Phase 2, Randomized Study of the Tolerability and Safety of the OsciPulse Device for the Prevention of VTE

Principal Investigator Adam Cuker, MD, MS
Department of Medicine
[redacted]
Philadelphia, PA 19104
[redacted]

Regulatory Sponsor University of Pennsylvania

Funding Provider University of Pennsylvania, "Dream Team" Grant

Medical Director [redacted]

Investigational Product OSCIPULSE mechanical therapy device for the prevention of VTE

IRB Number 844294
ClinicalTrials.gov Number NCT04625673

Original Protocol Date 2020

Version Number and Date Version 6.0, 1 June 2022

Table of Contents

Table of Figures

LIST OF ABBREVIATIONS

ADE *Adverse Device Effect*
AE *Adverse Event*
AESI *Adverse Event of Special Interest*
CDRH *Center for Device and Radiation Health*
CFR *Code of Federal Regulations*
CRC *Clinical Research Coordinator*
CRF *Case Report Form*
CSR *Clinical Study Report*
CTMS *Clinical Trial Management System*
DSMB *Data Safety Monitoring Board*
DSMP *Data & Safety Monitoring Plan*
DVT *Deep vein thrombosis*
eCRF *electronic Case Report Form*
EDC *Electronic Data Capture*
FDA *Food and Drug Administration*
GMP *Good Manufacturing Practice*
GCP *Good Clinical Practice*
GCS *Gradual Compression Stocking*
HIPAA *Health Insurance Portability and Accountability Act*
ICD *Intermittent Compression Device*
ICH *International Council for Harmonization*
ICU *Intensive Care Unit*
INR *international normalized ratio*
IP *Investigational Product*
IPC *Intermittent Pneumatic Compression*
IRB *Institutional Review Board*
ISS *Injury Severity Score*
NPUAP *National Pressure Ulcer Advisory Panel*
[redacted]
PE *pulmonary embolism*
PI *Principal Investigator*
PPMC *Penn Presbyterian Medical Center*
PT *Prothrombin Time*
PTT *Partial Thromboplastin Time*
QC *Quality Control*
RCT *Randomized Control Trial*
SAE *Serious Adverse Event*
SOP *Standard Operating Procedure*
UADE *Unanticipated Adverse Device Event*
VAS *visual analog scale*
VTE *Venous thromboembolism*

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	University of Pennsylvania
STUDY TITLE:	Phase 2, Randomized Study of the Tolerability and Safety of the OsciPulse Device for the Prevention of VTE
STUDY ID	IRB # 844294; NCT04625673
PROTOCOL VERSION	Version 6.0, 01 Jun 2022

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name	Adam Cuker, MD	Signature	
Affiliation:	University of Pennsylvania	Date	

1 STUDY SUMMARY

Title	A phase 2, randomized study of the tolerability and safety of the OsciPulse device for the prevention of VTE
Short Title	OsciPulse tolerability trial
Phase	Phase 2
Methodology	Randomized, crossover study
Study Duration	4 months
Study Center(s)	Penn Presbyterian Medical Center
Objectives	Part 1: Primary • To determine the tolerability of the OsciPulse device on healthy individuals. Secondary: • To determine the hemodynamic impact of the OsciPulse device on venous blood flow. Part 2: Primary: • To determine the tolerability and safety of the OsciPulse device • To evaluate device design with respect to initial clinical safety and device functionality. Secondary: • To assess the compliance of the OsciPulse device compared to a standard intermittent pneumatic compression device. • To evaluate the ultrasonographic hemodynamic parameters of the OsciPulse device compared to a standard intermittent pneumatic compression device.

Number of Subjects	Part 1: Three (3) subjects at a single site. Part 2: Fifteen (15) to Twenty (20) subjects at a single site.
Study Population	Part 1: Adults age ≥40 years healthy volunteers. Exclusion criteria include a current foot or ankle injury, current vascular disease. Part 2: Adults age ≥18 years admitted to the hospital. Exclusion criteria include contraindications for pneumatic devices, current or previous DVT, and pregnancy.
Investigational Product	OsciPulse mechanical therapy device for the prevention of VTE
Participant Duration	Part 1: Up to 3 hours Part 2: Up to 6-hours in hospital
Description of Facilities	Part 1: Enrollments will take place in the [redacted] offices clinical research space. Part 2: Enrollments will take place at the Penn Presbyterian Medical Center (PPMC). [redacted] coordinators will conduct bedside data collection in the hospital setting, and chart reviews will be conducted in the [redacted] office space located on the [redacted] at PPMC. This office space is locked with a front door security code.
Reference therapy	Intermittent pneumatic compression device
Statistical Methodology	Part1: Device tolerability will be assessed with a questionnaire focused on the comfort of the OsciPulse device. This data will only be used to validate the tolerability of the device for use in Phase 2 so no statistical analysis will be performed. Part 2: Device tolerability will be measured with a subject questionnaire focused on their comfort for both the OsciPulse device and the intermittent pneumatic compression device. The questions will have continuous visual analog scales to gauge responses, and we will use a paired t-test to evaluate the difference in responses between the OsciPulse device and the reference therapy. We will also monitor subject compliance, and venous valve sinus hemodynamics, when feasible, for each device and a paired t test will be used to compare those values.
Safety Evaluations	Part 1: Adverse events will be collected

