Template Protocol for non-CTIMPs

The Use and Reproducibility of Duplex Ultrasound to Provide Indices of Left Common Iliac Vein Diameter

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Protocol authorised by:

Name & Role	Date	Signature
Megan Coombs, Research Office	26.10.2023	M.Coombs

Study Management Group

Chief Investigator: Professor Alun Davies

Co-investigators: Sophie Connolly

Study Coordination Centre *(may not be applicable)*

N/A

Clinical Queries

Clinical queries should be directed to Sophie Connolly who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 1862**
Imperial College - Research Governance and Integrity Team (RGIT) Website

Funder

N/A.

This protocol describes the proposed study The Use and Reproducibility of Duplex Ultrasound to Provide Indices of Left Common Iliac Vein Diameter and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CIV	Common iliac vein
MTS	May Thurner Syndrome
DVT	Deep vein thrombosis
IVUS	Intravascular Ultrasound
CFV	Common femoral vein

KEYWORDS

Common Iliac Vein (CIV)
May-Thurner Syndrome (MTS)
Duplex Ultrasound

STUDY SUMMARY

TITLE	The use and reproducibility of duplex ultrasound to provide indices of left Common Iliac Vein (CIV) diameter, for improved diagnosis of May Thurner Syndrome (MTS) in patients presenting with unexplained left leg swelling.
DESIGN	Feasibility/Pilot Study.
AIMS	To investigate the use and reproducibility of duplex ultrasound to determine diameter indices of left CIV compression.
OUTCOME MEASURES	The diameter measurement of the left CIV in adults, and the inter- and intra-operator variation of the diameter measurement of the left CIV using duplex ultrasound.
POPULATION	Adult patients referred to the vascular ultrasound department.
ELIGIBILITY	Patients with or without venous disease, who have not had previous treatment for iliac vein disease.
DURATION	9 months

REFERENCE DIAGRAM

[if appropriate]

1. INTRODUCTION

1.1. BACKGROUND

May Thurner Syndrome (MTS) is a vascular condition whereby the left common iliac vein (CIV) becomes compressed between the right common iliac artery and the spine. This condition is often asymptomatic, however MTS can cause severe left lower limb complications such as swelling, pain, oedema, reflux, varices, skin changes and deep vein thrombosis (DVT). It is thought that approximately 2-3% of lower limb DVT's are caused by MTS, however there is an almost 56% predominance for left sided DVT suggesting this number is underestimated and cases of MTS are regularly missed (Peters et al., 2012). DVT can be a serious medical condition and can go on to cause pulmonary embolism, a sometimes fatal condition if not identified and treated quickly and effectively.

Diagnostic imaging studies such as ultrasonography, venography and intravascular ultrasound (IVUS) are used to evaluate the CIV and identify the site and severity of any narrowing that is present. Duplex ultrasound is often the first line of imaging as it is risk free, cost effective, and accurate at identifying lower limb venous insufficiency. However the location of the iliac veins deep in the abdomen has limited its use for identifying specific features of MTS. It is also highly operator dependent and the results obtained may be dependent on the experience level of the vascular scientist performing the scan. Abdominal ultrasound scans are also always performed with the patient lying completely flat, however this does not reflect the haemodynamic changes that occur within the venous system when a patient is standing. Indirect measurements can be taken to help indicate if there is an iliac vein obstruction, such as interrogation of the common femoral vein (CFV) to assess phasicity and reflux. However, these readings can suggest proximal problems but do not differentiate between compression and thrombus.

The gold standard for diagnosing MTS is venography, whereby a catheter is inserted into the iliac system and changes in pressure gradients are calculated across the region of compression. This procedure, however, is invasive, time consuming and exposes patients to radiation and contrast dyes. IVUS is also a well-used diagnostic tool for MTS. It is highly sensitive at identifying CIV compression and the development of intraluminal "spurs" and neointimal hyperplasia that is associated with MTS. IVUS however is also invasive, is unable to provide information related to extravascular lesions and there are fewer studies that have looked into the use of IVUS and the benefit to patient outcomes.

