PI: Dr. Lev-Tov
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# The Effect of Inelastic Compression System on Quality of Life in People with Chronic Venous Insufficiency

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## 1) Protocol Title

The Effect of Inelastic Compression System on Quality of Life in People with Chronic Venous Insufficiency

## 2) Objectives

The purpose of this protocol is to measure the effect of the use of an inelastic compression system (ICS) on quality of life (QOL) in patients with chronic venous insufficiency (CVI) who have demonstrated limited or no compliance with prescribed compression stockings or bandage wraps. The primary outcome of interest is the change in QOL of people who have CVI and use ICS over 6 weeks.

## 3) Background

Chronic venous insufficiency (CVI) is a common condition that affects about one third of adults in the US[1]. The social and economic burden on both patients and society is significant; for instance, venous leg ulcers, a severe manifestation of CVI, costs the US healthcare system billions in dollars and the UK an amount of similar magnitude[2,3].

Notably, CVI negatively impacts patients' quality of life (QOL), particularly in those at advanced stages of disease[4]. This has been reported throughout various domains of well-being, including pain, physical functioning and mobility, and social isolation[5]. While generic scales like the 36-Item Short Form Survey (SF-36) are helpful to discern QOL measures across different disease groups, tools with specificity towards chronic venous diseases have been established[6,7]. For instance, the Chronic Venous Insufficiency Questionnaire (CIVIQ-20) has been demonstrated to appropriately assess QOL in patients with CVI[8] These tools may be used to guide clinical research practices in efforts to improve the well-being of these patients.

Several decades ago, the Clinical, Etiology, Anatomic, Pathophysiology (CEAP) classification was created to standardize the diverse manifestations of chronic venous insufficiency to allow for easier classification and communication of disease severity[9]. Specifically, within the Clinical portion of the CEAP system, the subcomponents C3-C5 refer to edema (C3), changes in skin and subcutaneous tissue (C4 -pigmentation, dermatitis, lipodermatosclerosis or atrophie blanche), and a healed ulcer (C5); these subcomponents increase numerically in proportion to the severity of the patient's condition[10].

Currently, compression therapy is the first line treatment for all the manifestations of CVI [11]. However, existing compression hosiery are met with resistance by some patients. This results in a gap in compliance as for example up to 80% of patients who are prescribed compression stockings or bandaging wraps do not wear them as prescribed[12]. This practice gap may contribute to the overall burden of CVI and solutions that address the need of patients who cannot wear compression stockings are needed. Inelastic compression wraps may help to solve this practice gap by offering easier application without compromising outcomes. One example of such a system is the Compreflex Compression Wrap system (Sigvaris Inc. Peachtree City, GA). This proposal is focused

on determining if the usage of this specific inelastic compression wrap system in patients with CVI stages C3, C4, and C5 improves their quality of life.

## 4) Inclusion and Exclusion Criteria

**Inclusion Criteria**

- Subject is age 18 or older, able and willing to provide consent and agrees to comply with the study procedures
- Subject must have chronic venous insufficiency of stages C3, C4, or C5 according to the CEAP classification system
- Not compliant with their currently prescribed compression system

**Exclusion Criteria**

- Active malignancy other than non-melanoma skin cancer
- Study ulcer suspicious for cancer
- Unable to provide consent
- Subjects who are pregnant and/or breastfeeding
- In the opinion of the PI the subject cannot comply with study procedures

5) **Study Design**

*a)* **Primary Purpose:** *Treatment*
***b)*** **Interventional Study Model:** Single Group
***c)*** **Allocation:** N/A
***d)*** **Enrollment:** 40

This is a single center, single intervention, unblinded, prospective cohort study.

6)

## 7) Procedures Involved

This is a single center prospective cohort study that will last up to six 6 weeks per subject. A total of 30 patients will be enrolled, through the University of Miami Hospital and Clinics. The study is comprised of 3 visits per subject (see table 1) two in person and one over the phone. V0 will occur on the first day of the study. V1 will occur during the second week (between days 714) and the final visit, V2 on day 42 of the study.