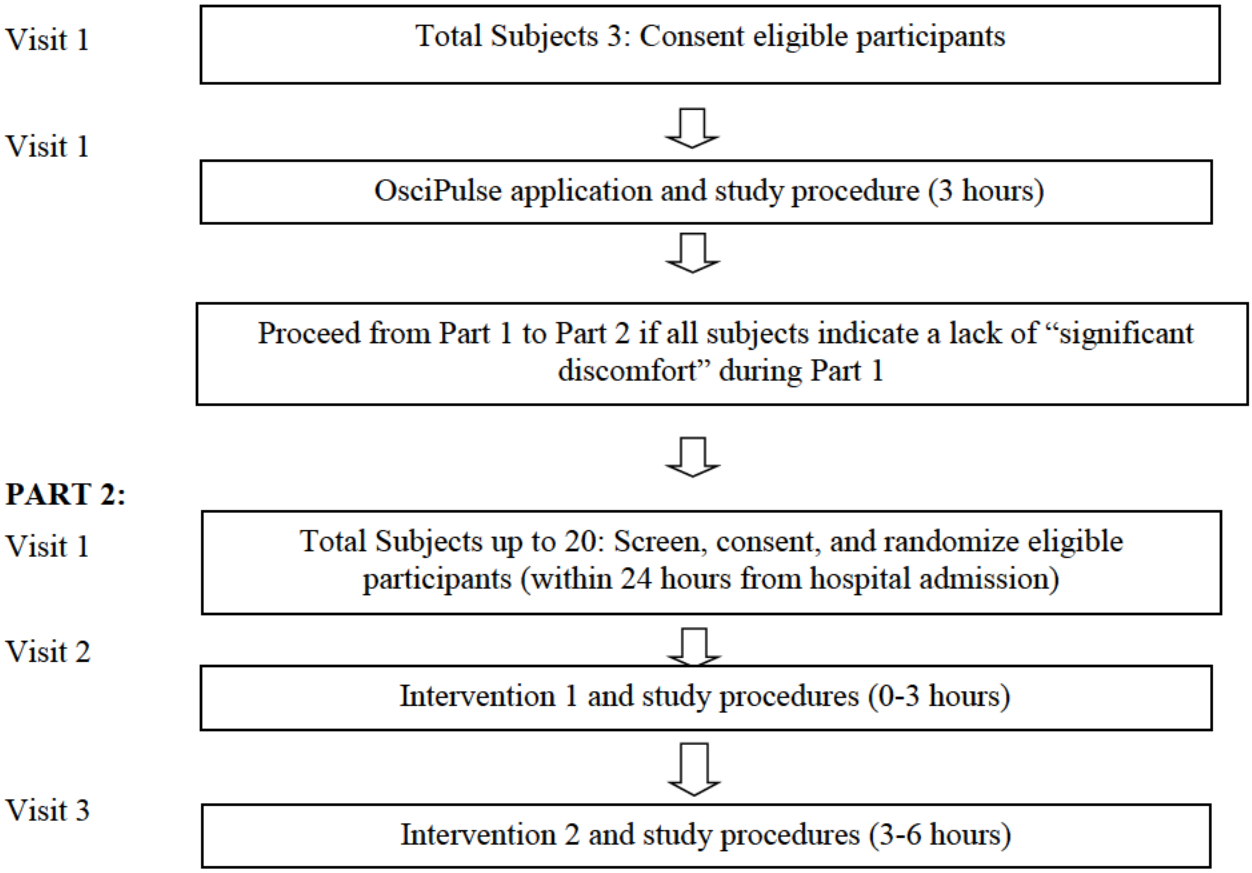
	Part 2: Adverse events will be collected. Expected AEs in this population include VTE, skin ulceration, peripheral nerve palsy, limb ischemia, and falls.
Data and Safety Monitoring Plan	The Sponsor is responsible for monitoring the data quality and the ongoing safety of subjects.

1.1 Key Roles and Study Governance

Sponsor Representative	*Medical Director*
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

1.2 Schema

Figure 1. Study Schema



2 BACKGROUND AND STUDY RATIONALE

This document is a clinical research protocol and the described study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and

all applicable Federal and state laws and regulations including Good Clinical Practice standards. All episodes of noncompliance will be documented.

2.1 Study Rationale

Venous thromboembolism (VTE) is a major complication occurring in hospitalized subjects. Although anticoagulants and mechanical prophylaxis are commonly used to prevent VTE it remains a leading cause of complications and death in the hospital population. Anticoagulation has been demonstrated to reduce the rates of hospital acquired VTE, but also has increased rates of bleeding complications. Mechanical prophylaxis is typically used together with anticoagulation and has no bleeding risk. However, existing methods of mechanical thromboprophylaxis have some limitations including equivocal efficacy and subject discomfort, which may undermine adherence. The new OsciPulse device was designed based on recent advancements in our understanding of the molecular basis of deep vein thrombosis (DVT) formation to improve the efficacy of mechanical devices in preventing DVT/VTE. The objective of this study is to evaluate device design with respect to initial clinical safety and device functionality.

2.2 Background and Relevant Literature

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease with over 1 million new cases per year in the United States[1]. VTE is associated with significant morbidity and mortality. The mortality rates after first VTE events are 6% at 30 days and 21% at 1 year[2]. Long term complications include recurrent VTE, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Approximately 50% of VTE cases are attributable to current or preceding hospitalization, while 12% and 7% are associated with trauma and neurological disease with extremity paresis, respectively[3]. Immobilization and lower-limb paralysis are independent risk factors for VTE in hospitalized subjects[4]. These well-recognized risks establish the need for effective VTE prevention in high-risk populations. If administered appropriately, a significant number of VTE cases will be preventable by thromboprophylaxis.

Thromboprophylaxis strategies can be categorized into pharmacological (with anticoagulants) and mechanical (with gradual compression stockings [GCS] or intermittent pneumatic compression [IPC] devices). Current clinical practice guidelines suggest using pharmacological thromboprophylaxis over mechanical thromboprophylaxis, and they are often used in conjunction with each other [5,6]. However, many subjects are not suitable candidates for anticoagulants because of contraindications such as bleeding or thrombocytopenia. In such cases, mechanical thromboprophylaxis provides the only prophylactic option. In suitable acutely ill medical subjects who do not receive pharmacological thromboprophylaxis, the American Society of Hematology VTE guideline suggests mechanical prophylaxis over no prophylaxis. One of the advantages of mechanical prophylaxis is its favorable safety profile. Although possible, the risk of serious harmful effects associated with the currently available options for mechanical thromboprophylaxis, such as limb ischemia or skin ulceration, are exceedingly rare.

