satisfaction scale will be assessed at baseline, at clinical follow-up at 90 days. Additionally, the BPI will also be administered via phone at 6 weeks.

Compliance with stocking use will be measured by a daily diary entry and will be the accumulated total of hours worn over 90 days.

H. SECONDARY OBJECTIVES

- To identify subgroups that may benefit more from custom hosiery.
- To determine whether improved fit affects likelihood to progress to invasive treatment.

Secondary outcome measures

- The sample size (200 subjects) will allow us to investigate subgroup effects. Preliminary a priori hypotheses are that patients with difficult to fit legs (eg., large calf/ankle ratio) with have significant improvements in compliance and satisfaction with custom fit hosiery.
- Progression to ablation therapy will be determined by patient preference for further intervention. We will measure efficacy as a simple proportion between the randomized groups.

IX. STUDY POPULATION

The target population of our study will be comprised of patients that are 18 years-old and above that present to our group at The University of Texas Medical School at Houston with venous disease requiring treatment with compression.

Inclusion/Exclusion Criteria

Patients will be *eligible for the study if*:

- 18 years-old or older, and
- Ability to comprehend and sign an informed consent and complete study questionnaires
- Patient is participating in usual work and home activities with no changes anticipated for the duration of the study
- The use of compression stocking is prescribed in accordance with the usual practice and management of venous disorders
- The patient will confirm they are willing to pay for the compression stockings.

Patients will be *excluded from the study if*:

- The patient has a known allergy to any component of the stocking (latex, etc)
- The patient has non-venous source of pain in either leg that could, in the opinion of the investigator, confound the results of the study i.e.Neuropathy, Arterial insufficiency, Diabetes
- The patient is confined to bed
- The patient has uncontrolled Congestive Heart Failure
- The patient has acute dermatitis
- The patient has weeping dermatosis
- Patients with venous ulcers will be excluded.

Protocol Deviation:

- Patient is randomized but does not receive the correct treatment assignment

IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

Withdrawal criteria:

- Voluntary: patients who had consented and enrolled in the trial will maintain their right to withdraw at any point during the study as explained in the informed consent.
- In case of unexpected/unpredicted events, the Principal Investigator and research staff may determine that patient meets criteria for withdrawal.

X. STUDY DEVICES

The Custom stocking, (Isobar Compression Garment) is an FDA Class 1 device. The control stocking (Sigvaris) is also an FDA Class 1 device. These devices are rated at 15 mmHg compression and are comparably priced.

XI. STUDY SCHEDULE

Expected start date after IRB Approval: Eligible to begin January 2017

Expected end date for enrollment: January 2019

Length of treatment-phase enrollment for each patient: 90 days

Length of follow-up for each patient: 90 days from initiation of compression for primary endpoint; six months for assessment of likelihood to receive follow-on ablation therapy.

XII. STUDY DESIGN/METHODOLOGY

This will be a single institution, prospective, blinded, randomized, controlled

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

clinical trial with a 2-arm parallel-group design to assess the efficacy of custom-fitted compression hosiery vs off-the-rack compression hosiery.

The custom stockings take 2 weeks to manufacture. In order to maintain the blind, stockings will be procured by the UT CV Surgery purchasing personnel and distributed to the subjects in unmarked packaging within three weeks of randomization. Neither the prescribing physician nor the patient will know the treatment assignment.

Screened patients meeting the eligibility criteria will have a below-knee laser measurement scan, and will be randomized into one of the two study groups.

At the screening visit, patients will be evaluated for trial eligibility and the study will be explained. For eligible patients who wish to participate, informed consent will be obtained and the patient will receive history and physical exam and will complete baseline HRQoL and pain scale surveys. Volumetric scans will be performed and the data will be stored. Patients will be randomized by a study coordinator, and will be instructed to expect stockings in the mail within 3 weeks.

After stockings are dispensed, patient should call the office to inform the study nurse or coordinator of the day they are beginning therapy, and biweekly log will be kept as a measure of compliance.

