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

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1. APPROVALS

Reference DCN 3038 for approvoals.

2. REVISION HISTORY

Version	Date (dd/MMM/yyyy)	Action	Performed by
00	13-Aug-2017	Initial Release	Chris Martin
01	09-Oct-2017	Protocol revision no change to SAP	Chris Martin

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

4.1 Abbreviations

AAA	Abdominal Aortic Aneurysm
ABI	Ankle Brachial Index
ACT	Activated Clotting Time
AE	Adverse Event
A-P	Anteroposterior
BARC	Bleeding Acadamic Research Consortium
BAV	Balloon aortic valvulopasty
BP or bp	Blood Pressure
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRO	Contract Research Organisation
DSMC	Data Safety Monitoring Committee
EC	European Commission
eCRF	Electronic Case Report Form
EDC	Electronic Data Capturing
EEC	European Economic Community
EN	European Norm (European Standard)
EU	European Union
EVAR	Endovascular Aortic Aneurysm Repair
F	French gauge
GP	General Practitioner
Hb	Haemogloben
HR or hr	Heart Rate
ICF	Informed Consent Form
IFU	Instructions for Use
IS	Irish Standard
ISO	International Standards Organisation
ITT	Intent-toTreat
LVAD	Left ventricular assist device
M-L	Mediolateral
mITT	modified ITT
OPT	Overall Procedural Time
PDO	Polydioxanone
PDS	Polydioxanone suture
PIS	Patient Information Sheet
PP	Per-Protocol

PSR	Procedure Success Rate
RBC	Red Blood Cell
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SVD	Source Data Verification
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TEVAR	Thoracic Endovascular Aortic/Aneurysm Repair
TSR	Technical Success Rate
TTA	Time to Ambulation
TTD	Time to Discharge
TTDD	Time to Device Deployment
TTH	Time to haemostasis
U	Units of Blood (1 pint or 450 ml)
USADE	Unanticipated Serious Adverse Device Effect
VARC	Valve Academic Research Consortium
VCD	Vascular Closure Device
WMA	World Medical Association

4.2 Definitions of terms

i. **Pulse Grading System** – The peripheral pulse pressure shall be indicated using the following grading:

0 – Absent
1 – Diminished/weak
2 – Normal
3 – Strong

ii. **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; ORleading to death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment.

- 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].

iii. **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
  - Pseudoaneurysm (> 3 cm)
  - Haematoma (> 6 cm)
  - Percutaneous closure device failure

  not leading to death, life-threatening or major bleeding (BARC type 3a), 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.
- 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)

[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 (Ref. 6).

* Adapted from VARC-2[1]

iv. **BARC Bleeding Definitions (Ref. 7)**

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 3.0 g/dL to ≥5 g/dL (provided haemoglobin drop is related to access site 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.

v. **Haemostasis** – Clinically acceptable cessation of arterial bleeding.

vi. **Study Variables**:

a. Have a direct impact on claims for the device.
b. Should be directly observable.
c. Objectively determined measures subject to minimal bias and error.
d. Should be directly related to biological effects of the clinical condition.

vii. **Influencing Variables**:

a. Any aspect of the study that can affect the outcome or study variables.
b. Any aspect of the study that can affect the relationship between treatment and outcome.

viii. **Device Failure** – Failure of the PerQseal® to provide percutaneous access site closure resulting in interventional (e.g. stent-graft) or surgical correction.

ix. **Time to Haemostasis** – Time to haemostasis (TTH) is determined as the elapsed time from when the Introducer-sheath and PerQseal® closure device have been removed from the patient to first observed cessation of bleeding (excluding cutaneous or subcutaneous oozing) at the target access site arteriotomy.

x. **Time to Ambulation** – Time to Ambulation (TTA) is defined as the time from post procedure sheath removal until the patient is comfortable walking approximately 6 m.

xi. **Time to Device Deployment** – Time to Device Deployment (TTDD) is defined as the time from insertion of the PerQseal® closure device into the Introducer-sheath to complete removal of the PerQseal® closure device and Introducer-sheath from the patient following deployment.

xii. **Overall Procedural Time** – Overall Procedural Time (OPT) is defined as the time from first invasive contact with the patient's groin to completion of all aseptic procedures related to the groin.

xiii. **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® closure 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.

xiv. **Surgical Closure** – Standard surgical vascular access and sutured closure.

xv. **Baseline** – Prior to interventional procedure.

xvi. **Endovascular Aortic/Aneurysm Repair (EVAR)** – Endovascular surgery used to treat an abdominal aortic aneurysm (AAA).

xvii. **Thoracic Endovascular Aortic/Aneurysm Repair (TEVAR)** – Endovascular surgery used to treat a Thoracic aortic aneurysm.

xviii. **Transcatheter Aortic Valve Replacement (TAVR)** – Procedure in which a bioprosthetic valve is inserted through a catheter and implanted within the diseased native aortic valve. Also known

as Transcatheter Aortic Valve Implantation (TAVI) or Percutaneous Aortic Valve Replacement (PAVR).

xix. **Activated Clotting Time (ACT)** – Measures the intrinsic clotting activity of whole blood in seconds.

xx. **Source Data Verification (SDV)** – Evaluation of the conformity of the data presented in eCRFs with source data (medical records/notes, lab results, x-rays, etc.).

xxi. **Ankle-brachial index (ABI)** – The ratio of ankle systolic pressure to the arm systolic pressure, used in assessing the status of lower extremity arteries. It is calculated by dividing the higher of the left and right ankle pressures by the higher of the two brachial artery pressures.

xxii. **Time from PerQseal® Introducer insertion to PerQseal® closure device deployment** – defined as the time from insertion of the PerQseal® Introducer to complete removal of the PerQseal® closure device and Introducer-sheath from the patient following deployment.

5. INTRODUCTION

There are 15 million [Ref. 1] interventional, catheter based procedures performed annually. The rapid development of percutaneous 'minimal invasive therapy' and the increase of the aging population of which this therapy is apposite, has led to the need for instrumentation to minimise the risk of complications associated with closing the access site, post procedure. At the end of these procedures the arterial puncture must be closed in order to achieve haemostasis and restore the continuity and function of the artery through which the intra-vascular access was gained.

Examples of currently emerging percutaneous endovascular procedures include:

- Aortic Valve Replacement
- Mitral Valve Repair
- Abdominal Aneurysm Repair
- Thoracic Aneurysm Repair
- Tricuspid Valve Replacement

These procedures require larger size access sites ranging from 12 to 24 F. Currently, these large access sites are routinely closed via surgical access and sutured repair, performed in an operating theatre whilst patients are typically under general anaesthetic. 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 named VIVASURE CLOSURE DEVICE, also known as

PerQseal®, Figure 1, to induce arterial haemostasis in patients undergoing transfemoral endovascular procedures.