The benefit of mechanical prophylaxis, however, remains controversial. In a systematic review of randomized controlled trials (RCT) of stroke subjects[7], mechanical prophylaxis (GCS and IPC) did not show a significant reduction in VTE or death. In another large RCT in stroke

subjects, IPC reduced the risks of asymptomatic DVT and symptomatic proximal or calf DVT. However, the reduction in symptomatic proximal DVT was not significant[8]. In trauma subjects, mechanical thromboprophylaxis reduced the risk of DVT, but not PE or death[9]. Pharmacological prophylaxis was more effective in reducing DVT but had higher risk of minor bleeding[9]. In critically ill subjects, adjunctive use of IPC in addition to pharmacological prophylaxis did not reduce DVT, PE, or death[10]. This lack of consistently clear evidence for benefit of mechanical prophylaxis suggests an unmet need for a more effective device to improve the efficacy of mechanical prevention of VTE.

Virchow's triad (venous stasis, endothelial injury, and hypercoagulability) constitutes the mechanistic pathogenesis of VTE. Immobilization leading to venous stasis is a major factor leading to VTE in trauma and stroke subjects. [redacted]

2.3 Name and Description of the Investigational Product

The study intervention will be the OsciPulse device system. The OsciPulse system is a non-invasive device [redacted].

[redacted]

2.3.1 Clinical Data to Date

2.4 Known Potential Risks

The application of mechanical thromboprophylaxis is a standard practice in many populations and is not considered to pose serious health risk. The risks include mild discomfort, interference with sleep and movement, injury due to falling, skin breakdown ulceration, and worsening of leg ischemia in patients with peripheral arterial disease. Risks of serious events including peripheral nerve palsy, circulatory compromise such as limb ischemia, deep vein thrombosis, pulmonary embolism, pressure ulcers (NPUAP category III and IV), and neuropathy is exceedingly rare but may occur as a result of use of intermittent pneumatic compression. Subjects who are at higher risk of such complications (subjects with pre-existing severe peripheral vascular disease or severe edema of lower extremities) will be excluded from the study. Adverse events of special interests are outlined in section 10.1.4

Additional adverse events expected in the target population include, but are not limited to, infection, bleeding, delirium, thrombosis, shock, respiratory failure, kidney injury, liver injury, and death.

All subjects will be monitored for adverse events over the course of the intervention as outlined in Section 10.

2.5 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study. Study procedures, including, the hemodynamic ultrasonography are not known to pose any additional health risk. If during the hemodynamic ultrasonography a DVT is incidentally identified, the findings will be reported to the subject's treating clinical team. The subject will be removed from the study and further testing or treatment will be at the discretion of the clinical team.

Direct benefits to the participating subjects include the potential benefit of VTE prevention by mechanical thromboprophylaxis. Indirect benefits include collecting more clinical data in terms of safety and tolerability to assist the development of better devices for VTE prevention in the future.

3 STUDY OBJECTIVES

3.1 Primary Objective

Part 1: To determine the tolerability of the OsciPulse device on healthy individuals.

Part 2: To assess the safety and tolerability of the OsciPulse device compared to a standard intermittent pneumatic compression device.

3.2 Secondary Objectives

Part 1: To determine the hemodynamic impact of the OsciPulse device on venous blood flow.

Part 2: To assess the compliance of the OsciPulse device compared to a standard intermittent pneumatic compression device.

To evaluate the ultrasonographic hemodynamic parameters of the OsciPulse device compared to a standard intermittent pneumatic compression device.

4 STUDY PLAN

4.1 Study Design

This is a single site, two-part study. Part 1 is in healthy subjects testing the tolerability of the device. Part 2 is a Phase 2, randomized crossover study in subjects with the potential to develop VTE evaluating the OsciPulse device compared to a standard intermittent pneumatic compression device. Our hypothesis is that the safety and tolerability of the OsciPulse device is equivalent to the standard compression device.

4.2 Justification for treatment regimen

Three hours of use for each device to allow for sufficient time for subjects to become familiar with the functional differences in each device to provide meaningful feedback on their experiences.

4.2.1 Screening and Enrollment Phase

Part 1: Subjects who are recruited from the general population will be screened for eligibility by answering questions about their general health and foot or ankle injuries. Subject demographics will be collected; however no medical record review will be conducted. Written informed consent will be obtained from eligible subjects.

Part 2: Subjects who are admitted for inpatient care following admission to Penn Presbyterian Medical Center will be identified and screened for eligibility. Written informed consent will be obtained from eligible subjects by Pennsylvania licensed medical professional. Video consent may be used.

4.2.2 Study Intervention Phase

Part 1: Enrolled healthy subjects will have the OsciPulse device applied by study or medical personnel according to the OsciPulse Instructions for Use. The subject will wear the device for a maximum of 3 hours while laying down. At the end of the study period the subject will receive an ultrasound scan of the deep venous system of the thigh/groin region to measure hemodynamics at a venous valve during immobility and during use of the OsciPulse device. Finally, the subject will participate in a questionnaire evaluation of their comfort and experience with the OsciPulse device. Participants will be compensated at $50/ hour for their participation.

Part 2: After informed consent is obtained, baseline demographic and clinical data will be collected. The subjects will be randomized with equal allocation to either of the two treatment sequence groups:

- Group A (OsciPulse device then standard IPC device)
- Group B (standard IPC device then OsciPulse device)

For group A, the OsciPulse device will be applied to the subject on both legs in the first 3 hours. The subject will wear the device for the maximum number of hours as possible up to 3 hours. The [redacted] research team inquire with the subject if the device was removed during the testing period.. During the 3-hour period the study team will monitor for adverse events and a hemodynamic ultrasonography may be performed (when feasible) following the Ultrasound SOP. After 3 hours, the subject will complete the questionnaire evaluating the tolerability and safety of the device. In the following 3 hours, the standard IPC will be applied. Subjects will undergo the same procedure for compliance monitoring, adverse event monitoring, hemodynamic ultrasonography (when feasible), and questionnaire evaluation.