Patients in the study should also complete the Brief Pain Inventory (BPI) before randomization (at baseline following enrollment), by phone during week six, and at clinical follow-up after completing 90 days of compression therapy. Additionally, patients will be assessed on their satisfaction at week six and at 90-day clinical follow-up. This

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

will be done using the 5-point satisfaction scale with 1 being “very dissatisfied” to 5 being “very satisfied”. The SF-12 HRQoL instrument will also be completed at enrollment, at six weeks and at 90-day follow-up. This will conclude the 90-day treatment period. Patients will be re-contacted at six months post-treatment to determine whether they are still using their stockings (or have replaced them) or have progressed to invasive treatment. After the six-month assessment, the study will be concluded and enrollment will be terminated.

Study Conduct

1. Screening

The PI and research staff will assess patients as possible candidates for enrollment based on the inclusion criteria described previously. A member of the research team - the PI, a Co-investigator, research coordinator, or research nurse will obtain the consent from interested patients who met the preliminary inclusion criteria. The consent process will take place during the clinic visit. Patients will be given adequate time and education about their condition to ask questions about the protocol and research study. Those who wish to participate will be informed they are responsible for the cost of the hosiery as it may not be covered by insurance (most plans do not cover stockings even though they are required prior to preauthorization for ablation therapy). Patients would be responsible for this cost whether or not they are enrolled in the trial – no additional cost to the patient will result from trial participation. The preoperative baseline pain level, using BPI and HRQoL will be recorded at this time. A copy of the signed informed consent shall be provided to the patient, a copy will be

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

placed in the patient's hospital chart, and a copy will be kept by the research team. Medical/surgical history, vital signs measurements, and standard clinical testing will also be performed as per the usual practice for assessment and management of CEAP class 2-5 venous disease.

2. Quality of life assessment - Brief Pain Inventory

The impact of pain on patient's quality of life will be assessed through a brief pain inventory (BPI) that should be done at enrollment, at the six week point during compression therapy and at the final clinic visit after 90 days of treatment. The BPI will be presented as an easy to comprehend questionnaire for the patients to quantify and communicate their pain experience and how it is affecting their life. It is designed such that patients with 6th-grade education should be able to complete the questionnaire on their own. Question and answers will be provided in a check-box format. The BPI that will be used on this study will be the short version. Patients with difficulty reading or who are physically unable to complete the questionnaire will be assisted by the research team based on their verbal responses to the BPI questions.

3. Enrollment

After screening for eligibility, if all inclusion/exclusion criteria are met and the patient has consented; the patient will be enrolled in the trial.

4. Randomization and Allocation Concealment

Randomization and allocation concealment will be performed by study personnel using a restricted-access randomization file. The sequence will be generated by a UT

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

statistician in a random permuted block design and copied to a secure drive accessible only to unblinded study personnel. At enrollment patients will be assigned a study ID number. The laser scan data will be identified by this study number and noted in the CRF. Depending on the group assignment, either an order for a custom pair of stockings will be generated and tagged to the scan data – which will then be transmitted to the manufacturer – or the appropriate pair of Sigvaris stockings will be procured. After two weeks, the stockings as allocated by randomization will be packed in unbranded packaging and mailed to the research subject by trackable means (UPS, FedEx, US Postal Service, etc.). The clinical personnel who assess the patients will not handle the hosiery and will not see it on the patient. The patient will not know whether the stockings are custom or off-the-rack, so the double masking will be maintained.

5. Baseline assessment

History, physical exam and review of symptoms will conducted at enrollment and captured to an electronic case report form that will be implemented at UT in REDCap. The examining physician will draw a diagram of the involved veins for comparison with the 90-day examination. Pain assessment and HRQoL will be captured as described previously.

6. Follow-up

After the initiation visit is completed, the follow-up will be:

i. Compression therapy per physician directive throughout 90 days with a compliance log to be kept bi weekly.