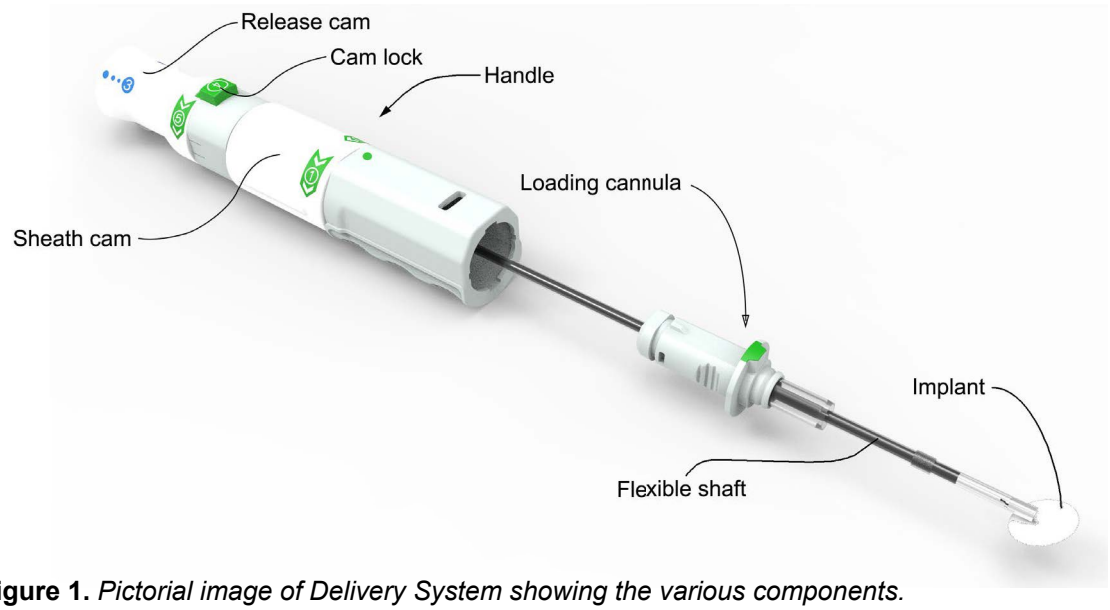


Figure 1. *Pictorial image of Delivery System showing the various components.*

5.1 Implant

The implant, Figure 2, has three components; the foot-core (scaffold), flexible-wing (patch) and extraarterial-pin (locator). The foot-core is attached to the flexible-wing at its base and has a neck inclined at an angle (30°) from the base. *In situ* the foot-core neck is mostly extraarterial. The foot-core also acts as a scaffold to secure the flexible-wing against the vessel inner wall.

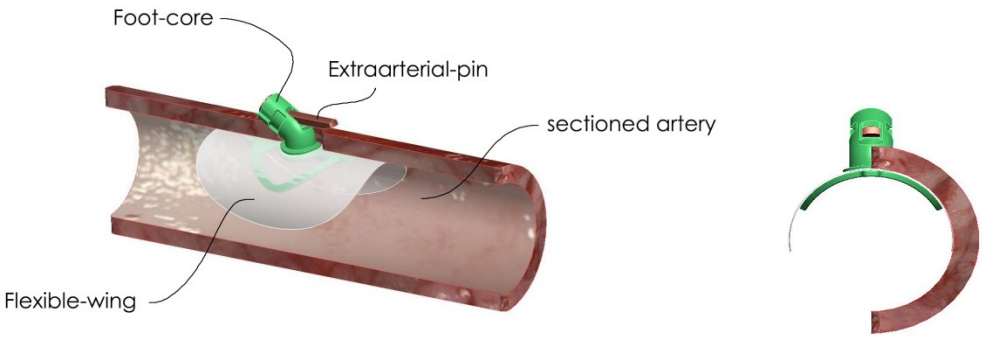
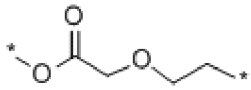


Figure 2. *Pictorial image of PerQseal® closure device implant in situ, showing components and end on view of Implant deployed within a sectioned artery.*

The flexible-wing of the implant is supplied in the packaging in its relaxed, flat state attached to the shaft of the Delivery System, Figures 4. As the device is removed from the packaging tray the flexible-wing is coiled into a cylindrical shape (via the loading funnel), into the device's loading cannula ready for insertion into the artery. The implant is inserted into the artery through the Introducer-sheath and over a guidewire. The flexible-wing unfolds when exposed in the artery. The implant is designed to be centrally positioned relative to the arteriotomy with the intraarterial

components acting as an internal tamponade. Hemodynamic hydraulic pressure within the artery helps to push the flexible-wing against the luminal surface of the artery and effect a seal. The anterior surface of the wing is coated in a fine mesh of Polydioxanone material designed to entrap circulating erythrocytes, leukocytes and platelets, which help oppose the flexible-wing to the artery wall (surrounding the arteriotomy). These cells are activated via the intrinsic pathway by the exposed collagen of the arteriotomy and become adhered to the collagen by a cross-linked fibrin clot within the arteriotomy and arterial wall surrounding the arteriotomy.

All implant materials are medical grade synthetic absorbables. The materials have been selected to ensure the implant does not cause adverse tissue reaction, haemolysis, severe thrombogenesis or emboli formation. The implant components are manufactured from Polydioxanone (PDO). PDO is commonly used as an absorbable suture material PDS™, (Ethicon), indicated for cardiovascular use, with excellent clinical history for over 30 years [Ref. 2 and 3]. All three components are made from the same Polydioxanone Resomer X 206 S bioabsorbable materials.


Polydioxanone

The PerQseal® closure device implant is designed to achieve a secure and rapid seal of the access site at conclusion of the endovascular procedure, with implant absorption within 180 days.

5.2 Introducer

The PerQseal® Introducer consists of a sheath and dilator with a blood signal port, which accommodates up to a 0.035 in. (0.89 mm) guidewire. The Introducer is supplied in two sizes. The Introducer is designed to allow the operator to easily position the Introducer relative to the arteriotomy for optimum delivery of the implant. Refer to Figure 3, which shows the key features of the Introducer.

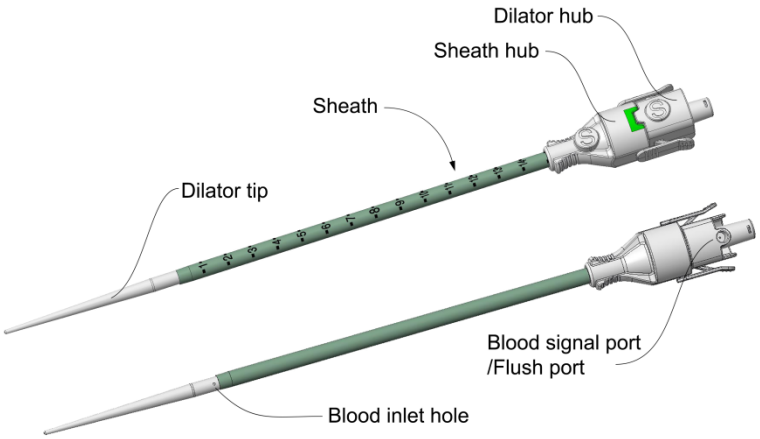


Figure 3. *Pictorial image of Introducer, showing features.*

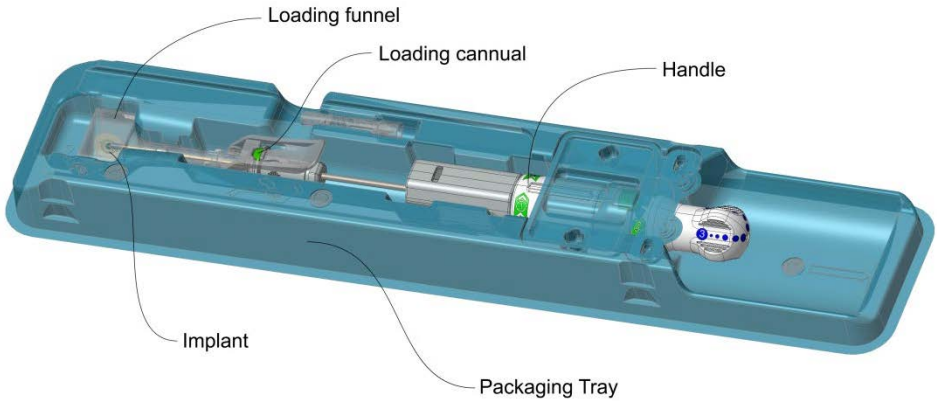


Figure 4. *Pictorial image of device in tray, as supplied, showing location of various components.*