For group B, the same procedure will be performed but with the standard IPC in the first 3 hours and the OsciPulse device in the next 3 hours.

Participants will be compensated $100 for their participation.

4.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed the intervention phase of the study.

4.4 Allocation to Interventional Group

All enrolled subjects will be assigned to both interventions. [redacted] will allocate the treatment sequence groups (group A: OsciPulse then IPC and group B: IPC then OsciPulse) in a 1:1 ratio by using block randomization. Prior to the study launch, [redacted] will create 4 envelopes. Each envelope will contain a GreenPhire card that will contain subject compensation, and a randomization form for either group A or for group B. This group of 4 envelopes will maintain the 1:1 ratio of randomization to group A or group B. Once all 4 envelopes have been sealed, they will be shuffled so that none of the research team knows which envelope contains each randomization form. Once the envelopes have been shuffled, the [redacted] study team member will place them in a random order and write subject study ID number on the outside of the envelope, indicating which subject they will be used for. For the first group, this will generate randomization for subjects one through four. When a subject is enrolled, the subject will be assigned a study identification number and the CRC will select the envelope with corresponding study-ID number—this will serve as the patient randomization. This process will be repeated 4 additional times in order to provide randomization for subjects 5 – 20. Once the envelope has been selected, the study team member will open the envelope, deliver the GreenPhire card to the subject and record the subject's intervention group onto a spreadsheet. The randomization sequence spreadsheet, randomization assignment sheet, and envelope will be kept and maintained a [redacted], which will be secure and accessible only by [redacted] staff and the nursing staff.

4.5 Protocol-defined Enrollment Hold

Part 2: In the event a disproportionate number of subjects are enrolled with a singular diagnosis, the Investigator in consultation with the Sponsor may pause the study to enrollment to reevaluate or revise, or both, the enrollment strategy, the intended subject population, the statistical analysis, or several of these activities.

4.6 Study Endpoints

4.6.1 Primary Study Endpoints

The primary endpoint will be subject safety and tolerability. Safety will be evaluated by the presence of adverse events (See section 10) during the intervention. Tolerability will be evaluated by a subject reported questionnaire. Tolerability will be measured by the 100-mm visual analog scale (VAS) and through open ended question answers. The average distance on the VAS in each domain of the questionnaire will be compared between the OsciPulse device and standard IPC.

4.6.2 Secondary Study Endpoints

- Percentage of time wearing the OsciPulse and standard IPC devices
- Ultrasonographic hemodynamic parameters (Change in venous centerline velocity in the femoral vein and volume of venous valve sinus reversing flow at the sapheno-femoral junction or other valve site imaged)

5 STUDY POPULATION AND DURATION OF PARTICIPATION

5.1 Inclusion Criteria

Part 1:

1. Adult age ≥40 years old
2. Generally healthy without a current foot or ankle injury
3. No history of diagnosed vascular disease including: DVT, PE, VTE, peripheral vascular disease, post-phlebitic syndrome, or chronic venous insufficiency.
4. Mentally alert and understand English proficiently.
5. Able to give informed consent.

Part 2:

1. Adult age ≥18 years old
2. Admitted to Penn Presbyterian Medical Center.
3. Anticipated decreased level of mobility for at least 6 hours as determined by the clinical team in collaboration with [redacted].
4. Mentally alert and understand English proficiently.
5. Able to give informed consent.

5.2 Exclusion Criteria

Part 1:

1. Injury to the lower limbs
2. Skin breaks, abrasion, or irritation in the area of the limb in contact with the OsciPulse device

Part 2:

1. Inability or contraindication to applying IPC to both legs
    - Evidence of bone fracture in lower extremities
    - Burns in the lower extremities, lacerations, ulcers, active skin infection or dermatitis, & ischemic limb in the legs at the site of IPC placement
    - Acute ischemia in the lower extremities
    - Severe peripheral vascular disease
    - Amputated foot or leg on one or two sides
    - Compartment syndrome
    - Severe lower extremity edema
2. Subjects anticipated to require surgical intervention within six (6) hours of admission
3. Subjects with history of VTE (DVT or PE)

4. Previous vascular surgery
5. Pregnancy or within 6 weeks of postpartum period
6. Limitation of life support, life expectancy < 7 days or palliative care
7. Admitted to an outside hospital more than 24 hours prior to screening
8. A head-unit is unavailable for the 6 hours or more
9. At the discretion of the attending physician and / or clinical team, the subject's participation in the study is believed not to be in the best interest of the subject.

5.3 Subject Recruitment

Part 1: Subjects will be recruited with IRB approved recruitment materials

Part 2: Subjects admitted to Penn Presbyterian Medical Center will be screened by [redacted] for eligibility within the first 24 hours of admission.

5.4 Duration of Study Participation

Part 1: The duration of study participation will continue for a maximum of 3 hours.

Part 2: The duration of study participation will continue for 6 consecutive hours.

5.5 Total Number of Subjects and Sites

Part 1: Recruitment will end after 3 subjects have been enrolled.

Part 2: Recruitment will end when no fewer than fifteen (15) evaluable subjects and no greater than twenty (20) evaluable subjects have completed the clinical protocol. In the event a subject begins the clinical protocol, however, does not meet protocol defined requirements of "evaluable" status (see section 9.2, Part 2), the Sponsor reserves the right to replace that subject, which may result in greater than twenty (20) subjects being enrolled. In the unlikely event a disproportionate number of enrolled subjects do not meet the protocol defined requirements for reaching "evaluable" status, the Sponsor may pause the study to enrollment to reevaluate recruitment, inclusion and/or exclusion, or any other activity deemed necessary at the time.

5.6 Vulnerable Populations

Vulnerable populations are not included in this study.