Metzger et al. (2016) examined the suitability of using velocity ratios to determine CIV stenosis. They used ultrasound to examine 76 patients with a range of chronic venous insufficiency symptoms. They took velocity measurements before an area of obstruction and within it, to create a venous iliac velocity ratio (VR). All patients were also assessed using IVUS, and diameter and area reduction measurements were recorded. Results found that a VR of >2 equated to a significant iliac lesion (defined as >50%). The results of this research are consistent with the case study by Oğuzkurt et al. (2007), who found an increase in velocity from 40cm/s to 100cm/s in the left CIV. This would equate to a VR of 2.5, and therefore a >50% obstruction on IVUS. The use of velocities to examine iliac veins, however, is controversial as peak systolic velocity measurements originated from arteries, where a critical stenosis is defined as >75% reduction in the diameter of the artery (Sloves and Almeida, 2018). Applying the same method to veins is difficult, as veins differ in shape and size, particularly those that are diseased or compressed as they become more elliptical in shape. Also, it is venous pressure rather than venous flow that plays the key role in venous stenosis. Additionally, all patients in this study were required to fast for 6 hours prior to having the ultrasound scan and were administered with dimethicone to aid visualisation of the iliac vessels. This is therefore not an accurate representation of the kind of scans that take place on a day to day basis, with few patients asked to fast before coming to a hospital appointment and none given medication to aid the process. Although in this study the VR was comparable to IVUS, it may not be reproducible in a workplace setting.

Another study used ultrasound to interrogate the CFV as a means of determining a value for identifying iliac vein stenosis. Mousa et al. (2016) examined the CFV and saphenofemoral junction in 36 patients with chronic venous ulcers, to see if reflux in the CFV (described as persistent reverse

flow for more than 1.0 second demonstrated on the Doppler spectral display) can be used to determine iliac vein stenosis greater than 50% (which was quantified using IVUS). They found that reflux in the CFV of greater than 2.5 seconds correlated to an iliac vein stenosis of greater than 50% (Mousa et al., 2016). This finding may be of great importance for deciding on effective treatment strategies for patients with chronic venous ulcers, such as the potential for iliac vein stenting when reflux is found to be greater than 2.5 seconds in the ipsilateral CFV. However, these measurements may not directly correspond to iliac vein compression and MTS, and further evaluation of these two parameters would be needed.

Similar research by Hui et al. (2020) looked at the use of lower extremity ultrasound as a screening tool for detecting iliocaval obstruction. The retrospective study examined images from 132 patients who had undergone lower extremity venous procedures over a 22 year period. Images from CT, MR and conventional venography were compared to the spectral Doppler image taken from the CFV on the same patient. The investigators examined phasicity and response to the Valsalva manoeuvre as a predictor of iliac vein patency. The study found that overall sensitivity of using nonphasic flow or response to Valsalva manoeuvre as an indicator of iliocaval obstruction was poor, whereas the specificity was reasonably good. It was suggested from this that positive results are likely to indicate a true obstruction in the ipsilateral iliac system, whereas negative results may not be reliable and the usefulness of these results may be questionable (Hui et al., 2020). Relating this to MTS, interrogation of the flow patterns in the CFV could indicate a complete compression of the CIV, but could not be used to indicate the degree of compression or used as a diagnosis tool. Therefore further research is required in this area to determine if duplex ultrasound can be used to directly image CIV compression, and if it can be used to determine a specific diameter measurement at which the CIV is considered compressed or not compressed.

1.2. RATIONALE FOR CURRENT STUDY

More widespread use of ultrasound for examining the iliac veins would be beneficial as it may avoid the need to expose patients to the invasive procedures requiring radiation and contrast agents that are necessary for venography and IVUS. Previous studies examining duplex ultrasound and iliac veins, as mentioned above, have examined the use of velocity ratios, interrogation of the CFV and examination of phasicity but have not investigated using ultrasound to measure the absolute diameter of the CIV. There is currently no definitive diameter that the CIV can be considered compressed or not compressed. All of the previous studies used symptomatic patients only and so it cannot be assumed that the results would correlate in asymptomatic patients. Also, it is known that ultrasound is highly operator dependent but none of the previous studies examined the impact of this on measuring the CIV diameter. Therefore, further work needs to be carried out to assess the use of ultrasound for imaging the left CIV and aiding MTS diagnosis.