5.3 Delivery System

The PerQseal® closure device delivery system comprises the user interface for the percutaneous delivery of the implant to the arteriotomy and a deployment mechanism. The delivery system has a handle at its proximal end and a flexible shaft, which attaches to the implant at the distal end, Figure 1.

All materials of the delivery system are medical grade polymers, selected for their biocompatibility and functional requirements.

The implant is loaded into the loading cannula upon removal from the protective tray. The delivery system is designed to interface with the supplied Introducer and designed to deliver the implant with minimal movement and to ensure single use of the device.

5.4 Delivery of the Implant

The implant has been designed to be delivered into the artery via a supplied Introducer-sheath and over a 0.014" guidewire. Hence, the delivery sequence starts with the Introducer-sheath and 0.014" guidewire *in situ* (approx. 4 cm) within the vessel.

The loading cannula (containing the implant) is first inserted into the Introducer-sheath hub. This engages the loading cannula with the sheath hub.

The Sheath-cam is rotated (Figure 1), which withdraws the Introducer-sheath, allowing the implant to unfold within the artery. The implant is then positioned against the artery wall closing the arteriotomy. Once tamponade is confirmed the guidewire is removed, the Cam lock depressed, and the Release-cam is rotated to deploy the extraarterial-pin and release the implant. This completes the deployment and seals the arteriotomy.

6. PURPOSE OF THE STATISTICAL ANALYSIS PLAN (SAP)

The purpose of this SAP is to define the analysis variables and detail the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol P528-00. Exploratory analyses not necessarily identified in this SAP may be performed to support the PerQseal® clinical programme. Any post-hoc, or unplanned analyses not identified in this SAP, will be clearly identified in the respective CSR.

7. STUDY OBJECTIVES

To confirm safety and performance of the *PerQseal®* closure device (DP2-FA1-4) 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. Refer to *Section 4.2*, *Definitions of Terms* for the meaning of haemostasis.

8. STUDY DESIGN

This study will be a prospective, multi-centred, non-randomized study to investigate the safety and performance of the PerQseal® in 75 patients in approximately 10 European investigational sites.
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.

9. STUDY ENDPOINTS

9.1 Primary Endpoint

Incidence of major vascular access site complications related to the PerQseal® closure device up to 1 month from implantation, is no worse than those associated with cut-down and sutured close.

9.2 Secondary Endpoints

Safety: Incidence of minor vascular access site complications directly related to the PerQseal® closure device up to 1 month from implantation.

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

9.3 Study population

Patients will not be excluded on the basis of age, race, concomitant therapy or co-existing disease. Each centre will continue to enrol eligible patients until a minimum combined Clinical Investigation population of 75 patients is achieved.

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 only for the purposes of Performance Analysis.

Consented patients who receive contact with the PerQseal® closure device become an enrolled subject.

9.3.1 *Subject withdrawal/exclusion*

A patient is enrolled in the study by signing an Ethics Committee approved Informed Consent Form; if he/she meets all eligibility criteria (both pre-procedure and during the procedure) and there is intent to close the femoral artery puncture site using the PerQseal® and the PerQseal® closure device contacts the patient[1].

Patients on whom the PerQseal® closure device is not used due to failure to meet eligibility criteria/withdrawal of consent are considered not enrolled in the study. Patients not exposed to the PerQseal® closure device will not require additional post procedure, pre-discharge or post discharge follow-up assessments and will not be included in safety and performance analyses. For

[1] The PerQSeal® closure device is considered to have contacted the patient if the loading cannula of the PerQSeal® closure device is inserted into the Introducer sheath.

enrolled patients that have received exposure to the PerQseal® closure device, but the device was not deployed for reasons other than device failure their data will be included in safety, but not performance analyses and all post procedure, pre-discharge and post discharge follow-up assessments will be performed.

A patient may withdraw from the study at any time if he/she decides to do so. However, all data collected to the time of withdrawal will be recorded in the worksheet, with a note to indicate that the patient has withdrawn their consent to further participate in the study. No further follow-up or data will be recorded for that patient on the worksheet or eCRF. Note that routine management and standard practice of care should continue for the patient without prejudice.

9.3.2 *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 requirements.

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

9.3.3 *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.

10. SAMPLE SIZE

The sample size estimate outlined below is based on primary endpoint assessment only for the PerQseal® closure device.

The primary endpoint of safety will be assessed by comparison of the proportion of PerQseal® closure device closures with device related major vascular access site complications up to 1 months (P_{safety}) against a performance goal for safety (PG_{safety}) estimated from literature to be 12.5%.

The minimum sample size to demonstrate non-inferiority of safety against the literature based non-inferiority limit of 0.17 (refer to: *Section 11.6 Primary Endpoint Analysis*) 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). Refer to the independent statistical report for safety sample size in the CIP *Appendix F: Independent Statistical Sample Size Report for Safety* for details.

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.

For Performance, in order to claim non-inferiority against technical success rate for 'perclose' or 'preclose' technique the lower bound or a (95%) confidence interval for PerQseal® technical success rate must be shown to be greater than the performance non inferiority limit. In order to achieve this, a minimum sample size of 44 closures is required to demonstrate non-inferiority in a single sample fixed one-sided significance level of 0.025 and power of 0.90 level. The secondary performance endpoint therefore does not drive sample size. The total planned sample size remains at 75 treated subjects.

11. STATISTICAL METHODS

11.1 Analysis populations

All Enrolled subjects (see Section 9.3 Study Population) will be analysed on an Intent-to-Treat (ITT) basis for the Primary and Secondary Endpoint of Safety.

For avoidance of doubt: The ITT analysis population includes all enrolled subjects who undergo attempted access site closure with Vivasure PerQseal® device (i.e. PerQseal® closure device is attempted to be placed into the vasculature and contacted the patient).

All closures from Enrolled subjects will be analysed on a modified Intent-to-Treat (mITT) basis for the Secondary Endpoint of Performance, excluding enrolled subjects which met an exclusion criteria (documented by a protocol deviation).

For avoidance of doubt: The mITT analysis population includes all closures from enrolled subjects who undergo attempted access site closure with Vivasure PerQseal® device (i.e. PerQseal® closure device is attempted to be placed into the vasculature and contacted the patient), with the exception of devices that were prevented from deploying for reasons listed in the exclusion criteria or due to issues associated with the primary procedure.