6 STUDY INTERVENTION; OSCIPULSE DEVICE

6.1 OsciPulse Description

The OsciPulse device consists of a wearable calf band that contains an inflatable air bladder, and is wrapped around the patient's calf. [redacted]

Figure 2 OsciPulse Device

6.2 Intervention Regimen

Part 1: The OsciPulse device will be worn by the subjects while they are in bed during the study duration. The subjects will be permitted to get up to use the restroom and for periods of stretching or walking for their comfort but will be encouraged to remain in bed for most of the study time. The device will be removed and reapplied by a clinical research coordinator or other trained personnel.

Part 2: The OsciPulse device should be worn by the subjects any time that they are in bed or seated in their room during the assigned 3-hour period. During operation, the device will inflate, compressing the calf 4-6 times per minute. The device will be worn during periods of subject immobility, including while sleeping. The device will be removed if the subject is getting out of bed and is ambulatory, or if the subject is receiving clinical care that requires that the device be removed as dictated by the clinical care team.

6.3 Receipt

Both the head units and wearable bands will be received from , who will oversee device manufacturing and quality assessment prior to shipping. Instructions for use will ship with each head unit and wearable band. Both head units and calf bands will be supplied by in sufficient quantities to complete the study.

6.4 Storage

The head unit with air tubing and wearable bands of the OsciPulse device will all be stored in the [redacted] office in the [redacted] at Penn Presbyterian Medical Center when not in use. The devices will be kept at room temperature in a locked cabinet. The head units will be initially wrapped in plastic, and in between uses the head units will be wiped with antiseptic wipes before storage and again after removal from storage. The wearable bands will be stored in the manufacturer packaging for single use.

6.5 Preparation and Packaging

Preparation of the device will be limited to the head unit being removed from a storage box or locked cabinet and hung from the end of the hospital bed and plugged into a standard power supply. A set of air tubing (2 pieces) will be delivered with the head unit in sealed plastic and should be kept together with the head unit between uses. The wearable calf bands will be removed from their sealed plastic bag packaging and strapped onto the legs of the subject. Instructions for Use will be provided to each subject.

6.6 Blinding

The intervention will not be blinded in this study

6.7 Administration and Accountability

The OsciPulse Instructions for Use will be provided to each subject and available in room for clinical staff. In summary, to administer the OsciPulse device, the calf bands will be fitted to the subject's calf with the aim to be snug without being too tight to restrict blood flow. [redacted]. [redacted] The clinical staff applying the device should confirm the first inflation to ensure that the device is set up correctly.

A pair of calf bands will be used for each subject, and at the end of the 3-hour period the bands will be disposed of in the hospital waste stream. The head unit can be wiped down with antiseptic wipes and returned to central storage along with the tubing.

The [redacted] staff will maintain accountability records for both the head units and the bands. The accountability log will include the following:

- the date of receipt of each item
- the unique identifiers of each item
- the date each device is distributed
- the protocol defined subject number to which each device was assigned
- Date of return or destruction

6.8 Product Problems and Complaints

The study staff will record any product problems and complaints on the IP Quality Complaint form and notify [redacted] and the Sponsor according to section 10.4.3.

6.9 Return or Destruction of Investigational Product

Wearable bands used on subjects will be disposed of in the hospital waste stream upon completion of the 3-hour period of use. The head units and unused bands will be picked up by [redacted] at the completion of the study.

7 STUDY PROCEDURES

Figure 3 Schedule of Study Procedures

Part 1:

Study Phase	Enrollment / Screening	Intervention and Assessment	
Study Hour	**-0.5 hrs**	**0 – 3 hrs**	**3 hrs**
Screening and enrollment:			
Informed Consent	X		
Demographics	X		
Review inclusion/exclusion criteria	X		
Intervention			
OsciPulse device		X	
Assessment			
Ultrasound scan			X
Adverse Event Monitoring	X	X	X
Compliance Monitoring			X
Questionnaire			X

Part 2:

Study Phase	Enrollment / Screening	Intervention and Assessment			
Study Hour	**- 24 hrs**	**0 – 3 hrs**	**3 hrs**	**3(+/-1) – 6 hrs**	**6 hrs**
Screening and enrollment:					
Informed Consent	X				
Review inclusion/exclusion criteria	X				

Study Phase	Enrollment / Screening	Intervention and Assessment			
Study Hour	**- 24 hrs**	**0 – 3 hrs**	**3 hrs**	**3(+/-1) – 6 hrs**	**6 hrs**
Demographics	X				
Laboratory Test Results		X			
Medical Record Review and History	X				
Vital Signs: BP, HR, RR	X				
Height and Weight	X				
Randomization of treatment sequence	X				
Intervention (Group A):					
OsciPulse device		X			
IPC device				X	
Intervention (Group B):					
IPC device		X			
OsciPulse device				X	
Assessment:					
Compliance monitoring*			X		X
Adverse Event Monitoring	X		X		X
Questionnaire(s)			X		X
Hemodynamic ultrasonography (when feasible)		X		X	

*Inquire with subject if the device was removed during the testing period

7.1 Pre-screening

Part 2 only:

- Medical record review to determine subject eligibility

7.2 Screening and enrollment

Part 1:

- Informed consent
- Review inclusion / exclusion criteria
- Demographics

- Adverse Events

Part 2:

- Informed consent
- Review inclusion/exclusion criteria
- Medical record review & Demographics
- Vital signs
- Randomization of treatment sequence
- Adverse Events

7.3 Study Intervention Phase

7.3.1 Part 1 Hour 0-3

- Application of the OsciPulse device
- Adverse Event monitoring
- Hemodynamic ultrasonography
- Tolerability Questionnaire

7.3.2 Part 2 Hour 1-3

- Application of OsciPulse device (Group A) or IPC device (Group B)
-
- Hemodynamic ultrasonography (when feasible)
- Questionnaire assessment at the end of 3 hours
- Adverse Events
- Laboratory Results

7.3.3 Part 2 Hour 3(+/-1)-6

- Application of IPC device (Group A) or OsciPulse device (Group B)
- Hemodynamic ultrasonography (when feasible)
- Questionnaire assessment at the end of 6 hours
- Adverse Events

7.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care.