The principle research question is whether duplex ultrasound could be used to image the left CIV and investigate diameter ranges that can help in the diagnosis of MTS. The first objective is to use duplex ultrasound to image the left CIV in a cohort of patients referred to the vascular ultrasound clinic. The second objective is to determine inter- and intra-observer variation of the diameter measurement of the left CIV using duplex ultrasound. The hypothesis is that ultrasound can be used to image left CIV compression and the measurements obtained during the examination are highly reproducible both within an operator and between operators.

If the results of this research study find that ultrasound can be used to image the left CIV, can define ‘normal’ diameter ranges and is a reproducible diagnostic tool, then this could reduce the time taken for patients presenting with symptoms of MTS to be diagnosed. Ultrasound is a quick and readily available imaging tool, and so creating an appropriate scanning protocol will enable regular scanning and screening of patients who may have this condition. As well as aiding diagnosis it should also help reduce the number of patients with this condition that go on to suffer from further severe complications such as DVT. These results should also help identify which patients need to go on to have the more invasive tests and rule out patients that do not require them. Iliac vein scanning with ultrasound is not routinely performed in all vascular departments across the country, with many only taking indirect measurements from the CFV’s. If a benefit is found to doing this scan then it could be introduced to many more/all departments, benefiting many more patients.

2. STUDY OBJECTIVES

The primary objective of this study is to investigate diameter variation of the left CIV based on posture in adults referred to the vascular ultrasound department, using duplex ultrasound.
The secondary objective of this study is to determine inter- and intra-observer variation of the diameter measurement of the left CIV using duplex ultrasound, in adults referred to the vascular ultrasound department.

3. STUDY DESIGN

The study will be a feasibility/pilot study lasting approximately six months, recruiting 40 patients from the vascular ultrasound department at Imperial College Healthcare NHS Trust. 20 patients will be symptomatic for lower limb venous disease and 20 patients will be asymptomatic. The following outlines the timeline of events for the patients recruited onto the study.

OUTPATIENT APPOINTMENT

At their outpatient appointment patients who may be eligible to take part in the study will be identified and approached. Patient notes and GP referral letters will be read prior to seeing the patient in the outpatient appointment, to identify suitable participants. Suitable participants will be those that will be requiring a vascular ultrasound scan in the vascular ultrasound department. The study will be explained and if the patient gives verbal consent to receiving study information material, then this will be given to the patient for consideration. They will be told that formal consent will be taken at their scan appointment if they agree to partake in the study and that if they choose not to partake this will not affect their usual clinical care. Participants will be given up to six weeks to decide if they would like to take part.

TELEPHONE CALL

Patients will be contacted two weeks after their outpatient appointment to enquire as to whether they would like to take part in the study. Those that decline will have their scan request form passed on to the department receptionist for booking in the usual way. Those that would like to take part in the study will have a date and time arranged to come to the department to have their scan as part of the study, followed by the scan requested by the clinical team. The study scan and the routine scan will be made on the same day to avoid the patient having to come to the hospital multiple times. Some patients form the symptomatic group may have been referred for this type of scan.