At the enrollment visit (V0), subjects will undergo baseline assessments to determine eligibility for the study (inclusion and exclusion criteria, demographics, medical history, medication history, focused physical exam). *Medical records will be reviewed for* ***the subject's basic demographics, medical and surgical history, and current treatments.*** Once eligibility is confirmed, the patient will be assessed for measurements of disease severity (presence of varicose veins, atrophe

blanche, lipodermatosclerosis, hyperpigmentation, the Venous Clinical Severity Score VCSS (See Appendix A), itch severity using itch Numerical Rating Scale NRS (See Appendix B), pain using the Visual Analogue Scale VAS (See Appendix C), and limb circumference in mm.) Upon proper consent, photographs of the extremity will be captured and quality of life assessments will be completed. The two quality of life assessments used will be the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ – 20) (See Appendix D), and the Short Form Healthy Survey (SF-36) (See Appendix E). The initial visit will conclude with proper product application training and time to address any questions.

Subjects will report for 2 successive follow-up visits. The first follow-up visit will be completed at least one week but no later than 14 days after the initial visit and be completed via phone (V1). During this visit, study staff will document concomitant medications, itch severity, pain, and assess patient adherence to usage of the inelastic compression system. If in the opinion of the study staff the subject is not able to apply the ICS effectively, they may convert the visit to video conferencing or even in person visit.

The third and final visit (V2) will be completed in person at the University of Miami Hospital Dermatology Clinical Trials Unit 6 weeks after the initial in person visit. During this visit, similar to the initial visit, study staff will document concomitant medications, perform a focused exam, measure disease severity and itch severity, and assess pain. Additionally, limb circumference measurements will be obtained and photographs of the extremity will be captured again. The visit will conclude with the same two quality of life assessments and assessment of adherence.

All subjects will continue to follow their care for all medical conditions as prescribed by their physician.

| Visit | V0 | V1 (phone) | V2 |
|---|---|---|---|
| Day | 0 | 7-14 | 42 (+/- 3) |
| Informed consent | X | | |
| Eligibility | X | | |
| Medical history | X | | |
| Concomitant medications | X | x | X |
| Focused exam | X | | X |
| Disease severity assessments | X | | X |
| Itch severity | X | X | X |
| Pain assessment | X | X | X |
| Limb circumference | X | | X |
| Photography | X | | X |
| QOL assessment (CIVIQ-20, SF 36) | X | | X |
| Product application training | X | | |
| Adherence assessment | | X | X |

8) **Study Endpoint**

**a) Primary Outcome Measure**

**i) Title:** Change in the Quality of Life

**ii) Description:** As measured by the Chronic Venous Disease Quality of Life Questionnaire (CIVIQ-20) which is a questionnaire made up of 20 multiple choice questions subdivided into four categories: psychology , pain, physical repercussion and social repercussions. The questions are equally weighted and the value indicates the degree of deterioration of quality of life; 0 being the highest quality of life and 100 being the lowest. It has been tested to be a reliable measurement tool in evaluating the quality of life in those with CVI.

**iii) Timeframe:** Baseline to 6 weeks

## 9) Data Banking

Physical study records will be in a locked cabinet in the Dermatology Clinical Trials Unit at University of Miami (University of Miami Hospital West Building, 1321 NW 14th St, Suites 504-507, 33136). Technological study records will be located on a spreadsheet within a project file located within a password protected server on Microsoft Teams.

## 10) Data Management

The collected, deidentified data will be arrayed in a spreadsheet within a project file located within a password protected server on Microsoft Teams. Only the PI and approved study staff will have access to this file. Subject identities as participants in this study will be kept confidential for the remainder of the study and in any publication, and no identifiable patient information will be attributed to the dataset, thereby keeping them anonymous.

