

# STUDY PROTOCOL

**PROTOCOL TITLE:**

Pilot Study to InVestigate the Efficacy and Safety of High Intensity Focused Ultrasound in PATients with Varicose Veins in Singapore (VESPA)

**PROTOCOL NUMBER:**

VESPA 1.0

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## **PROTOCOL SIGNATURE PAGE**

Pilot Study to Investigate the Efficacy and Safety of High Intensity Focused Ultrasound in Patients with Varicose Veins in Singapore (VESPA)

Protocol Number: VESPA

Protocol Version/ Date: 1.0 / 29 Nov 2019

Sponsor Name: NA

### Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: \_\_\_\_\_ Dr Tang Tjun Yip \_\_\_\_\_

Principal Investigator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## **1. BACKGROUND AND RATIONALE**

Varicose veins of the lower limbs affect many people worldwide with incident reports of its extent in 40% of women and 20% of men<sup>1-2</sup>. Varicose veins occur as a result of weakening valves in veins, causing reversal of blood flow and venous reflux<sup>3</sup>. Risk factors for varicose veins includes family history, obesity, prolonged standing, gender and number of offspring<sup>4</sup>. Symptomatic presentation of varicose veins varies from itching, hyperpigmentation to phlebotic lymphedema, chronic swelling of legs, lipodermatosclerosis, and venous ulcerations<sup>1-2</sup>. Current treatment options include vein stripping, thermal ablation therapy, such as endovenous laser ablation and non-thermal methods such as Venaseal and Clarivein<sup>5-6</sup>. The goal of these treatments is to eliminate sources of reflux in order to control the progression of the disease, prevent recurrence and provide symptomatic relieve.

However, given the invasive and surgical nature of these current therapies, some patients do not undergo treatment in fear of the potential surgical complications and prolonged recovery periods<sup>7</sup>. These invasive procedures are also associated with risks of infections and low cost-effectiveness<sup>8</sup>. As such, novel non-invasive therapies are being researched and developed to better meet the need of patients with varicose veins.

More recently, echotherapy technology such as Sonovein®, a high intensity focused ultrasound (HIFU) treatment, has been introduced as a non-invasive alternative for the treatment of varicose veins. During echotherapy treatment, non-invasive high intensity ultrasound beam is focused on the troubled vein, delivering thermal energy. The vein then absorbs the thermal energy, shrinks, and is sealed. The non-invasive nature of echotherapy has the capacity to prevent infections, leaves no scars and discolouration, and removes the need for tumescence anaesthesia. Recovery period from echotherapy is also immediate and caters to all vein types. Further, the administration of echotherapy does not require the presence of external nurses, additional materials such as micro puncture kits, recovery or sterile rooms, making it a more cost-effective treatment compared to current invasive standards of care.

Currently, such high intensity focused ultrasound treatments have only been very recently been introduced as a treatment option for the local population. In this study, we wish to evaluate the safety, efficacy, and performance of HIFU, using the Sonovein® device for our local population. Although it has been shown to be safe and efficacious in its pre-clinical trials, these studies have been limited to generally a caucasian-based population, where the vein size, anatomy and distribution of venous incompetence can be different from their asian counterparts. The pain scores, compliance, quality of life scores, occlusion rate at baseline, 2 weeks, 3 months, 6 months and 12 months will be assessed.

## **2. HYPOTHESIS AND OBJECTIVES**

Primary Objective:

The aim of the study is to evaluate the efficacy of non-invasive echotherapy for the treatment of varicose veins, within local population, using the Sonovein® device. The quality of life scores at baseline, 2 weeks, 3 months, 6 months and 12 months will be assessed using the EQ-50D, AVVQ and CIVIQ scores. Patient satisfaction at these time points will also be assessed.

### **3. EXPECTED RISKS AND BENEFITS**

No additional risk for study patients because they would undergo HIFU as per the assessment by their primary physicians as suitable treatment for the patients. There will not be any study specific interventions for the patients. For this study, we are administering Quality of Life questionnaires, as well as reviewing medical history and procedural information. There will be additional follow-ups arising from participation. There will be a slight inconvenience of multiple returns to clinic and taking time for questionnaires, minimal risk for breach of confidentiality. However, in terms of standard care, this is above and beyond what is expected.

Subjects stand to benefit from the closer monitoring post-procedure. In the long run, the medical knowledge gain with regards to treatment outcomes is beneficial for future patients.

### **4. STUDY POPULATION**

#### **4.1. List the number and nature of subjects to be enrolled.**

15 subjects from inpatient / outpatients from Department of Vascular Surgery, Singapore General Hospital that will be undergoing HIFU for treatment of symptomatic varicose veins will be recruited if they are found to have primary great saphenous (GSV), small saphenous vein (SSV) or anterior accessory saphenous vein (AASV) incompetence on colour duplex scan.

#### **4.2. Criteria for Recruitment and Recruitment Process**

Patients diagnosed with venous reflux on duplex scan and has decided on HIFU as treatment modality will be screened by primary care consultant. The procedure and risk/benefits, as well as other alternative treatment modalities will be explained to patient. At the same time, they will be briefed about the study (what to expect, such as questionnaires and additional follow-ups arising from participation). There will be sufficient time and opportunity given to ask any questions with regards to procedure and study. Patients will be given enough time to consider their participation and can let the study team know of this decision at next visit / surgery day. Should patient be agreeable, informed consent will be taken.