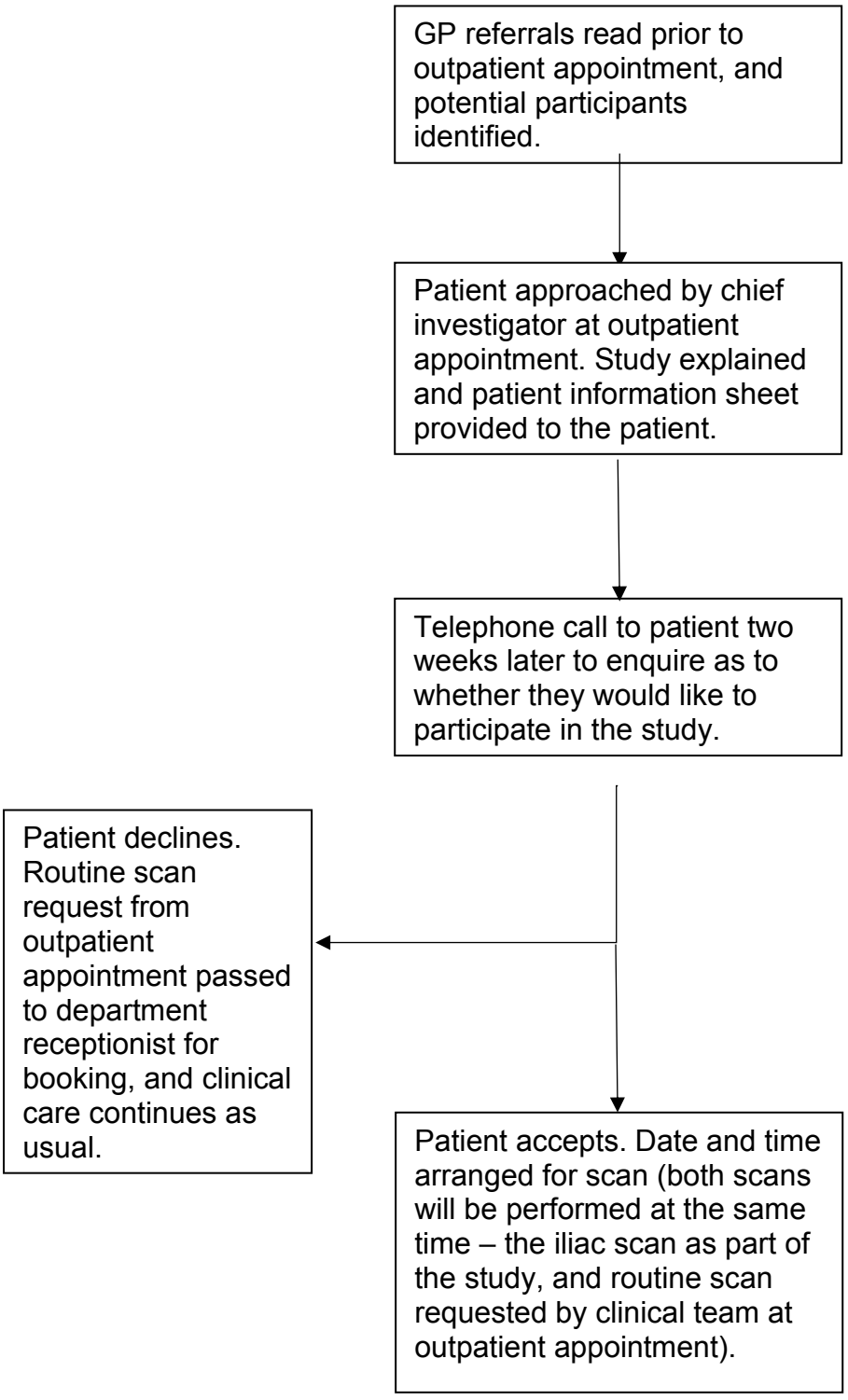
ULTRASOUND SCAN APPOINTMENT

Order of events at the scan appointment will be as follows;