## 11) Risks to Subjects

The risks to the patient proposed by this trial are minimal as they do not pose greater potential for harm than routine clinical care. The potential risks are discussed below:

Potential Risks of the Inelastic Compression System

- Minor severity:
  - Skin Irritation or Discomfort
  - Pain
- Major severity
  - Soft tissue injury

- Nerve Injury

These potential risks are unlikely. The risks listed under major severity have a lower likelihood of occurrence compared to the risks located under the minor severity category. Proper application of the inelastic compression system minimizes the probability of experiencing these potential risks.

## 12) **Adverse Events and Serious Adverse Events**

DEFINITION OF ADVERSE EVENTS (AE)
Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). In the context of our study, an intervention refers to a study research procedure.

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)
A Serious Adverse Event (SAE) is any serious unfavorable and unintended sign, symptom, or disease temporally associated with this study protocol, whether or not considered related, including those that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, the important medical event should be reported as serious, if it is determined that the event may jeopardize the Participant and/or may require intervention to prevent one of the other adverse event outcomes.

CLASSIFICATION OF AN ADVERSE EVENT
SEVERITY OF EVENT
The Investigator will provide an assessment of the severity of each adverse reaction by recording a severity rating on the appropriate SAE reporting page of the Participant's file. Severity, which is a description of the intensity of manifestation of the SAE, is distinct from seriousness, which implies a patient outcome or SAE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale. If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

| | |
|---|---|
| MILD | Does not interfere with Participant's usual function. |
| MODERATE | Interferes to some extent with Participant's usual function. |
| SEVERE | Interferes significantly with Participant's usual function. |

RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. A binary assessment (related/not related) will be made and take into consideration the natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors. While the relationship to the study tissue biopsy procedure (study research intervention) (related/not related) is part of the documentation process, it is not a factor in determining what is or is not reported in the study. All AEs are recorded regardless of relatedness.

Related: The AE is known to occur with the study research procedure, there is a reasonable possibility that the study research procedure caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study research procedure and the AE. An AE can be deemed related even if other factors may have contributed to the event.

Not Related: There is not a reasonable possibility that the study research procedure caused the event, there is no temporal relationship between the study research procedure and event onset, or an alternate etiology has been established or appears to provide a plausible explanation (e.g. the participant's clinical condition, underlying disease or concomitant treatments).

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

At each visit, AEs/SAEs will be evaluated by the Investigator and recorded. All AEs must be recorded irrespective of whether they are considered study related. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

Any AEs/SAEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented.

ADVERSE EVENT REPORTING
All adverse events should be tracked from the time the Participant provides informed consent, and through the time of discharge from the study. Adverse events (serious and non-serious) should be recorded in the CRF for the duration of the reporting period. Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.
All AEs that occur during the study will be recorded in the case report form and reported to IRB.

SERIOUS ADVERSE EVENT REPORTING
If a serious adverse event related to the study research procedures occurs, the IRB should be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to IRB must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.
In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient study Participant initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

## 13) **Potential Benefits to Subjects**

A medical benefit cannot be guaranteed by this study. However, since study protocols mirror standard of care, subjects can reasonably expect to benefit medically (e.g. a decrease in lower extremity swelling or skin discoloration). Further, since the participation in the study is conditional of "failing" use of other standard care compressions devices, successful use of the ICS as part of this study, will be considered an improvement in medical care provided. Since study staff are part of the UM Wound Care Team, subjects will be cared for by expert wound care clinicians. Subjects' participation in this protocol will also help future patients with chronic venous insufficiency, as future patients may experience a high quality of life through usage of inelastic compression systems. Notably, medical care including dressings and medical advice are provided at no cost to subjects throughout the study period. Finally, as part of the informed consent subjects are reminded of alternative therapies that are available. It is our experience that subjects are very satisfied with the overall care in the UM clinical trials unit and often return

for additional trials. Thus they are offered the psychological benefit of knowing that the UM clinical trials unit is always an option for them.

## 14) Setting

Study procedures will take place one of the following locations:

- Dr. Philip Frost Department of Dermatology and Cutaneous Surgery – Clinical Trials Unit. UMH West Building, Suites 504-508. 1321 NW 14th street, Miami FL, 33136.
- University of Miami Dermatology Outpatient Wound Care Clinic. 1295 NW 14th St. South building, 1st floor. Miami FL 33136
- University of Miami Dermatology Outpatient Clinic. South Building, Suites K, L, M. 1295 NW 14th Street, Miami FL, 33136.