A secondary analysis population for the primary safety endpoint will include Per-Protocol (PP) for Primary Safety. The PP is a subset of the ITT analysis population with no major protocol deviations and who experienced the safety endpoint or did not prematurely withdraw from the study prior to being evaluated for the primary safety endpoint.

11.2 Time points of analyses

A report will be completed once the primary endpoint and all 3 months follow-up assessments has been reached for all subjects included or remaining in the study. This report will be shared with Ethics Committees, Competant Authorities and other relevant parties. A full study termination report will be produced if the study is terminated prior to completion for any reason or at the exit of all enrolled subjects from the study.

An interim analysis may be performed once sufficient subjects have completed their primary safety endpoint to ensure the study has at least 80% power.

11.3 Statistical methods

For continuous variables, the mean, median, standard deviation, interquartile range and minimum-maximum value will be presented. In order to compare subgroups, the differences in means of the subgroups will be tested with a two-sample t-test (in case of 2 subgroups) or with one-way ANOVA (in case of >2 subgroups) in case the assumptions for the required tests are valid. If these assumptions are violated, testing will be done using independent samples Mann-Whitney U tests or Kruskal-Wallis tests (instead of one-way ANOVA).

For categorical variables counts and percentages will be presented. In order to compare differences between subgroups, categorical variables with an expected cell count of at least 5 in 80% of the cells (but no zero expected cell counts) will be tested using the Pearson chi-square test. For categorical variables that do not have an expected cell count of at least 5 in 80% of the cells (or that do have at least one zero expected cell count) and require the differences between the two treatment groups to be tested, the following will be done: Fisher's exact test will be performed for 2x2 contingency tables or the likelihood ratio test will be performed for larger contingency tables.

The tests for all subgroup comparisons assume a significance level of 0.05. No adjustment for multiple testing will be done for any of these variables, as these do not consider the primary endpoint.
Specification for the test concerning the primary endpoint can be found in Section 11.6.

11.4 Baseline characteristics

Demographic and baseline characteristics shall be tabulated and summarised for the study. The following characteristics will also be tabulated and summarised both per centre and per procedure type:

-Age

-BMI

-Gender
-Procedural ACT
-Sheath size
-Sheath size to femoral artery diameter ratio
-Hypertension
-Diabetes
-Severe acute non-cardiac systemic disease, autoimmune disease or terminal illness
-Bleeding Diatheses
-Clinically significant peripheral vascular disease

Subgroup comparisons will be tested and the results of these tests will be summarised by their respective p-values. As the primary endpoint will be analysed per centre and per procedure type (among others), we will compare the above baseline characteristics between these subgroups as well, in order to further explore any possible confounders for the relationships between the primary endpoint and both the centre and the procedure type.

11.5 Variables

The study variables identified for comparisons/summaries are:

Primary Variables:

i. Major device related vascular access site complication rate.
ii. Serious Adverse Device Effect (SADE), Unanticipated Serious Adverse Device Effect (USADE) rate, as defined in the '*Clinical Investigation Definitions'* (which is maintained in the Site File for each site).

Secondary Variables

i. Safety: minor vascular access site complications related to the closure.
ii. Adverse Device Effect (ADE), Serious Adverse Event (SAE) or Adverse Event (AE) rate, as defined in the '*Clinical Investigation Definitions'*.

Performance: assessed by technical success rate for the PerQseal® closure device.

The potential influencing variables identified include:

i. Patient age, gender, weight or Body Mass Index (BMI)
ii. ACT
iii. Co-existent diseases
iv. Sheath size used
v. Common Femoral Artery (CFA) diameter
vi. Procedure to be performed

11.6 Primary endpoint analysis

The Safety of the PerQseal® closure device will be assessed by comparison of the proportion of PerQseal® closure device subjects with device related major vascular access site complication up to 1 months (P_{safety}) against a performance goal for safety (PG_{safety}). (The performance goal for safety for this study will be based on historical data extracted from literature for cut-down and suture closure.)

This will be achieved by testing for non-inferiority against a safety non-inferiority limit (N_{LS}), which is the predetermined PG_{safety} plus a non-inferiority margin delta. In order to claim non-inferiority against a safety driven PG_{safety} the upper bound of a one-sided (95%) confidence interval for the proportion of subjects with complications "P_{safety}" (using the exact method for estimating a Binomial proportion) must be shown to be less than the non-inferiority limit.

The PG_{safety} and non-inferiority margin delta have been derived from a Meta-analysis of major vascular access site complication rates for cut-down and suture closure from equivalent patient populations and sheath sizes of 12 – 24 F reported in the literature:

The proportion of complications is estimated to be 0.125 with a 95% Confidence Interval of 0.09 to 0.17. Given that the upper bound is 0.17 this justifies the use of 0.13 as valid PG_{safety} plus a non-inferiority margin of 0.04 yielding an overall non-inferiority limit (N_{LS}) of 0.17 for Safety.

The test for non-inferiority for safety will be based on a one-sided test (at the 0.025 significance level) for a binomial proportion with hypotheses:

H_{0S}: $P_{safety} \geq N_{LS}$ versus H_{1S}: $P_{safety} < N_{LS}$

Where: P_{safety} is the actual proportion of subjects with device related major vascular access site complications within the analysis population (ITT and PP).

And: N_{LS} is the non-inferiority limit for proportion of expected major vascular access site complications associated with cut-down and suture closure.

Non-inferiority analysis will be done by using the study data to calculate a confidence interval for the population proportion with major vascular access site complications directly related to the device. Demonstrating non-inferiority for safety necessitates rejecting the null hypothesis (H_{0S}) in favour of the alternative hypothesis (H_{1S}), in this case based on the upper limit of a 95% confidence interval for a population proportion being less than the non-inferiority limit.

11.7 Secondary endpoints

Two secondary endpoints will be summarised for the entire group of subjects/closures:

-Minor device related vascular access site complications per subject up to 1 months (safety endpoint)

-Technical success rate for the PerQseal® closure device at discharge per closure is no worse than the technical success rates associated with the 'perclose' or 'preclose' technique following EVAR or TAVR.

The criteria for successful performance of the investigational device have been aligned with what is reported within the literature, ensuring a like for like comparison. A literature based performance control is the only effective source of data available for this study, as it is not applicable to compare the performance of a device with that of a surgical technique of cut-down and sutured closure, used for the safety control. Therefore, the performance of the PerQseal® (i.e. the proportion of successful closures) will be assessed by comparison of the proportion of PerQseal® closures which achieve acute haemostasis at the arteriotomy site and do not lead to alternative treatment (other than manual compression or adjunctive endovascular ballooning) ($P_{performance}$) from the mITT group against a performance goal for performance ($PG_{performance}$). This will be achieved by testing for non-inferiority against a performance non-inferiority limit (N_{LP}), which is the predetermined $PG_{performance}$ minus a non-inferiority margin delta. In order to claim non-inferiority against a performance driven $PG_{performance}$ the lower bound of a (95%) confidence interval for the proportion of successful "$P_{performance}$" (using the exact method for estimating a Binomial proportion) must be shown to be greater than the non-inferiority limit.
The $PG_{performance}$ and non-inferiority margin delta have been derived from a Meta-analysis of performance rates for percutaneous device closure (Prostar® XL and Perclose ProGlide®) from comparable patient populations reported in the literature.