#### **4.3. Inclusion Criteria**

To participate in study, all the following inclusion criteria must be met:-

1. Age >21 years, able to understand the requirements of the study and provide informed consent.
2. C2 – C5 varicose veins / CVI
3. Symptomatic primary GSV, SSV or AASV incompetence, with reflux >0.5 seconds on colour duplex, including one or more of the following symptoms: aching, throbbing, heaviness, fatigue, pruritus, night cramps, restlessness, generalized pain or discomfort, swelling.
4. Patients who has GSV, SSV or AASV diameters of 3mm to 12mm in the standing position.

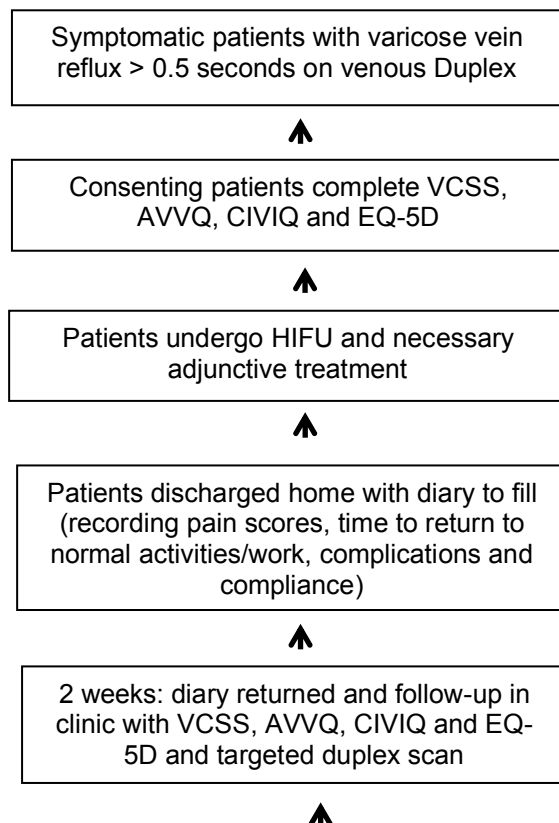
#### 4.4. Exclusion Criteria

Subject will not be eligible for the study if any of the following exclusion criteria is met:-

1. Current DVT or history of DVT
2. Recurrent varicose veins
3. Pregnant patients
4. Arterial disease (ABPI<0.8)
5. Sepsis
6. Patients who are unwilling to participate
7. Inability or unwillingness to complete questionnaires
8. Adverse reaction to sclerosant or cyanoacrylate
9. GSV, SSV or AASV severely tortuous
10. Life expectancy < 1 year
11. Active treatment for malignancy other than non-melanoma skin cancer
12. Current, regular use of systemic anticoagulation (e.g. warfarin, heparin)
13. Daily use of narcotic analgesia or NSAIDS to control pain associated with venous disease

#### 5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

The study involves prospective data collection of 30 patients that will be undergoing HIFU as choice of treatment for their varicose veins / CVI. Questionnaires will be conducted at 5 timepoints – baseline before procedure, 2 weeks, 3 months, 6 months and 12 months. Subjects will be seen at outpatient clinic post-procedure. Besides questionnaires, physical examination and duplex ultrasound scan will be conducted at 2 weeks, 3 months, 6 months and 12 months to ensure occlusion of treated vein.



3, 6 and 12 months: follow-up in clinic with VCSS, AVVQ, CIVIQ and EQ-5D as well as targeted duplex scan to look for anatomical recurrence



Analysis of results and cost evaluation

Physical Examination includes the assessment of:-

- GSV/SSV/AASV reflux
- CEAP Classification (Clinical, Aetiological, Anatomical and Pathophysiology)
- Venous Clinical Severity Score (VCSS)

Duplex ultrasound will be performed by vascular sonographers / vascular consultants. Reflux is determined at the sapheno-femoral (SF) / sapheno-popliteal (SP) junction in the lying and standing position using the Valsalva manoeuvre or manual distal compression with rapid release respectively. Reflux as documented by ultrasound is defined and considered significant as retrograde flow of >0.5 seconds.

Quality of Life questionnaires include:-

- ED5Q
- CIVIQ-14
- AVVQ (Aberdeen Varicose Vein Questionnaire)
- Pain Diary
- Patient Satisfaction Survey

Sonovein® is a unique echotherapy solution, combining therapeutic ultrasound and ultrasound for monitoring. The high-intensity ultrasound beam is focused on the vein through a magnifying glass. As thermal energy is delivered, the thermocoagulation property of ultrasound energy affects the vein wall, causing shrinking and collapsing of the target vein. Thus creating a fibrotic seal and occluding the vessel. The treated vein is immediately closed after the procedure, and its diameter will continuously reduce over time, becoming a fibrotic chord. The treatment along the vein is steered automatically via a touch screen monitor. In-beam linear ultrasound probe allows visualisation of the vein in real-time and insures optimal accuracy.