## 15) Resources Available

The University of Miami Wound Center is one of the largest and most advanced wound clinics in the United States, and together with its Hyperbaric Oxygen Unit attracts a large amount of patients with chronic wounds each week and venous disease. The investigators involved in this protocol are experienced clinicians with world-renowned expertise in wound healing and venous disease. Their staff consists of highly trained doctors, nurses and research fellows with extensive knowledge in the diagnosis and management of chronic wounds.

## 16) Recruitment Methods

Patients with chronic venous insufficiency seen for their routine care at the Dermatology or Wound Care outpatient clinics at the University of Miami Hospital will be identified for possible study eligibility by any of the dermatologists in our practice. If the treating dermatologist is a study team member, the patient will be asked if they are interested in being contacted by the study team to learn more about a protocol for chronic wounds. If interested, additional information will be provided and an informed consent form will be sent to the potential subject before scheduling a Screening Visit. A partial HIPAA waiver is needed, so that if the patient gives permission to be contacted by a member of the study team they will then be approached by a team member in clinic or will be contacted by phone if they consent. If the treating dermatologist is not a study team member, they will provide the potential subject with the contact information for the study team such that the patient can contact the study team for more information. If it is then determined that they are interested in participating, they will be scheduled for a visit at our Dermatology Clinical Trials Unit where informed consent and all other baseline visit study procedures will take place. The risks and benefits of the study will be presented, as well as the disclaimer that refusal to participate in the study will in no way, shape or form alter the type or quality of their care.

Will Protected Health Information (PHI) be accessed prior to enrollment/consent? If so, please indicate "yes" below to request a Partial Waiver of HIPAA Authorization for Recruitment Purposes.
☒Yes ☐No

17) **Confidentiality**

PHI will be collected from the EMR or subjects at UHealth. Data will be stored locally:

☒ Other, specify: ***PHI will be stored in a binder inside a locked cabinet in the UMH Dermatology CTU. All PHI will be stripped of information that may be used to identify the subjects.***

The research team will maintain the research data in compliance with applicable regulatory requirements and University of Miami data retention requirements as outlined in the Investigator Manual.

## 18) Provisions to Protect the Privacy Interests of Subjects

Throughout the duration of the entire study, the privacy interests of participants will be maintained by ensuring the presence of members approved to be involved in the study and maintaining absence of those who are not. Additionally, phone visits will be held in the UMH Dermatology CTU away from the public and personnel from other departments of the hospital.

## 19) Authorization for Use and Disclosure of Protected Health Information (HIPAA)

Confirm that you will destroy the Protected Health Information (PHI) you and/or your Study Team acquire receive from JHS and/or UHealth at the earliest opportunity.

☒ ***I confirm***

Confirm that the Protected Health Inform (PHI) you acquire from JHS and/or UHealth will not be re-used or disclosed to any other person or entity, except as required by law or for authorized oversight of the research study or for other research for which the use or disclosure of PHI is permissible.

☒ ***I confirm***

Notwithstanding the preceding "I confirm" statements above, I agree that neither I nor any member of the study team listed on the IRB submission for this Protocol shall ever

re-use or re-disclose any of the information acquired from Jackson Health System in any format, whether **identifiable or de-identified,** to any individual or entity without first obtaining written permission from Jackson Health System, even if such re-use or re-disclosure is permissible by law (e.g., HIPAA).

_____

PI Signature Date

## 20) Consent Process

Once patients are identified and consent to be contacted, they will be approached by a member of the study team during their outpatient visit OR will be contacted by a member of the study team by phone. Participants will be given ample time to consider their agreement. The study team will be available to answer any question in the method the participant prefers to communicate. No one in a perceived coercive position in relation to the participant will engage in the consenting process. Consent will be obtained voluntarily prior to initiating any study procedures.

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