The proportion with successful closure is estimated to be 0.84 with a 95% Confidence Interval of 0.81 to 0.87. Given that the lower bound is 0.81 this justifies the use of 0.84 as valid $PG_{performance}$ minus a non-inferiority margin of 0.03 yielding an overall non-inferiority limit (N_{LP}) of 0.81 for performance.

11.8 Other safety assessments

Based on the CRF data, cumulative adverse event / complication rates for all time points will be presented for all subjects combined. This will also be done for serious adverse events / complications and for deaths.

A summary for all subjects combined will be presented for the Serious Adverse Event (SAE) rates, the rates of Serious Adverse Device Effects (SADEs)/ Unanticipated Serious Adverse Device Effects (USADEs), the rates of procedure related SAEs and the rates of minor/major vascular access site complications at the end of the study. Additionally, cumulative rates for all time points will be presented for SAEs, major device related vascular access site complications and minor device related vascular access site complications.

11.9 Other performance assessments

Time from insertion of the PerQseal® closure device into the introducer sheath to departure from theatre, device deployment time and time to haemostasis will be summarised for the entire group of subjects in the study

11.10 Missing data

Historically (which includes 120 subjects and 136 closures across all Frontier studies) there have not been any device related access site complications beyond patient discharge from hospital. So it is expected that all safety data will be captured for all enrolled subjects. All subjects with available data will be used in the statistical analyses. All implanted subjects will be assessed for technical success. With regard to assessment of device related complications through 1 months, data on all subjects through the point of last follow up prior to or at 1 months will be included in the analysis. For the primary analysis, no imputation is expected to be performed for missing data. However, in the unlikely event that there is missing critical safety data Bayesian models may be utilised for sensitivity to investigate the impact of incomplete follow-up.

11.11 Protocol Deviations

All protocol deviations will be summarised and listed in detail in the Clinical Study Report. Protocol deviations will be categorised as follows: deviations that occurred with respect to baseline inclusion/exclusion criteria, follow-up visits or assessment not completed, visit or assessment not completed per study protocol, or visit or assessment out of window. All the protocol deviations will be assessed for their potential influence on the safety and/or performance results of the study.

11.12 Changes to the analysis specified in the protocol

There are no planned additional analysis other that what has been outlined within the Protocol and SAP. In the event that any additional or ad-hoc analysis is performed not already listed within the SAP or protocol, this will be clearly indicated within the Clinical Study Report.

12. DATA MANAGEMENT

All data management will be documented in a seperate Data Management Plan.

13. OVERVIEW OF TABLES TO BE GENERATED

14. OVERVIEW OF LISTS TO BE GENERATED

15. OVERVIEW OF FIGURES TO BE GENERATED

16. TABLES, LISTS AND FIGURES SHELLS

This section will give the format and structure of all tables, lists and figures to be produced in the final Clinical Study Report (CSR).

These detailed specifications can undergo minor revisions during the production phase without needing to revise the SAP. Minor revisions are defined as revisions that do not invalidate any of the specifications in Section 11.

16.1 Tables to be generated

Table 1. Enrollment summary

Centre	Procedure	No. Subjects Enrolled	No. of closures	Males/Females	Mean Age	No. 1 month FU	No. 3 month FU
F4-1	TAVI	xx	xx	xx/xx	xx.x	xx	xx
F4-1	EVAR	xx	xx	xx/xx	xx.x	xx	xx
F4-1	TEVAR	xx	xx	xx/xx	xx.x	xx	xx
F4-1	Other…	xx	xx	xx/xx	xx.x	xx	xx
…							

Table 2. Primary endpoint

	% (n/N)
Major device related vascular access site complications up to 1 months	xx.x (xx/xx)

Table 3. Primary endpoint subgroup comparisons[1]

	% (n/N)	p-value

[1] This table will be omitted in the case of low major complication rates and a note will be made of this in the report.

Major device related complications up to 1 months		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
Male gender	xx.x (xx/xx)	
Female gender	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
BMI ≤ 30 kg	xx.x (xx/xx)	
BMI > 30 kg	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No hypertension	xx.x (xx/xx)	
Hypertension	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No diabetes	xx.x (xx/xx)	
Diabetes	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No severe acute non-cardiac systemic disease,	xx.x (xx/xx)	

autoimmune disease or terminal illness		
Severe acute non-cardiac systemic disease, autoimmune disease or terminal illness	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No bleeding diatheses	xx.x (xx/xx)	
Bleeding diatheses	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No peripheral vascular disease	xx.x (xx/xx)	
Peripheral vascular disease	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No previous peripheral vascular surgery involving the aorta or lower extremities	xx.x (xx/xx)	
Previous peripheral vascular surgery involving the aorta or lower extremities	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No claudication	xx.x (xx/xx)	
Claudication	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
No previous arterial access procedure using proposed artery	xx.x (xx/xx)	

Previous arterial access procedure using proposed artery	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
Largest procedural sheath size used ≤ 18 F	xx.x (xx/xx)	
Largest procedural sheath size used > 18 F	xx.x (xx/xx)	x.xxx
CFA size?		
Age		
Age at procedure ≤ 77	xx.x (xx/xx)	
Age at procedure > 77	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
Sheath size to femoral artery diameter ratio ≤ 1.05	xx.x (xx/xx)	
Sheath size to femoral artery diameter ratio > 1.05	xx.x (xx/xx)	x.xxx
Major device related complications up to 1 months		
ACT level at surgery ≤ 160 s	xx.x (xx/xx)	
ACT level at surgery > 160 s	xx.x (xx/xx)	x.xxx

Table 4. Secondary endpoints

	% (n/N)
Minor device related vascular access site complications up to 1 months	xx.x (xx/xx)
Technical success rate	xx.x (xx/xx)

Table 5. Compliance to eligibility criteria

	% (n/N)
Patients with 100% compliance to eligibility criteria	xx.x (xx/xx)
Inclusion criteria	**Yes: % (n/N)**
Patient is over 18 years of age	xx.x (xx/xx)
Patient signed informed consent	xx.x (xx/xx)
Patient indicated for an endovascular procedure using a common femoral arteriotomy created by a 12 – 20 F sheath.	xx.x (xx/xx)
Exclusion criteria	**No: % (n/N)**
Severe acute non-cardiac systemic disease or terminal illness with a life expectancy of less than six months	xx.x (xx/xx)
Evidence of systemic bacterial or cutaneous infection, including groin infection	xx.x (xx/xx)
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	xx.x (xx/xx)
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.	xx.x (xx/xx)
Known allergy to any of the materials used in the PerQseal® (refer to Instructions for Use)	xx.x (xx/xx)
Subject has undergone a percutaneous procedure using a non-absorbable vascular closure device (excluding suture mediated) for haemostasis in the ipsilateral target leg	xx.x (xx/xx)
Patients that have undergone a percutaneous procedure in the ipsilateral leg, within the previous 30 days	xx.x (xx/xx)
Patients that have undergone a percutaneous procedure using an absorbable intravascular closure device for haemostasis, in the ipsilateral leg, within the previous 90 days	xx.x (xx/xx)