## **6. SAFETY MEASUREMENTS**

### **6.1. Definitions**

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

### **6.2. Collecting, Recording and Reporting of Serious Adverse Events to CIRB**

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

### **6.3. Safety Monitoring Plan**

All patient data will be anonymised and stored on a password protected database under the guidelines of Personal Data Protection Act (PDPA). Patient data will also be kept on paper in the form of data collection forms (questionnaires etc.). These will be kept in a locked filing cabinet and stored in SGH for 10 years in accordance with local policy.

### **6.4. Complaint Handling**

Complaints will be addressed by the Principal Investigator, who will speak to the parties involved and identify the areas of discontent.



## **7. DATA ANALYSIS**

### **7.1. Data Quality Assurance**

Accuracy and completion of data collection will be the responsibility of PI and research co-ordinator. Research co-ordinator will review data entered in database and hardcopies of data collection sheet on a regular basis to ensure data integrity. PI will audit the data entered into the database against hardcopies to ensure maintenance of data integrity. Active feedback about data input performance will be given.

### **7.2. Data Entry and Storage**

Raw data will be collected on a standardized data collection sheet. These hardcopy documents will be filed and kept in a locked cabinet. Only study team members have access to cabinet.

Data will be keyed into a password-protected database. Only study team members have access to this database.

## **8. SAMPLE SIZE AND STATISTICAL METHODS**

### **8.1. Determination of Sample Size**

A pilot group of 15 patients will be recruited for this prospective study to investigate the safety and efficacy of HIFU for the treatment of varicose veins.

### **8.2. Statistical and Analytical Plans**

Categorical data will be presented as frequency (percentage). Numeric data will be presented as mean (standard deviation) for parametric distribution and median (interquartile range) for non-parametric distribution.

The primary endpoint of complete closure at different time points will be reported as frequency and percentage (95% CI). Comparisons of the quality of life and functional results at baseline and after treatment at different time points will be examined using pair t-test or Wilcoxon Signed Rank test, where appropriate.

A two tailed, p-value of <0.05 was considered statistically significant. Statistical analysis will be performed with SPSS statistical software, version 19.0 (IBM Corp. Armonk, NY).

## **9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Accuracy and completion of data collection will be the responsibility of PI and research co-ordinator. Research co-ordinator will review data entered in database and hardcopies of data collection sheet on a regular basis to ensure data integrity. PI will audit the data entered into the database against hardcopies

to ensure maintenance of data integrity. Active feedback about data input performance will be given.

## **11. ETHICAL CONSIDERATIONS**

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

### **11.1. Informed Consent**

PIs/Co-Is/Authorised Study Team Members will recruit eligible patients that are admitted / on follow-up with the Department of Vascular Surgery, Singapore General Hospital for varicose veins / chronic venous insufficiency. Prior to procedure, patients will first be screened and given enough time to consider participation. They will be briefed on what the study involves, as well as any risks/benefits involved. If they decide to participate, informed consent will be taken by PI/Co-I/authorised study team members.

Patients will be assured that the standard of care will not be affected, regardless of participation in study.

If there are non-English speaking patients, the study will be explained in their preferred language through a translator.

### **11.2. Confidentiality of Data and Patient Records**

PI will ensure that subject's anonymity is maintained. On all study documentation, with the exception of consent forms and identification logs, subjects will only be identified by unique identification codes and initials, not by name.

## **12. PUBLICATIONS**

Authorship will include co-investigators, collaborators and research co-ordinators. All co-authors will review manuscript before it is sent for peer review.

## **13. RETENTION OF STUDY DOCUMENTS**

PI will maintain all documents relating to study in a secure storage facility, and maintain adequate records to enable the conduct of study to be fully documented. These documents will be retained for 10 years after the end of study.

No study documents will be destroyed without prior written agreement between PI and sponsor.

#### **14. FUNDING and INSURANCE**

There will not be any funding required for this study. However, as goodwill, Theraclion (owner of Sonovein®) will be providing the consumables free of charge for study patients only.

## List of Attachments

### Appendix 1 References

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3. Tan, K. K., Nalachandran, S., & Chia, K. H. (2009). Endovenous laser treatment for varicose veins in Singapore: a single centre experience of 169 patients over two years. *Singapore medical journal*, 50(6), 591.
4. Jawien A. The influence of environmental factors in chronic venous insufficiency. *Angiology* 2003; 54 Suppl 1:S19-31.
5. Navarro, L., Min, R. J., & Boné, C. (2001). Endovenous laser: a new minimally invasive method of treatment for varicose veins—preliminary observations using an 810 nm diode laser. *Dermatologic surgery*, 27(2), 117-122.
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7. Teruya, T. H., & Ballard, J. L. (2004). New approaches for the treatment of varicose veins. *The Surgical clinics of North America*, 84(5), 1397-417.
8. Subramonia, S., & Lees, T. (2010). Radiofrequency ablation vs conventional surgery for varicose veins—a comparison of treatment costs in a randomised trial. *European Journal of Vascular and Endovascular Surgery*, 39(1), 104-111.