7.4.1 Data Collection and Follow-up for Withdrawn Subjects

There will be no attempts to collect data from participants who have withdrawn consent. However, the Sponsor will retain all data collected for each subject prior to withdrawal.

7.5 Early Termination Visits

Subjects who terminate their participation early will receive no further follow up.

8 STUDY EVALUATIONS AND MEASUREMENTS

8.1 Demographics

The following demographic information will be obtained

- Date of birth
- Gender
- Race

8.2 Medical Record Review (Part 2 only)

The Medical Record review will be conducted to provide a description of the enrolled patients to aid in the interpretation of the reported outcomes of the study.

- Height
- Weight
- Admitting diagnosis and co-morbidities related to DVT/VTE risk, including:
  Heart Failure; diabetes; known thrombophilic states (protein C, protein S, or antithrombin deficiency; thrombotic thrombocytopenic purpura; hemolytic-uremic syndrome; activated protein C resistance; factor V Leiden thrombophilia, prothrombin gene mutation; antiphospholipid antibody; hyperhomocysteinemia); post-partum status (within 6 months); estrogen therapy (oral contraceptive or hormone replacement); active malignancy (treatment within the past 6 months or palliation); history of malignancy (within the past 5 years, other than non-melanoma skin cancer); paralysis or immobilization of a lower or upper extremity related to stroke or injury before this hospital admission; hospitalization in the past 3 months for any reason (excluding this hospital admission); trauma (including acute spinal cord injury, hip fracture, pelvic fracture, femoral fracture and tibial, fibular, knee or other fractures below knee); recent surgery (in the last 48h); acute stroke (in this index hospital admission); prior DVT or VTE; tumor or malignancy; hospitalization in previous 3 months
- Length of stay
- Use of pharmacological thromboprophylaxis and types of agents if used
- Use of pharmacological anticoagulant/antiplatelet therapy, type, dose
- Injury Severity Score (ISS)

8.3 Laboratory Tests (Part 2 only)

Of the initial labs drawn by the clinical team upon patient admission to the hospital, results from the complete blood count (hemoglobin, platelets) and coagulation panel (PT, PTT, INR) will be recorded on the case report form.

8.4 Vital Signs (Part 2 only)

Body temperature, heart rate, respiratory rate, and blood pressure will be measured by standard procedure at the time of subject enrollment.

8.5 Hemodynamic ultrasonography

A hemodynamic ultrasonography will be performed (when feasible) by certified technician/radiologist or physician trained in venous valve sinus imaging. The study specific ultrasound procedure SOP will be followed. All efforts will be made to conduct the ultrasound procedure with the assigned device even if subject is no longer clinically wearing the assigned device but agrees to wear for ultrasound procedure.

The following parameters will be measured both at rest and during the inflation period of the OsciPulse device and the calf ICD: centerline flow velocity, centerline flow, [redacted].

Video clips of the 2D color Doppler exams will be collected by the imaging personnel and transferred via a data storage device to [redacted] study personnel. The data will then be blinded and sent to Dr. [redacted], an expert in ultrasound image quantification, to perform the analysis and quantify the above parameters which will be provided back to the [redacted] team for data entry.

8.6 Questionnaires

For heathy subjects a questionnaire will assess tolerability of the device and open-ended feedback on the device. Part 2, a questionnaire with a 100-mm visual analog scale will be used to assess tolerability. The questionnaire will assess the comfort level, level of noise, and interference with sleep and movement. The questionnaire will also consist of a question to evaluate compliance and binary-response questions for the subject's future preferences.

8.7 Safety Evaluations

Adverse events will be monitored over the course of the intervention.

8.8 Compliance Monitoring

Compliance monitoring will be carried out by research staff from [redacted], and will consist of inquiring with the subject if the devices were removed for any period of time during the 3 hour study period. If the device was removed the [redacted] staff will note the reason and duration of the interruption.

9 STATISTICAL PLAN

9.1 Part 1

Part 1 of the trial is designed to test the tolerability of the OsciPulse system on healthy subjects for 3 hours prior to the 6-hour trial on patients. This is to determine if there are any immediate comfort issues that can be addressed prior to use in the clinical setting. Healthy volunteers are not the target population for the OsciPulse device and will have different tolerability for discomfort than hospital patients, but we feel that this test will be a qualitative analysis of the product prior to use in the target population. Subjects will indicate if the device caused 1) no discomfort, 2) mild discomfort, or 3) significant discomfort. **We will require that all three subjects indicate that there was not "significant discomfort" as reported on the subject questionnaire before continuing to Part 2**. This will be confirmed by the monitor prior to continuation to Part 2.

9.2 Part 2

Part 2 of the trial is designed to assess the tolerability and hemodynamic efficacy of the OsciPulse device in the clinical setting. The Primary endpoint is tolerability, which will be evaluated with questionnaires scored with a visual analog scale and will be directly compared between the OsciPulse device and a reference therapy device. Evaluable subjects will have completed the 6-hour study time that includes 3 hours with both therapies. This allows for the comparison between the therapies that makes the data quantitative rather than subjective. We will further measure hemodynamic efficacy through vascular ultrasound measurements of venous flow [redacted]

9.2.1 Primary Endpoint

The primary endpoint of this study is OsciPulse device tolerability compared to the current standard of care device. This endpoint will be measured by quantifying the differences in the responses to the questions on the subject questionnaire for each device. We will compare the visual analog scale ratings for the first 4 questions for each subject between the OsciPulse device and the reference therapy device. There are also 4 questions on the 6-hour questionnaire that ask the participants to directly compare the two devices, to determine the difference in tolerability. The ratings are reported in millimeters and the average differences between the responses will be statistically evaluated using a paired t-test.