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

ii. At 6 weeks questionnaire completion via phone.

iii. At 90 days clinic follow-up and questionnaire completion

iv. At six months after treatment initiation by telephone

7. Termination of enrollment

Patient will be considered to have his/her enrollment terminated:

i. After completion of the six month telephone survey

ii. If any medical/surgical/environmental condition develops that would affect or impair primary or secondary outcomes measurements results

iii. If the study is terminated

iv. If the patient dies

8. Termination of Study

i. End of study period

ii. Unanticipated safety problems that would make continuation unethical

iii. If the trial does not look as though it can achieve its enrollment targets within two years

XIII. ADVERSE EVENT REPORTING

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

Patients enrolled in the trial will be instructed to report any unwanted effect at any time during the study. For this study, only adverse events that are directly related to the use of compression stocking will be reported. Expected adverse effects of compression therapy will be described to the patients during the screening/enrollment as well as in the informed consent process. Most adverse side effects are minor and may include rash, contact dermatitis, discomfort, lack of symptomatic relief, and in rare cases, local skin ischemia and breakdown.

Safety monitoring will include assessment of:

i. Adverse Effects (AE)
ii. Vital Signs
iii. Wound healing status
iv. Pain
v. Satisfaction

All parameters will be closely monitored in a continuous manner, as part of our standard clinical care. Any abnormalities found will be promptly assessed and described in the patient's medical records. Patients will be instructed to call the clinic if problems arise, and will also be assessed at clinic visits. If need be, an immediate unscheduled visit shall be arranged if the patient so desires.

The PI will review AEs as they occur, and requirement for changes to the study design or device use will be determined on an ongoing basis. This study does not require a DSMB.

XIV. STATISTICAL ANALYSIS PLAN

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

A. Primary Outcomes

The trajectory of BPI, HRQoL and Patient Satisfaction scores at 45 and 90 days of treatment will be measured by mixed-effects linear models between the groups. Appropriate score transformations will be performed as necessary to meet distributional assumptions of the tests. Randomization is expected to balance the groups with respect to pre-intervention risk factors.

Total time worn over 90 days as reflected in diary entries will be compared by Wilcoxon rank-sum test between the two groups..

A. Secondary Outcomes

Additional analyses will be performed to determine whether patient characteristics such as calf/ankle ratio and other measurements made using laser scan data show differential (interaction) effects in the custom-stocking group vs the off-the-rack group.

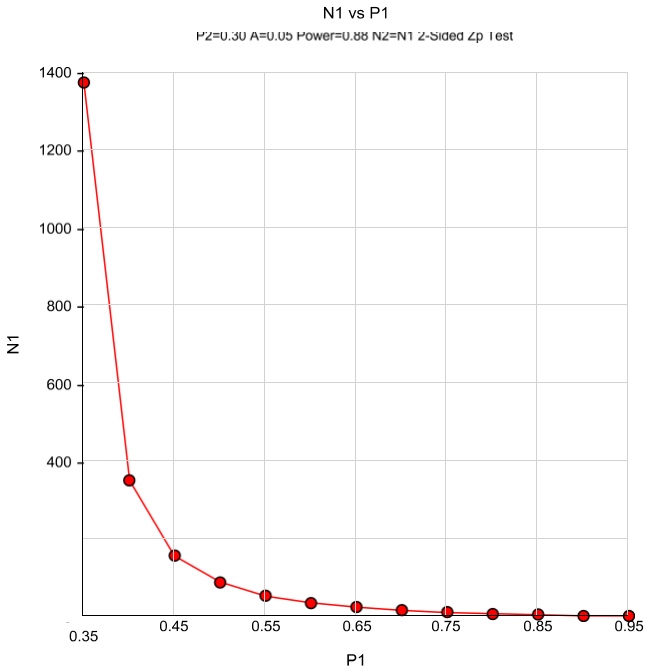
Progression to ablation will be measured as simple text of proportions (Fisher's Exact test) of those seeking ablative therapy in the custom vs OTR groups.

B. Sample Size Determination

C. A sample size of 200 (100 per arm) patients would allow for detection of a difference as small as 20% in the proportion of patients with a post-treatment change in QOL. . This detection threshold assumes that 30% of the controls experience some positive change in HRQoL and 40% of the custom group experience improvement. Larger

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

differences can be detected with a much smaller sample size, but a larger sample will allow us to investigate predictors of improvement such as measurements and patient characteristics.[3] The relationship between sample size and proportion of successes in the custom group is shown in the figure below.