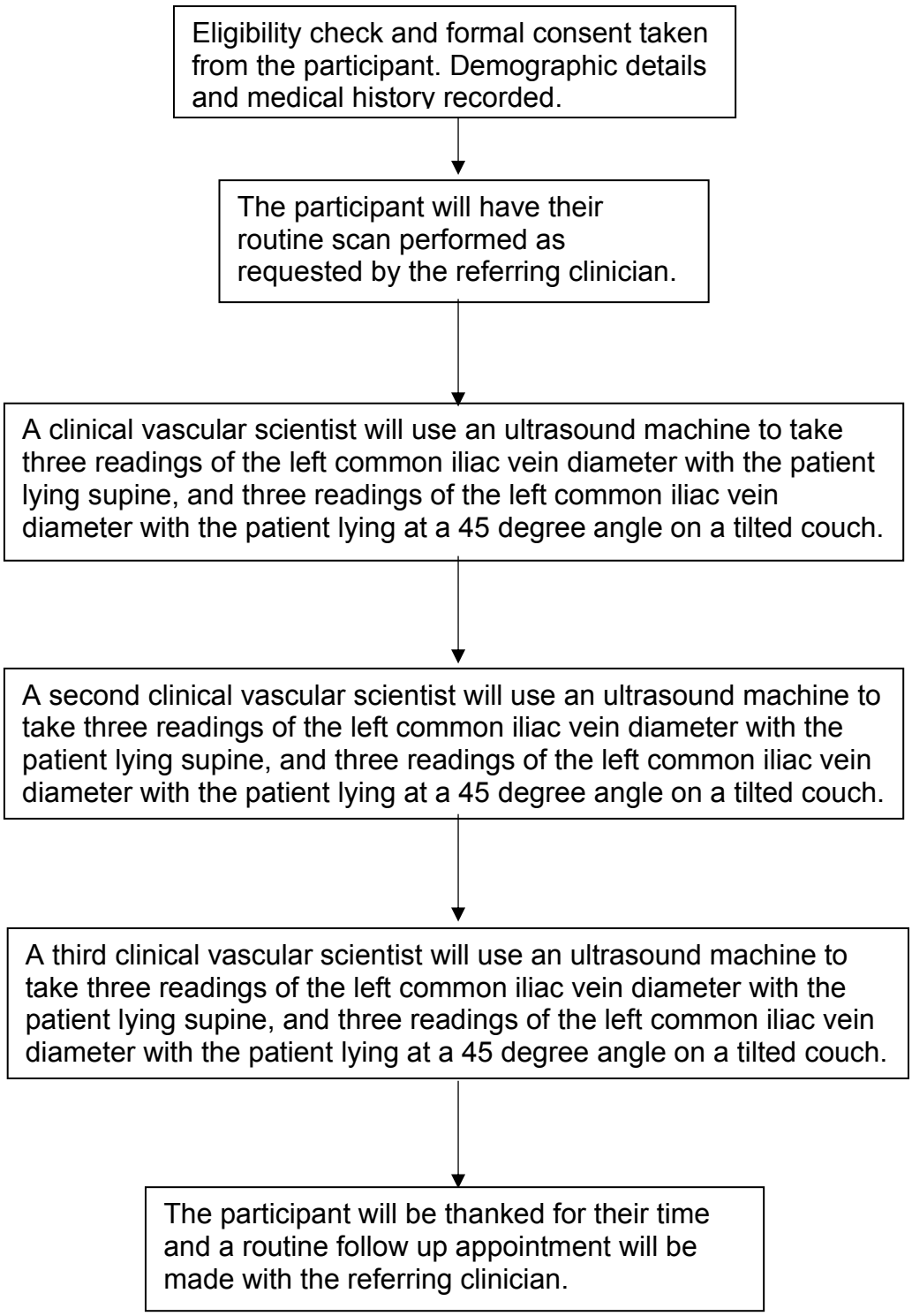
- Eligibility check and formal consent - 5 minutes
- Recording of demographic details and medical history - 5 minutes
- The patient will have their routine scan performed as requested by the referring clinician - Between 30 and 90 minutes, dependent on the scan type requested.
- A clinical vascular scientist will perform the study ultrasound scan and take three readings of the left CIV with the patient lying flat and three readings of the left CIV with the patient at a 45 degree angle on a tilted examination couch - 10 minutes
- Two further clinical vascular scientists will perform the same study scan and take the same readings - 20 minutes
- Patient will be thanked for their time and a routine follow up appointment will be made with the referring clinician.

The below flow chart illustrates this order of procedures:

Prior to the ultrasound scan appointment:



During the ultrasound scan appointment:



3.1. STUDY OUTCOME MEASURES

The primary outcome measure is the diameter variation ranges of the left CIV in adults referred to the vascular ultrasound department.

The secondary outcome measure is the inter- and intra-operator variation of the diameter measurement of the left CIV using duplex ultrasound, in adult patients referred to the vascular ultrasound department.

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

Patients notes, GP referrals and current scan request forms will be examined to determine that the patient does require a vascular ultrasound scan.