9.2.2 Secondary Endpoints

The secondary endpoints of this study are the hemodynamic effects of each device on venous return dynamics. The hemodynamic endpoints will result from vascular ultrasound measurements [redacted] These hemodynamic parameters will be averaged across subjects and the difference between the measurements for each device will be evaluated using a paired t-test. The hemodynamic data will demonstrate the efficacy of the OsciPulse device to create the desired valve sinus reversing flow profile that has been shown in previous clinical studies with healthy volunteers. Confirming this flow in the subject population will demonstrate that the OsciPulse device can be successfully deployed in the clinical setting by clinical staff.

Safety will be monitored by tracking all adverse events during the 3-hour period of wearing each device and evaluated by determining the total number of events under each condition.

9.2.3 Sample Size and Power Determination

This study is a Phase 2 trial aimed at determining the tolerability and safety of an external device so we will use a convenience sample size of up to 20 enrolled subjects. This was determined in part by allowing that within our targeted population up to 6 subjects could experience an event during the 6-hour study window (discharge, unexpected surgery, loss of consciousness, death), and we would still have 14 subjects with evaluable tolerability and safety data.

9.2.4 Statistical Methods

The statistical approach to analysis will be to use paired t-tests to evaluate the difference between the standard of care cleared intermittent pneumatic device and the OsciPulse device using a

paired t-test. We will evaluate the primary endpoint of tolerability through quantification of the difference between the visual analog scale markings on the patient questionnaire for each device. We will also use a paired t-test to evaluate the changes in venous flow that occur in each patient during use of both devices.

9.2.5 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

9.2.6 Efficacy Analysis

Efficacy will be scored by the ultrasound measurements of venous blood flow during the use of the OsciPulse device and reference therapy device. Ultrasound measurements during device action will provide quantification of centerline venous flow velocity, the amount of flow within the sinus of the valve at the sapheno-femoral junction, and the amount of reversing flow in the sinus of the sapheno-femoral junction valve. Measurements may be taken at other vascular sites if the visualization window is not of sufficient quality for data collection at the sapheno-femoral junction. These measurements will be compared for each device and difference for each individual patient will be quantified and a paired t-test will be used to evaluate the overall efficacy.

9.2.7 Safety Analysis

All subjects entered into the study and randomized at the baseline visit will have detailed information collected on adverse events for the overall study safety analysis

9.3 Subject Population(s) for Analysis

We will analyze the Protocol-compliant population defined as any subject who was randomized and received the protocol required investigational product exposure, the reference therapy product exposure, and completed the required questionnaires and ultrasound examinations. Subjects who are enrolled but do not complete the protocol requirements will not be analyzed.

10 SAFETY AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event/Adverse Device Effect (AE/ADE)

An **adverse event** (AE) is any untoward medical occurrence that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes. A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

- Is not otherwise refuted by a repeat test to confirm the abnormality
- Suggests a disease and/or organ toxicity
- Is of a degree that requires active management

10.1.2 Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.1.3 Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event
- require intervention to prevent permanent impairment or damage

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

10.1.4 Adverse Events of Special Interest (AESI)

Newly developed DVT, pulmonary embolism, peripheral nerve palsy, skin ulceration NPUAP category III and IV, limb ischemia due to OsciPulse or IPC device are adverse events of special interest. These events may be related to use of the OsciPulse device and any incidence of these events should be reported to the sponsor.

10.2 Recording and Classification of Adverse Events

While admitted to the hospital and enrolled in the study, the electronic medical record will be screened upon completion of the subject's participation in the study for the presence of adverse events by the [redacted] research team. The subject will be questioned about adverse events during the 6-hour Interventional Phase of the study.. Information on all adverse events will be recorded in a timely manner in the appropriate adverse event module of the case report form (CRF) in PennCTMS.

While in-hospital, the [redacted] team will assess for the development of adverse events by talking to the clinical team and reviewing the electronic medical record. The development of adverse events will be reported to the principal investigator daily. After discussions with the clinical team it will classify these events as definitely related, probably related, possibly related, unlikely or unrelated to the OsciPulse device or study procedures. Serious adverse events (SAE), will be **reported to the principal investigator (PI) by telephone within 12 hours of the event**. The SAE CRF will be completed within 24 hours and the PI and Medical Director will be notified.

All adverse events occurring during the study period will be recorded. The clinical course of each adverse event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

10.2.1 Severity of Event

The following guidelines will be used to describe severity.

- Grade 1 (Mild): Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- Grade 2 (Moderate): Sufficient discomfort is present to cause interference with normal activity.
- Grade 3 (Severe): Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
- Grade 4: Life threatening or disabling adverse event.
- Grade 5: Death related to the adverse event.

10.2.2 Relationship of AE to Study

All adverse events (AEs) must have their relationship to the study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medical device). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related"

soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the OsciPulse device) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.3 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

The PI must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Subject number
- A description of the event
- Duration (start and end dates)
- Expectedness
- Action taken
- Severity Grade
- Relationship to study treatment or process
- Current status
- Whether study intervention was discontinued
- Whether the event is serious and the reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally, all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints) will be recorded and reported with respect to institutional and federal policies.

Reporting Period: Adverse events will be reported from the time of informed consent until study completion at 3 hours for Part 1 and 6 hours for Part 2.

The study investigator shall complete an SAE Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB). The study sponsor is responsible for conducting an evaluation of the event and shall report the results of such evaluation to the FDA Center for Device and Radiologic Health (CDRH) and to all reviewing IRBs and participating investigators per the applicable regulation.

10.3.1 Follow-up report

If an SAE/UADE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted.

The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

10.3.2 Investigator Reporting: Local Reporting Requirements

The investigator will adhere to local regulatory reporting requirements including the IRB/EC of record reporting requirements as well as IRB reporting requirements per 21 CFR 812. These additional reporting requirements include: failure to obtain informed consent, UADEs, device recall/repair/disposal, change in risk determination, or FDA or IRB withdrawal of the study.

10.4 Investigator Reporting: Notifying the study Sponsor

The following shall be reported to the Sponsor and Medical Director within 24 hours.

