Vivasure medical	**Clinical Investigational Plan Synopsis**

TITLE: Synopsis of Clinical Investigation Plan (CIP) for Safety and Performance Study of Large Hole Vascular Closure Device – FRONTIER IV Study

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Plan Title: Clinical Investigation Plan (CIP) for Safety and Performance Study of Large Hole Vascular Closure Device – FRONTIER IV study

CIP No.: Clinical Investigation Plan P528-00

Study Device: PerQseal® closure device, PerQseal® Introducers – 'S' & 'L'. The term '*PerQseal®*' used singularly refers to both the closure device and Introducer, individually referred to as PerQseal® closure device and/or PerQseal® Introducer, respectively.

The PerQseal® is supplied with two different PerQseal® Introducers in sizes "S" or "L". The nominal outer diameter of the "S" sheath is 6.1 mm and the "L" sheath is 7.2 mm which is approximately equivalent to a 14 F and 18 F sheath, respectively. Note: sheath sizes are measured by internal diameter; hence, their outer diameter is dependent on wall thickness.

Expected Study Duration: 12 months total – 9 month recruitment with 3 month patient follow-up.

Study Rationale:
The rapid development of percutaneous 'minimal invasive therapy' in which multiple disciplines are involved including Vascular Surgery, Cardiac Surgery, Interventional Radiology and Interventional Cardiology, has led to the need for instrumentation to minimise the risk of complications associated with closing the access site, post procedure. The currently emerging endovascular or transcatheter procedures include: Aortic Valve Replacement, Mitral Valve Repair and Abdominal and Thoracic Aneurysm Repair. These procedures require larger size access sites ranging from 12 to 27 French (F). These large access sites are typically created via surgical cut-down to the common femoral artery and closed by surgical repair.

In order to provide a less invasive, percutaneous, safe, secure and simple mechanical closure of these large arteriotomies and shorten the time taken to perform these closures, Vivasure is developing a new large hole percutaneous vascular closure device to induce arterial haemostasis in patients undergoing endovascular interventional therapeutic.

Clinical Sites:
Multi-centred clinical trial.

Study Objectives:
To assess safety and performance of the PerQseal® to percutaneously close femoral artery punctures and to induce arterial haemostasis in patients undergoing endovascular procedures requiring an arteriotomy created by 12 to 20 F sheaths.

Study Design:
This study will be a prospective, multi-centred, non-randomized study to investigate the safety and performance of the PerQseal®. The study shall not be blinded prior to, during or post the procedure. All patients undergoing an endovascular procedure requiring an arteriotomy created by 12 to 20 F sheaths, via the common femoral artery will be screened against the inclusion/exclusion criteria.

Closures may be performed by either clinical specialty, namely; Interventionalist or Vascular Surgeon.

Patients with bilateral percutaneous access in the common femoral arteries where both arteries meet all eligibility criteria may, at the discretion of the investigator, both be closed with the PerQseal® closure device. If a PerQseal® is used on the contralateral femoral artery then this will be treated as an independent closure i.e. each limb will be counted as a separate closure.

All subjects shall have a 1 & 3 follow-up assessment. Safety data from the follow-ups will be assessed by the Data Safety Monitoring Committee. Details of follow-up assessments are contained in Table 1.

Primary Endpoint
Incidence of major vascular access site complications directly related to the PerQseal® closure device up to 1 month from implantation, (as per definitions) is no worse than those associated with cut-down and sutured closure.

Overall Secondary Endpoints
Safety: Incidence of minor vascular access site complications directly related to the PerQseal® closure device up to 1 month from implantation (as per definitions).

Performance: assessed by technical success rate for the PerQseal® (as per definitions) of the PerQseal® at discharge is no worse than the technical success rates associated with the 'perclose' or 'preclose' technique following EVAR or TAVR.

SAMPLE SIZE:
The sample size estimate outlined below is based on primary endpoint assessment only.

The minimum sample size to demonstrate non-inferiority of safety against the literature based non-inferiority limit of 0.17 with a one-sided significance level of 0.025 and study power of 90% is estimated to be 68 closures (assuming a 5% major vascular access site complication rate for the PerQseal® closure device).

A one sided confidence interval is appropriate as the study is only interested in the upper bound of the major complication rate. Each complication will be analysed as a separate event.

Completion of 75 patients is recommended, this number of patients should be sufficient to demonstrate non-inferiority whilst allowing for approximately 10% dropout rate.

Subject Cohort: Patients with a femoral arteriotomy created with a 12 – 20 F sheath will be included.

Inclusion criteria:

i. Over 18 years of age.

ii. Subject is willing and able to provide appropriate study-specific informed consent, follow protocol procedures, and comply with follow-up visit compliance.

iii. Clinically indicated for an endovascular procedure using a common femoral arteriotomy created by a 12 – 20 F sheath.