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	xx.x (xx/xx)
Females who are pregnant or lactating or in fertile period not taking adequate contraceptives	xx.x (xx/xx)
Patients that have a lower extremity amputation from the ipsilateral or contralateral limb	xx.x (xx/xx)
Arterial access other than common femoral artery obtained for ipsilateral target leg	xx.x (xx/xx)
Subject has a tissue tract expected to be greater than 10 cm	xx.x (xx/xx)
Use of thrombolytic agents within 24 hours prior to or during the endovascular procedure which causes fibrinogen < 100 mg/dl	xx.x (xx/xx)
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	xx.x (xx/xx)
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	xx.x (xx/xx)
Target puncture site is located in a vascular graft	xx.x (xx/xx)
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	xx.x (xx/xx)
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.x (xx/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	xx.x (xx/xx)

Table 6. Baseline demographics and medical history

	N	Mean	Median	Standard deviation	IQR	Min - Max
Age (years)	xx	xx.x	xx.x	xx.x	xx – xx	xx – xx
Height (cm)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
Weight (kg)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
	% (n/N)					
Hypertension	xx.x (xx/xx)					
Diabetes	xx.x (xx/xx)					
Severe acute non-cardiac systemic disease, autoimmune disease or terminal illness	xx.x (xx/xx)					
Clinically significant peripheral vascular disease	xx.x (xx/xx)					
Bleeding diatheses	xx.x (xx/xx)					
Previous peripheral vascular surgery involving the aorta or lower extremities	xx.x (xx/xx)					
Claudication	xx.x (xx/xx)					

Table 7. Baseline physical examination

	N(%)	Mean	Median	Standard deviation	IQR	Min - Max
Age	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
Males	xx(xx.x)					
Females	xx(xx.x)					
Weight	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
Height	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
	% (n/N)					
Location of groin puncture to be used with Frontier Closure device						
Left leg	xx.x (xx/xx)					
Right leg	xx.x (xx/xx)					
Both legs	xx.x (xx/xx)					

Table 8. Baseline characteristics subgroup comparisons

	N	Mean	Median	Standard deviation	IQR	Min - Max	p-value
Age (years)							
Centre 1	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	
Centre 2	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	
…							
Centre x	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	x.xxx
Age (years)							
TAVI	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	
EVAR	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	
TEVAR	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	
Other	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x	x.xxx
BMI (kg/m²)							
Centre 1	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	
Centre 2	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	
…							
Centre x	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	x.xxx
BMI (kg/m²)							
TAVI	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	

EVAR	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	
TEVAR	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	
Other	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	x.xxx
ACT (s)							
Centre 1	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Centre 2	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
…							
Centre x	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	x.xxx
ACT (s)							
TAVI	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
EVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
TEVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Other	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	x.xxx
Sheath size (F)							
Centre 1	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Centre 2	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
…							
Centre x	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	x.xxx

Sheath size (F)

TAVI	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
EVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
TEVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Other	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	x.xxx
Sheath size to femoral artery diameter ratio							
Centre 1	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Centre 2	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
…							
Centre x	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	x.xxx
Sheath size to femoral artery diameter ratio							
TAVI	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
EVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
TEVAR	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x	
Other	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x	x.xxx

	% (n/N)	**p-value**
With hypertension		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

Without hypertension		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
With hypertension		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
Without hypertension		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
With diabetes		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

Without diabetes		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
With diabetes		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
Without diabetes		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
Male gender		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

Female gender		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
Male gender		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
Female gender		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx
With severe acute non-cardiac systemic disease, autoimmune disease or terminal illness		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		

Centre x	xx.x (xx/xx)	x.xxx

Without severe acute non-cardiac systemic disease, autoimmune disease or terminal illness

Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

With severe acute non-cardiac systemic disease, autoimmune disease or terminal illness

TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

Without severe acute non-cardiac systemic disease, autoimmune disease or terminal illness

TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

With bleeding diatheses

Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

Without bleeding diatheses

Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx

With bleeding diatheses

TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

Without bleeding diatheses

TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

With clinically significant peripheral vascular disease		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
Without clinically significant peripheral vascular disease		
Centre 1	xx.x (xx/xx)	
Centre 2	xx.x (xx/xx)	
…		
Centre x	xx.x (xx/xx)	x.xxx
With clinically significant peripheral vascular disease		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

Without clinically significant peripheral vascular disease		
TAVI	xx.x (xx/xx)	
EVAR	xx.x (xx/xx)	
TEVAR	xx.x (xx/xx)	
Other	xx.x (xx/xx)	x.xxx

Table 9. Baseline laboratory tests

	N	Mean	Median	Standard deviation	IQR	Min - Max
Platelets (10^3 cells/µl)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
	% (n/N)					
Subjects on thrombolytic therapy	xx.x (xx/xx)					
	N	**Mean**	**Median**	**Standard deviation**	**IQR**	**Min - Max**
If yes, fibrinogen (mg/dl)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
	% (n/N)					
MRSA screening Positive Negative	 xx.x (xx/xx) xx.x (xx/xx)					

Table 10. Baseline CT angiogram / angiogram of femoral vasculature

	N	Mean	Median	Standard deviation	IQR	Min - Max
Common femoral artery lumen diameter (mm)	xx	xx.x	xx.x	x.x	xx.x – xx.x	xx.x – xx.x
	% (n/N)					
Evidence of stenosis within 20 mm of intended access site	xx.x (xx/xx)					
	N	**Mean**	**Median**	**Standard deviation**	**IQR**	**Min - Max**
If yes, estimate percentage	xx	xx.x	xx.x	x.x	xx.x – xxx.x	xx.x – xxx.x

Table 11. Procedural information

	% (n/N)					
Type of anaesthesia						
None	xx.x (xx/xx)					
Local	xx.x (xx/xx)					
Block	xx.x (xx/xx)					
General	xx.x (xx/xx)					
Patient sedated	xx.x (xx/xx)					
	N	Mean	Median	Standard deviation	IQR	Min - Max
ACT (s)	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x
Largest sheath size used (F)	xx	xx.x	xx.x	xx.x	xx.x – xx.x	xx.x – xx.x
	% (n/N)					
Anticoagulant/antiplatelet therapy given during procedure	xx.x (xx/xx)					
Significant blood loss/transfusion during procedure	xx.x (xx/xx)					
	N	Mean	Median	Standard deviation	IQR	Min - Max
Approximate depth of tissue tract (mm)	xx	xx.x	xx.x	x.x	xx.x – xx.x	xx.x – xx.x
	% (n/N)					
Haematoma formation at ipsilateral access site	xx.x (xx/xx)					
If yes, Leg/s: estimated	xx.x (xx/xx)					
If yes, Leg/s: measured	xx.x (xx/xx)					

	N	Mean	Median	Standard deviation	IQR	Min - Max
If yes, size (mm^2)	xx	xxxx.x	xxxx.x	xxx.x	xxxx.x – xxxx.x	xxxx.x – xxxx.x
	% (n/N)					
AV fistula at ipsilateral access site	xx.x (xx/xx)					
Pseudoaneurysm at ipsilateral access site	xx.x (xx/xx)					

Table 12. Angiogram of ipsilateral femoral vasculature

	% (n/N)
Arteriotomy puncture is within the common femoral artery	xx.x (xx/xx)
Arteriotomy in the profunda femoris or superficial femoral artery or is in cfa, but within 10 mm proximal of the bifurcation of the Superficial Femoral /Profunda Femoris artery	xx.x (xx/xx)
Perforation/dissection	xx.x (xx/xx)