Laser-measuring all subjects (not just those randomized to Custom) will allow us to investigate the influence of leg size and shape on likelihood to see improvement in HRQoL and satisfaction, and to identify a variety of other patient-specific factors that predict improvements in outcome. Understanding these relationships may allow us to tailor therapy towards optimization of predicted outcome, and could, for example, help identify a subset of patients for whom progression to ablation therapy may not be necessary.

XV. ETHICS

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

A. Informed Consent Process

All eligible patients who meet the inclusion criteria will be consented, if willing, after an in-depth description of the study, the study device and potential adverse effects, the risks and benefits, follow-up routine, enrollment and termination processes. The importance of follow-up will be emphasized; however, the patient will retain the right to voluntarily withdraw from the study at any point. It will also be stressed that patient confidentiality will be kept at all times during study through de-identification of data.

Information will be stated clearly in a written consent form that will be designed at a 6th grade level of understanding. Information will also be presented verbally. A member of the research team, either the PI, Co-PI, or co-investigators will obtain the consent of the patient or other the legally authorized representative of the patient. The consent process will take place during the enrollment clinic visit. The member of the team who is obtaining the written consent will describe the research project in its entirety and answer the questions of the patient and/or family members should they ask any. Sufficient time will be provided to the patient to review the study before making an informed decision to participate or decline. Should they decide to participate a copy of the signed consent form will be given to the patient and the process will be documented in the patients' medical records and/or study documentation

B. Privacy and Confidentiality

The study will be conducted in compliance with all HIPAA guidelines to protect patient confidentiality. All sensitive information or patient identifiers will be stored in form of a patient linkage file that will link the patient study/trial number to their clinical records

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

and secured on the Zone 100 drive on specific networked computers of our department. Data capture will be performed in REDCap software hosted at the UT-Houston School of Biomedical Informatics in a Zone 100 server room. Access to any data pertaining to the study will be restricted to approved research team members, the FDA, institutional review boards of the University of Texas.

C. Risk/Benefit

Risks to participants

There is a small increased risk to the patients by participating in the study in addition to a possible chance of breach in patient confidentiality as the study involves evaluation of an FDA class one medical device. As detailed in the informed consent, the subjects are at some risk of developing adverse events described above, as well as currently unknown risks. The devices (stockings) to be used are considered low-risk devices by the FDA. In addition, there is risk of an unintentional disclosure of personal health information.

Benefits to participants

The patients may receive no direct benefit from participation the study. However, if the custom-fitted stockings are superior, the patients in this treatment group will have had the benefit of early access to them.

XVI. STUDY TIMELINE

Considering our group's monthly average for the given procedures and the

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

enrollment rates, we estimate recruitment of our sample size will take 2 years. Once the follow-up of all enrolled participants is finished, data will be analyzed and published. The following is a chronological estimate of the stages:

Stage 1: Patient screening and enrollment 0 - 2 years

Stage 2: Follow-up (0.5 – 2.5 years) six months after enrollment

Stage 3: Data collection and analysis 1 year

Stage 4: Presentation and publication period (at the end of data analysis)

XVII. DATA SAFETY MONITORING

Given the low risk of these commercially available class-1 devices, DSMB oversight is not required.

XVIII. CONFLICT OF INTEREST

There is no relationship between the PI or any other research staff member and the sponsor.

XIX. FUTURE PUBLICATION AND PRESENTATION

The results of this study will be analyzed and published after the approval of the principal investigator and biostatistician in a peer-reviewed scientific journal and/or presented at an international/national scientific conference or meeting regardless of outcome. The publication will acknowledge members of the study research group for their contributions and will maintain patient data protection.

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017

XX. REFERENCES

1. Cleeland CS, Ryan KM (March 1994). Pain assessment: global use of the Brief Pain Inventory". Ann. Acad. Med. Singap. 1994; **23** (2): 129–38.
2. Caraceni A, Cherny N, Fainsinger R, *et al*. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. J Pain Symptom Manage. 2002; **23** (3): 239–55.
3. Cohen, J. (1988). Statistical power analysis for the behavioral sciences (2nd ed.) Hillsdale, NJ: Lawrence Earlbaum Associates.

UTHealth The University of Texas Health Science Center at Houston
IRB NUMBER: HSC-MS-17-0015
IRB APPROVAL DATE: 03/02/2017