10.4.1 SAE and UADE

Every SAE and UADE regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

10.4.2 Failure to Obtain Informed Consent and Withdrawal of IRB Approval

The PI must report to the Sponsor within 24 hours if informed consent is not obtained for any subjects enrolled on the trial or if the IRB withdrawals approval of the study.

10.4.3 Product Complaints

OsciPulse device imperfections, malfunctions, or service required shall be reported to [redacted] and the Sponsor on the IP Quality Complaint Form. [redacted] will arrange for service or replacement of products for trial use.

10.4.4 Protocol Deviations

Protocol deviations of significant impact (see section 11.3) must be reported to the Study sponsor within 3 business days of learning of the deviation. Reporting shall be done using the Sponsor Exception & Deviation Form.

10.5 Stopping Rules

There are no specific stopping rules for the study.

10.6 Data and Safety Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring will be conducted by the University of Pennsylvania assigned monitor according to the Sponsor Data & Safety Monitoring Plan (DSMP).

Independent audits or compliance reviews may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the DSMP.

10.7 Data Safety Monitoring Board (DSMB)

The Sponsor has assessed that a DSMB is not needed for this trial.

11 STUDY ADMINISTRATION, DATA HANDLING AND RECORD KEEPING

11.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data and clinical laboratory data will be entered into the University of Pennsylvania's clinical trial management system (CTMS), a 21 CFR Part 11-compliant data capture system provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC supports programmable data entry validation rules and edit checks to identify data entry errors.

11.2 Records Retention

Study documents should be retained for a minimum of 2 years after the approval of a marketing application in an International Council for Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the OsciPulse device. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the

responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.3 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

Deviations of significant impact are to be reported to the study sponsor (see section 11.3) and according to local reporting requirements.

11.4 Regulatory, Ethical, and Study Oversight Considerations

11.4.1 Informed Consent Process / HIPAA Authorization

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Video consent may be used as well, which will be signed by the subject and a CRC witnessing the consent process, as well as the consenting physician at the earliest convenience. Recorded full face images during this process will be kept on an encrypted, password protected drive in the [redacted] offices and will only be available to the study team. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask

questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.4.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI at any site if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11.4.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

11.4.4 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6 (R2).

Each clinical site will perform internal quality management of study conduct, data, procedures, documentation and completion. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and procedures are followed, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.4.5 Funding Source

This study is financed through a grant from the [redacted].

11.4.6 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11.4.7 Subject Stipends or Payments

11.4.8 Part 1

Subjects enrolled in this study will receive compensation for their time with $150.00 ($50/hour) paid through the GreenPhire ClinCard system.

11.4.9 Part 2

Subjects enrolled in this study will receive compensation for their time with $100.00 paid through the GreenPhire ClinCard system.

11.5 Publication and Data Sharing Policy

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. The Sponsor must approve all sharing of information/data prior to its occurrence.

11.6 Protocol Amendment History

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the University of Pennsylvania. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes.

If in the judgment of, the sponsor, the IRB/IEC, and/or the investigator, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
V1	2020	Original Protocol	

Version	Date	Description of Change	Brief Rationale
V2	02 Feb 2021	Updated background information, clarified randomization procedures, updated vulnerable populations section, clarified monitoring procedures prior to moving to part 2, clarified SAE reporting procedures. Other minor and administrative changes for clarity and completeness.	To provide most current and accurate information.
V3	21 Apr 2021	Updated AE grading criteria to align with CTCAE definitions, as planned for use.	To align with CTCAE dictionary planned for use.
V4	01 Sep 2021	Updated applicable sections to clarify that ultrasound procedures will be completed when feasible	To account for variability in the availability of ultrasonographers during study procedures.
V5	12 Jan 2022; addl updates 17 Feb 2022	Updated eligibility criteria for Part 2, device description. Included description of video consenting process.	To facilitate recruitment and provide more current description of device. To provide accurate description of consenting process.
V6	01 Jun 2022	Updated eligibility criteria for Part 2, update study duration for Part 2, Removed requirement for physical examination, Updated procedure for compliance monitoring.	To facilitate recruitment and increase the frequency of subject's completing the study. To update study procedures based on the reduced study time.

12 REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
2. Huang W, Goldberg RJ, Cohen AT, et al. Declining Long-term Risk of Adverse Events after First-time Community-presenting Venous Thromboembolism: The Population-based Worcester VTE Study (1999 to 2009). *Thromb Res.* 2015;135(6):1100-1106.
3. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med.* 2002;162(11):1245-1248.
4. Spyropoulos AC, Anderson FA, Jr., FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest.* 2011;140(3):706-714.
5. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e195S-e226S.
6. Schunemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv.* 2018;2(22):3198-3225.
7. Naccarato M, Chiodo Grandi F, Dennis M, Sandercock PA. Physical methods for preventing deep vein thrombosis in stroke. *Cochrane Database Syst Rev.* 2010(8):CD001922.
8. Collaboration CT, Dennis M, Sandercock P, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet.* 2013;382(9891):516-524.
9. Barrera LM, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH. Thromboprophylaxis for trauma patients. *Cochrane Database Syst Rev.* 2013(3):CD008303.
10. Arabi YM, Al-Hameed F, Burns KEA, et al. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. *New England Journal of Medicine.* 2019;380(14):1305-1315.
11. Welsh JD, Hoofnagle MH, Bamezai S et. Al. Hemodynamic regulation of perivalvular endothelial gene expression prevents deep venous thrombosis. J Clin Invest. 2019;129(12):5489–5500.
12. Welsh, John, PhD, Mechanical Device to Modify Venous Flow, Clinical Study Report of an early feasibility study conducted at the University of Pennsylvania to determine the tolerability and measure the changes in venous blood flow in subjects using the OsciFlex device, 29 January 2020.
13. Welsh, John, PhD, Mechanical Device to Modify Venous Flow, Clinical Study Report of an early feasibility study conducted at the University of Pennsylvania to determine the tolerability and measure the changes in venous blood flow in subjects using the Osciflex device, Pending.