4.2. INCLUSION CRITERIA

Patients will only be included if:

- They have the capacity to consent.
- They are required to have a vascular ultrasound scan in the vascular ultrasound department at ICHT.

THEY ARE 18 YEARS OF AGE OR OLDER AT THE START OF THE STUDY.

4.3. EXCLUSION CRITERIA

Patients will be excluded if:

- They do not have capacity to consent.
- They do not require a vascular ultrasound scan as part of their routine care.
- They are under 18 years of age at the start of the study.
- They are pregnant.
- They have had previous interventions/treatment for iliac vein disease.
- They have had a previous diagnosis of iliac vein thrombus.

4.4. WITHDRAWAL CRITERIA

A participant may withdraw at any time by notifying the researcher in person or in written form. If a patient withdraws from the study, any data collected up until that time will remain on file and will be included in the final study analysis.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to a pre-existing, non-vascular related condition, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London – Riverside Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email a.h.davies@imperial.ac.uk (and contact details below)
Fax: N/A, attention N/A
Please send SAE forms to: Professor Alun Davies
Tel: 02033117320 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

This study is in addition to any NHS treatment the participants may be having, so there will be no assessment or follow-up required. In the event of discovering an

incidental finding, the participants' referring clinician will be informed via a telephone call or email from the researcher (dependant on urgency of findings e.g. the referring clinician or on-call vascular registrar will immediately be called if there is an incidental finding of acute thrombus in the iliac veins). The study will end when the last participant recruited on to the study has attended their ultrasound scan appointment.

7. STATISTICS AND DATA ANALYSIS

The sample size has been calculated using a sample size calculator assuming a prevalence of 2%, confidence level of 95% and margin of error of 5%. This calculation gives a sample size of 31. This sample size is in line with a previous study by Mousa et al. (2016) which had a sample size of 36.

A one-way ancova test will be performed to assess the difference in iliac vein diameter between the two groups. An intraclass correlation coefficient will be used to measure intra- and inter-observer reliability. Support will be provided from the Imperial Statistics Services during the analysis phase.

Statistics and data analysis aspects of the study have been reviewed by May Azzawi, the academic supervisor at Manchester Metropolitan University.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the London - Riverside Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data

analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be anonymised.

Personal data will be stored on NHS computers and will be password protected. Manual files e.g. consent forms will be stored in locked cabinets at the NHS site. All data will be collected according to the Data Protection Act 2018 and in line with general data protection regulation (GDPR).

Personal data will be anonymised by converting to a study code. Subject study data will be first collected on a paper case report form. This original source data will then be transcribed electronically onto a trial database, REDcap. The database is stored on a private network protected by a firewall. Access to the database is restricted to trial staff by login and password.

All personal identifying data will be kept electronically on NHS computers and in paper format stored in NHS premises with secure offices only accessible by authorised personnel.

Paper copies of consent forms will be kept in confidential files in a lockable office only accessible by authorised personnel.

Data and all appropriate documentation will be stored for a minimum of 10 years.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

There is no official funder for this study. Participants will not receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research. Individual researchers will not receive any personal payment over and above normal salary, or any other benefits or incentives for taking part in this research.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Principal Investigator.

10. PUBLICATION POLICY

The results will be included in the final clinical doctorate thesis. The results will be published in peer reviewed journals, as an internal report, conference papers and research presentations. The anonymity of the participants will be ensured when publishing. Participants will receive a newsletter outlining the findings on completion of the study.

11. REFERENCES

Hui, J. Z., Goldman, R. E., Mabud, T. S., Arendt, V. A., Kuo, W. T. and Hofmann, L. v. (2020) "Diagnostic performance of lower extremity Doppler ultrasound in detecting iliocaval obstruction." *Journal of Vascular Surgery: Venous and Lymphatic Disorders*. Elsevier Inc., 8(5) pp. 821–830.

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Sloves, J. and Almeida, J. I. (2018) "Venous duplex ultrasound protocol for iliocaval disease." *Journal of Vascular Surgery: Venous and Lymphatic Disorders*. Elsevier Inc., 6(6) pp. 748–757.

APPENDICES

PIS and Consent form, recruitment poster and letter to GP attached separately.