Evidence of stenosis within 20 mm of access site within artery	xx.x (xx/xx)					
	N	Mean	Median	Standard deviation	IQR	Min - Max
If yes, estimate percentage	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x
Measurement of common femoral artery (mm)	xx	xx.x	xx.x	x.x	xx.x – xx.x	xx.x – xx.x

Table 13. Device and deployment details

	N	Mean	Median	Standard deviation	IQR	Min - Max
Procedure time (minutes)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
Angle of device during deployment (°)						
Time taken to deploy the device from introduction into the introducer sheath to procedural sheath and device removal (minutes)	xx	xx.x	xx.x	x.x	xx.x – xx.x	xx.x – xx.x
Time from the PerQseal® device and introducer sheath removal to haemostasis for the access site arteriotomy (minutes)	xx	xx.x	xx.x	x.x	xx.x – xx.x	xx.x – xx.x
	% (n/N)					
Device malfunction during use	xx.x (xx/xx)					
Bleeding						
None	xx.x (xx/xx)					
Ooze	xx.x (xx/xx)					
Brisk	xx.x (xx/xx)					
Pulsatile	xx.x (xx/xx)					

Table 14. Post-procedural angiogram of femoral vasculature

	% (n/N)					
Evidence of leakage from arteriotomy	xx.x (xx/xx)					
Evidence of stenosis of artery	xx.x (xx/xx)					
	N	**Mean**	**Median**	**Standard deviation**	**IQR**	**Min - Max**
If yes, estimate percentage	xx	xx.x	xx.x	xx.x	xx.x – xxx.x	xx.x – xxx.x

Table 15. Pre-discharge examination

	N	Mean	Median	Standard deviation	IQR	Min - Max
Time to ambulation (hours post-procedure)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x
Time to actual discharge (hours post-procedure)	xx	xxx.x	xxx.x	xx.x	xxx.x – xxx.x	xxx.x – xxx.x

Table 16. Groin condition

		Immediate post-procedure		30 min post-procedure		1 hours post-procedure		Pre-discharge		1 month		3 month	
		Left leg	**Right leg**	**Left leg**	**Right leg**	**Left leg**	**Right leg**	**Left leg**	**Right leg**	**Left leg**	**Right leg**	**Left leg**	**Right leg**
Ipsilateral groin condition	Normal - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Haematoma - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Bleeding - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Ecchymosis - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Other - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)

Table 17. ABI

	Baseline		3 Month	
	Left	**Right**	**Left**	**Right**
N	xx	xx	xx	xx
Mean	x.xx	x.xx	x.xx	x.xx
Median	x.xx	x.xx	x.xx	x.xx
Standard deviation	x.xx	x.xx	x.xx	x.xx
IQR	x.xx – x.xx	x.xx – x.xx	x.xx – x.xx	x.xx – x.xx
Min	x.xx	x.xx	x.xx	x.xx
Max	x.xx	x.xx	x.xx	x.xx

Table 18. Lower extremity pulses (palpate)

		Pre-procedure		Immediate post-procedure		30 min post-procedure		1 hour post-procedure		Pre-discharge		1 month		3 month	
		Left leg	Right leg	Left leg	Right leg	Left leg	Right leg	Left leg	Right leg	Left leg	Right leg	Left leg	Right leg	Left leg	Right leg
Dorsalis pedis	Strong - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Normal - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Diminished - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Absent - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
Posterior tibial	Strong - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Normal - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Diminished - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)
	Absent - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)	xx.x (xx/xx)

Table 19. 3 Month Duplex ultrasonography

		At a point estimated to be the puncture site
Femoral artery diameter – mediolateral plane (mm)	N	xx
	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
Femoral artery diameter – anteroposterior plane (mm)	N	xx
	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
Blood velocity (cm/s)	N	xx
	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
Evidence of stenosis of femoral artery	Yes	xx.x (xx/xx)
	No	xx.x (xx/xx)
	Undetermined	xx.x (xx/xx)
If yes, estimate of percentage of stenosis of femoral artery	N	xx
	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
If yes, location of stenosis of femoral artery	Medial - % (n/N)	xx.x (xx/xx)
	Lateral - % (n/N)	xx.x (xx/xx)
	Anterior - % (n/N)	xx.x (xx/xx)
	Posterior - % (n/N)	xx.x (xx/xx)
Evidence of turbulent flow	Yes - % (n/N)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)
	Undetermined - % (n/N)	xx.x (xx/xx)
Evidence of access site related haematoma	Yes - % (n/N)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)
	Undetermined - % (n/N)	xx.x (xx/xx)

If yes, size x-axis	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
If yes, size y-axis	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
Evidence of access site related pseudoaneurysm	Yes - % (n/N)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)
	Undetermined - % (n/N)	xx.x (xx/xx)
If yes, size x-axis	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x
If yes, size y-axis	Mean	xx.x
	Median	xx.x
	SD	xx.x
	IQR	xx.x – xxx.x
	Min	xx.x
	Max	xxx.x

Table 20. Follow-up examination of the puncture site

		1 Month	3 Month
Any sign of infection (visual)	Yes - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)
Any palpable inguinal/haematoma mass present	Yes - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)
If yes, measure longest axis (cm)	N	xx	xx
	Mean	xx.x	xx.x
	Median	xx.x	xx.x
	SD	xx.x	xx.x
	IQR	xx.x – xxx.x	xx.x – xxx.x
	Min	xx.x	xx.x
	Max	xxx.x	xxx.x
Any tenderness/redness/discoloration	Yes - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)
	No - % (n/N)	xx.x (xx/xx)	xx.x (xx/xx)

Table 21. Medication

	% (n/N)
Heparin	xx.x (xx/xx)
Bivalirudin	xx.x (xx/xx)
Warfarin	xx.x (xx/xx)
Dextran	xx.x (xx/xx)
Aspirin	xx.x (xx/xx)
Ticlopidine	xx.x (xx/xx)
Clopidogrel	xx.x (xx/xx)
Dipyridamole	xx.x (xx/xx)
Abciximab	xx.x (xx/xx)
Tirofiban	xx.x (xx/xx)
Eptifibatide	xx.x (xx/xx)
Other	xx.x (xx/xx)

Table 22. Adverse events / complications summary (CRF data)

	n
Subjects with non-serious adverse events	
Up to and including haemostasis procedure	xx
Up to and including discharge	xx
Up to and including 1 month	xx
Up to and including 3 month	xx
Subjects with serious adverse events	
Up to and including haemostasis procedure	xx
Up to and including discharge	xx
Up to and including 1 month	xx
Up to and including 3 month	xx
Deaths	
Up to and including haemostasis procedure	xx
Up to and including pre-discharge	xx
Up to and including 1 month	xx
Up to and including 3 month	xx