Exclusion Criteria:
General Exclusion Criteria:

i. Severe acute non-cardiac systemic disease or terminal illness with a life expectancy of less than six months.

ii. Evidence of systemic bacterial or cutaneous infection, including groin infection.

iii. Known bleeding diathesis, definite or potential coagulopathy, platelet count < 100,000/µl or patients on long term anticoagulants with an INR greater than 1.2 at time of procedure or known type II heparin-induced thrombocytopenia.

iv. Severe; claudication or peripheral vascular disease (e.g. Rutherford category 3 or greater or ABI < 0.5), documented untreated iliac artery diameter stenosis > 50% or previous bypass surgery/stent placement in the common femoral artery of ipsilateral limb.

v. Known allergy to any of the materials used in the PerQseal® (refer to Instructions for Use).

vi. Subject has undergone a percutaneous procedure using a non-absorbable vascular closure device (excluding suture mediated) for haemostasis in the ipsilateral target leg.

vii. Patients that have undergone a percutaneous procedure in the ipsilateral leg, within the previous 30 days.

viii. Patients that have undergone a percutaneous procedure using an absorbable intravascular closure device for haemostasis, in the ipsilateral leg, within the previous 90 days.

ix. Evidence of arterial diameter stenosis > 20% or anterior or circumferential calcification within 20 mm proximal or distal to target arteriotomy site based on pre-procedure CT angiography.

x. Females who are pregnant or lactating or in fertile period not taking adequate contraceptives. A pregnancy test may be performed.

xi. Patients that have a lower extremity amputation from the ipsilateral or contralateral limb.

Procedural Exclusion Criteria*:

xii. Arterial access other than common femoral artery obtained for ipsilateral target leg.

xiii. Subject has a tissue tract expected to be greater than 10 cm.

xiv. Use of thrombolytic agents within 24 hours prior to or during the endovascular procedure which causes fibrinogen < 100 mg/dl.

xv. Significant blood loss/transfusion (defined as requiring transfusion of 4 or more units of blood products) during index procedure or within 30 days prior to index procedure.

xvi. Activated clotting time (ACT) > 350 seconds immediately prior to sheath removal or if ACT measurements are expected to be > 350 seconds for more than 24 hours after index procedure.

xvii. Target puncture site is located in a vascular graft.

xviii. Target arteriotomy in the profunda femoris or superficial femoral artery or is in common femoral artery, but within 10 mm proximal of the bifurcation of the Superficial Femoral /Profunda Femoris artery.

xix. PerQseal® Introducer-sheath to ipsilateral femoral artery diameter ratio is greater than or equal to 1.05. (For S Introducer vessel lumen diameter of less than 6 mm. For L Introducer vessel lumen diameter of less than 7 mm.)

xx. Subjects with an acute haematoma of any size, arteriovenous fistula or pseudoaneurysm at the target access site; or angiographic evidence of arterial laceration or dissection within the external iliac or femoral artery before the use of the PerQseal® closure device.

*May not be known until after the patient has given informed consent and the procedure has started. In this event, the PerQseal® should not be used and the patient should be considered excluded from the study and intention to treat analysis.
Note: The use of a secondary closure device in the same leg is prohibited during this study. A note to this effect should be entered into the patient's medical records.

Risks:
The following risks are the anticipated potential vascular complications associated with use of the PerQseal® closure device:

- Haematoma.
- Bleeding.
- Dissection
- Pseudoaneurysm.
- Stenosis at the closure site.
- Arteriovenous fistula.

Other events that could possibly occur include:

- Retroperitoneal bleeding.
- Pain, discomfort or transitory local irritation and inflammation at the puncture site.
- Access-site related nerve injury, vascular spasm.
- Local and/or distal pulse deficits, ischemia.
- Infection.
- Arterial or deep vein thrombosis.
- Corrective intervention due to any of the above complications such as surgery and/or transfusion.
- Vasovagal response is a common and expected response to manipulation of the blood vessels and may occur during any invasive vascular procedure.
- Occlusive intraluminal thrombus and/or emboli formation at the implant site.
- Sinus formation.
- Compartment syndrome
- Iliac artery dissection
- Partial or complete occlusion of the artery or peripheral arteries.
- Embolisation of the intraarterial implant components.
- Damage of the arterial wall (perforation or rupture).
- Allergic or adverse foreign body reaction.

The following risks are the anticipated potential vascular complications associated with use of the PerQseal® Introducer:

- Allergic response to materials
- Blood loss, bleeding or haematoma
- Retroperitoneal bleeding
- Embolisation (micro or macro) with transient or permanent ischemia
- Infection
- Vascular trauma (e.g. dissection, rupture, perforation, or tear)
- Procedural discomfort
- Thrombosis
- Transitory vessel occlusion

Potential benefits:
For the patients involved in this study, the potential advantages of the PerQseal® over surgical access and sutured closure include the following:

- Less invasive percutaneous sealing of arteriotomy compared to surgical cut-down
- Implant is fully bioabsorbed, leaving nothing permanent behind
- Minimal pain and discomfort associated with use of VCD
- Minimisation of secondary interventions to control haemostasis
- Minimal procedural steps required to achieve haemostasis
- Percutaneous closure leads to shorter overall procedure time
- VCD has lower major vascular complications rates than alternative therapy of cutdown and sutured closure of femoral arterial puncture sites in the indicated range
- Safe and Effective sealing of the puncture site for subjects treated with anticoagulation therapy, antiplatelet agents, intravenous glycoprotein IIb /IIIa inhibitors, or thrombolytic agents
- Delivered and deployed at the conclusion of the primary procedure (minimisation of steps for access in emergency procedures)
- Arterial wire access maintained throughout the device delivery
- Minimisation of the temporary disruption of arterial flow, which occurs with arterial clamping during surgical closure
- Reduction in scaring compared to surgical cut-down (as VCD use is percutaneous)

Schedule of Events
A schedule of study events is provided in Table 1 below as a guide. This is a tabular summary of the study activities and related scheduled procedures to be performed.

Table 1- *Schedule of Study Events for Reference Only*

Schedule of Events	**Screening**	**Pre-Proc.**	**Peri-Proc.**	**Immed Post Proc.**	**Post Procedure**			
					Approx. 30 mins post	**Post 1hr**	**pre-discharge**	**Follow-Up (1 & 3 Months)**
Determine Eligibility	√	√	√					
Obtain Informed Consent	√							
Demographic Information	√							
Patient Medical History	√							
Physical Examination	√							
Laboratory Results *(within 7 days pre-procedure)*	√							
CT Angiogram *(May be within 4 months pre-procedure)*	√***						*	
Angiogram	√***		√	*			*	
Duplex Ultrasound				*	*	*	*	√**
Pulses		√		√	√	√	√	√
ABI	√							√****
Record procedure sheath size & details of graft/valve			√					
ACT before PerQseal® closure device insertion			√					
Estimate tissue tract depth			√					
Record PerQseal® details			√					
Time to deploy PerQseal® closure device			√					
PerQseal® device TTH			√					
Alternative therapy required			√					
PerQseal® device performance assessment				√				
Time from PerQseal® Introducer insertion to PerQseal® closure device deployment				√				
Overall procedural time				√				
Time to Ambulation					√	√	√	
Adverse Event Assessment			√	√	√	√	√	√

*If Necessary, **3 month follow-up only otherwise if necessary, ***Either a CT Angiogram or Angiogram can be performed, **** at 1 month only if the patient has both dorsalis pedis and posterior tibial pulses absent in the ipsilateral leg.

Definitions

Major Vascular Access Site Complication – In the context of this CIP and related to the femoral artery access site, major complications* are any of:

- Major vascular access site complications leading to death, life-threatening (BARC type 5) or major bleeding (BARC type 3a), visceral ischemia or neurological impairment; OR
- Distal embolization from the vascular access site requiring surgery or resulting in amputation or irreversible end-organ damage; OR
- The use of unplanned endovascular or surgical intervention associated with access site related death, major bleeding (BARC type 3a), visceral ischemia or neurological impairment; OR
- Any access site related new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram; OR
- Surgery for access site-related nerve injury; OR
- Permanent access site-related nerve injury; OR
- Access-site-related infection requiring intravenous antibiotics and/or extended hospitalization

***** Adapted from VARC-2[1].

Minor Vascular Access Site Complications – In the context of this CIP and related to the femoral artery access site, minor complications* are any of:

- Access site or access-related vascular injury
  - Dissection
  - Stenosis
  - Perforation
  - Rupture
  - Arteriovenous fistula
  - Pseudoaneuysms (> 3 cm)
  - Haematoma (> 6 cm)
  - Percutaneous closure device failure

  not leading to death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment.
- Distal embolization from the vascular access site treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage.
- Localized access site infection treated with intramuscular or oral antibiotics.
- Any access site related unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication.

[1] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. European Journal of Cardio-Thoracic Surgery 42 (2012) S45–S60.

- Access site related vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent graft)
- Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Adapted from VARC-2[2].

BARC Bleeding Definitions
Life-threatening or disabling bleeding

- Fatal bleeding (BARC type 5) OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
- Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
- Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)

*Given one unit of packed RBCs typically will raise haemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated.

Major bleeding (BARC type 3a)

- Overt bleeding plus haemoglobin drop of 3 to <5 g/dL (provided haemoglobin drop is related to bleed); AND
- Does not meet criteria of life-threatening or disabling bleeding.

Minor bleeding (BARC type 2 or 3a, depending on the severity)

- Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major bleeding.

Technical Success Rate – Technical Success Rate (TSR) is defined as the number of PerQseal® closure devices that are deployed and achieve haemostasis (i.e. cessation of bleeding (excluding cutaneous or subcutaneous oozing)), without need for any alternative treatment (other than manual compression or adjunctive endovascular ballooning) at target access site, divided by the total number of PerQseal® devices where deployment was attempted (as per the PerQseal® closure device IFU). Device malfunction resulting in alternative therapy will be considered as a technical failure.

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AA	2772
AB	2966

[2] Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *European Journal of Cardio-Thoracic Surgery* 42 (2012) S45–S60.