Table 23. Protocol deviations summary

	Total number of deviations	% (n/N) of subjects with deviations
Subject did not sign informed consent/ inadequate consent process	xx	xx.x (xx/xx)
Subject did not meet inclusion/exclusion criteria	xx	xx.x (xx/xx)
Follow-up/assessment not completed		
Baseline	xx	xx.x (xx/xx)
Procedure	xx	xx.x (xx/xx)
Discharge	xx	xx.x (xx/xx)
1 month	xx	xx.x (xx/xx)
3 month	xx	xx.x (xx/xx)
Follow-up/assessment not performed according to the protocol		
Baseline	xx	xx.x (xx/xx)
Procedure	xx	xx.x (xx/xx)
Discharge	xx	xx.x (xx/xx)
1 month	xx	xx.x (xx/xx)
3 month	xx	xx.x (xx/xx)
Follow-up/assessment out of window		
Baseline	xx	xx.x (xx/xx)
Procedure	xx	xx.x (xx/xx)
1 month	xx	xx.x (xx/xx)
3 month	xx	xx.x (xx/xx)
AE/SAE reporting		
Procedure	xx	xx.x (xx/xx)
Discharge	xx	xx.x (xx/xx)
1 month	xx	xx.x (xx/xx)
3 month	xx	xx.x (xx/xx)
Other		
Baseline	xx	xx.x (xx/xx)
Procedure	xx	xx.x (xx/xx)
Discharge	xx	xx.x (xx/xx)
1 month	xx	xx.x (xx/xx)
3 month	xx	xx.x (xx/xx)

Table 24. Summary of major vascular access site complication types up to 1 months

	subjects with complication
Access site related major vascular complications leading to death, life-threatening (BARC type 5) or major bleeding (BARC type 3a), visceral ischemia or neurological impairment	xx
Distal embolization from the vascular access site requiring surgery or resulting in amputation or irreversible end-organ damage	xx
The use of unplanned endovascular or surgical intervention associated with access site related death, major bleeding (BARC type 3a), visceral ischemia or neurological impairment	xx
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	xx
Surgery for access site-related nerve injury	xx
Permanent access site-related nerve injury	xx
Access-site-related infection requiring intravenous antibiotics and/or extended hospitalization	xx
Other	xx

Table 25. Summary of minor vascular access site complication types up to 3 months

	subjects with complication
Access site or access-related vascular injury	xx
Dissection	xx
Stenosis	xx
Perforation	xx
Rupture	xx
Arteriovenous fistula	xx
Pseudoaneurysm (> 3 cm)	xx
Hematoma (> 6 cm)	xx
Percutaneous closure device failure	xx
Distal embolization from the vascular access site treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage	xx
Localized access site infection treated with intramuscular or oral antibiotics	xx
Any access site related unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication	xx
Access site related vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent graft)	xx
Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)	xx
Other[e]	xx

16.2 Lists to be generated

List 1. List of all centres that have enrolled subjects (colour coded by country).

Site No.	Name of Hospital	Principle Investigator	Site Address

List 2. Discontinued subjects

Centre ID	**Subject ID**	**Last contact**	**Reason for discontinuation**

List 3. Protocol deviations

Centre ID	**Subject ID**	**Associated evaluation**	**Deviation type**

List 4. Non-serious adverse events

Centre ID	Subject ID	Event type	Procedure date	Start date	Days since procedure	Unanticipated event	Directly associated with the device	Resolution date	Outcome

List 5. Serious adverse events

Centre ID	Subject ID	Event type	Procedure date	Start date	Days since procedure	Reason for serious	Unanticipated event	Directly associated with the device	Resolution date	Outcome

List 6. CEC adjudications

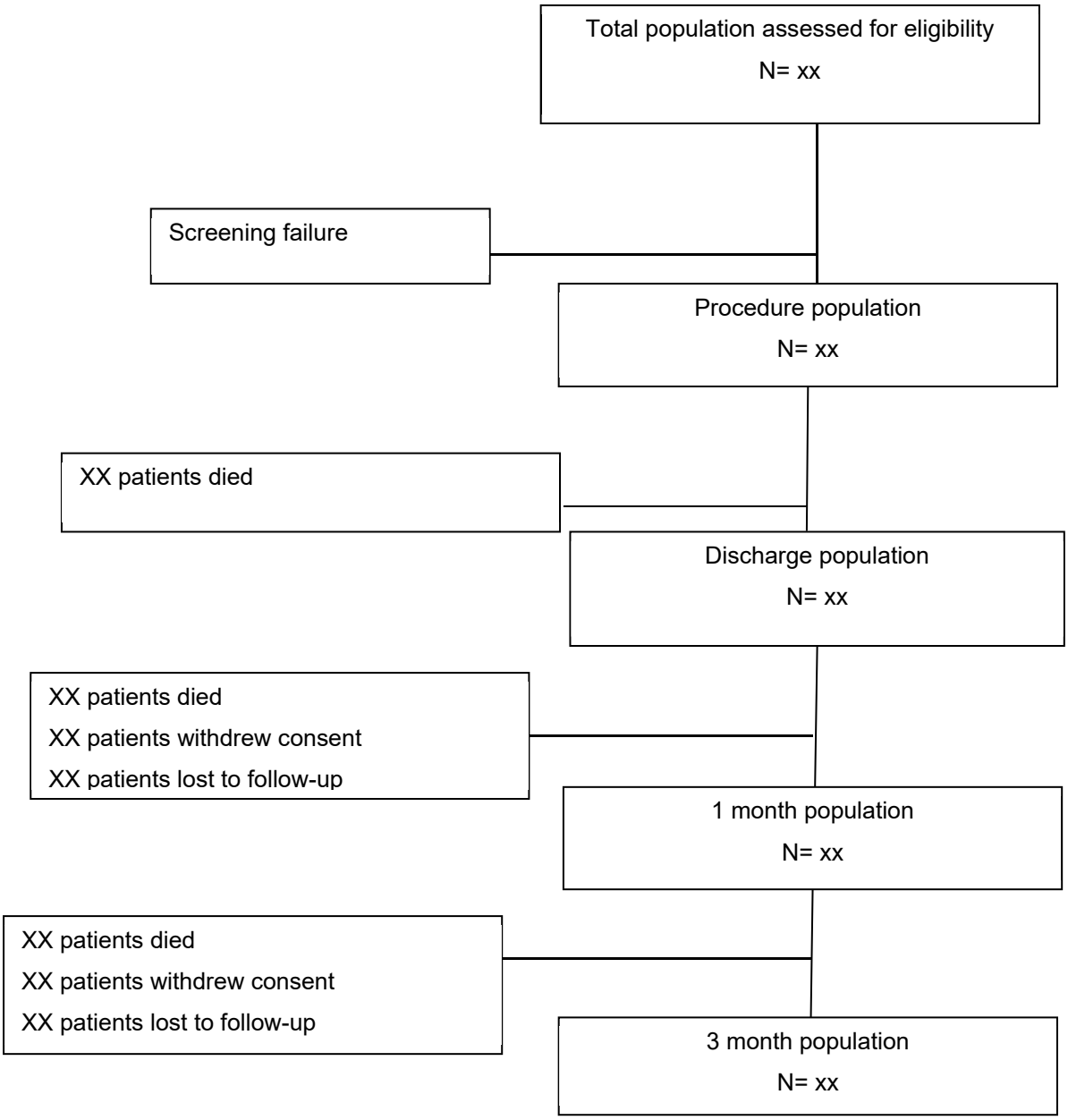
Centre ID	Subject ID	Event type	Event description	Occurred during	Serious	Related to the device	Related to the procedure	Severity	Type of complication

List 7. Demographics

Centre ID	Subject ID	Type of procedure	Gender	Age	Weight	Height	BMI	Largest procedural sheath size used	Treated leg

16.3 Figures to be generated

Figure 1. Subject disposition



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