Protocol number: CD0121

Study title: A multi-center prospective study to evaluate the safety and effectiveness of the VasQ external support for arteriovenous fistula

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[redacted]

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.

- Maintain all information supplied by sponsor in confidence.

and

I have read this protocol in its entirety and I agree to all aspects.

_____ _____

Investigator printed name Site

_____ _____

Signature Date

RETURN TO SPONSOR WITH THE ATTACHED PROTOCOL

Contents

Synopsis

STUDY TITLE	A multi-center prospective study to evaluate the safety and effectiveness of the VasQ external support for arteriovenous fistula.
STUDY TREATMENT	VasQ external support for arteriovenous (AV) fistulas
OBJECTIVES	1. Demonstrate the potential of the VasQ in meeting the specified performance goal in primary patency of AV fistulas. 2. Demonstrate the safety of the VasQ in vascular access.
STUDY DESIGN	<u>Structure</u> Main study cohort: Prospective, multi-center, single-arm, open label, enrolling a total of 129 patients referred to surgical creation of new brachiocephalic fistula (BCF). The VasQ will be applied to the AV fistula in all patients. The primary effectiveness endpoint for this trial will be measured at 6 months and compared to a performance goal (PG). Safety will compare descriptively between AE rates for Steal, Infection, Aneurysm and Seroma. Patients will be followed up for an additional 18 months for a total of 2 years. Additionally, this trial has several secondary endpoints. Supplementary study cohort: A total of 15 patients will be prospectively enrolled which are referred to surgical creation of a new forearm arteriovenous fistula. VasQ will be applied to the AV fistula in all patients. Patients will be followed in the same manner as in the Main study cohort, however, the data will be reported separately and also included in the secondary [redacted] analysis. <u>Duration</u> Primary endpoint is defined at 6 month post index procedure of fistula placement. Patients will be further followed up to 2 years post index procedure. <u>Visit schedule</u> Screening – per eligibility criteria. Index fistula procedure – VasQ implantation. 1, 3 months - Doppler US; Clinical examination, SAE follow up; Dialysis status; Access interventions. 6 months – Primary endpoint, Doppler US; Clinical examination, SAE follow up; Dialysis status; Access interventions. 9 months – Phone call; SAE follow up; Dialysis status. 12 months – Doppler US; clinical examination; X-ray imaging of the arm; SAE follow up; Dialysis status; Access interventions. 24 months - Doppler US; clinical examination; X-ray imaging of the arm; SAE follow up; Dialysis status

ENDPOINTS

Primary effectiveness endpoint:

Primary patency rate at 6 months post AVF creation

1 = Success = Intervention free access patency and flow ≥ 500 ml/min determined by Doppler ultrasound.

0 = Failure = Access occluded or flow < 500 ml/min determined by Doppler ultrasound.

The success rate on this primary endpoint will be compared to a PG of 55.0%.

Secondary [redacted] analysis:

Primary patency rate at 6 months post AVF creation as defined for the primary effectiveness endpoint, calculated for the main and supplementary cohorts (upper arm and forearm fistula) combined.

The success rate on this [redacted] analysis will be compared to a PG of 55.0%.

Safety

The main safety endpoints are occurrence of the following non-thrombotic safety events at up to 6 months: Steal, Infection, Aneurysm, Seroma. Each of these endpoints will be scored dichotomously for each subject as

0 = did not occur

1 = occurred

Thus, for the main safety analyses this study will have 4 rates assessing safety—one for each of the events enumerated.

COHORT

Sample size

144 subjects will be enrolled in this trial in the US.

1. 129 will be enrolled in the main cohort
2. 15 will be enrolled in the supplementary cohort

Inclusion criteria

1. Main study cohort: Patients referred for creation of a new brachiocephalic fistula who consent to take part in the study and which are not indicated for a more distal fistula per treatment guidelines.
   Supplementary study cohort: Patients referred for creation of a new forearm fistula who consent to take part in the study.
2. Male and female participants.
3. Age 18-80 years.
4. Patients willing and able to attend follow up visits over a period of 24 months.

Exclusion criteria

1. Patients with the planned index procedure being a revision surgery of an existing fistula.
2. Main study cohort: Target artery smaller than 2.5 mm or larger than 6 mm in inner diameter by preoperative ultrasound.
   Supplementary study cohort: Target artery smaller than 2 mm or larger than 4.1 mm in inner diameter by preoperative ultrasound.
3. Main study cohort: Target vein smaller than 2.5 mm in inner diameter by preoperative ultrasound.
   Supplementary study cohort: Target vein smaller than 2 mm in inner diameter by preoperative ultrasound.
4. Significantly stenotic target vein on the side of surgery (≥50%) as diagnosed on preoperative ultrasound. (Scan should include the area between the planned anastomosis site and the Axillary vein.)
5. Unusual anatomy or vessel dimensions (observed on pre-operative ultrasound or intraoperatively) and which preclude adequate fit of the VasQ.
6. Patients with central venous stenosis or obstruction on the side of surgery.
7. Depth of vein greater than 8 mm (on ultrasound) on side of surgery.
8. Known coagulation disorder.
9. Congestive heart failure NYHA class ≥ 3.
10. Prior steal on the side of surgery.
11. Known allergy to nitinol.
12. Life expectancy less than 30 months.
13. Patients expecting to undergo kidney transplant within 6 months of enrollment.
14. Women of child bearing age without documented current negative pregnancy test.
15. Inability to give consent and/or comply with the study follow up schedule.

TERMS AND DEFINITIONS

AE – Adverse event
AV – Arteriovenous
AVF – Arteriovenous fistula
BCF – Brachiocephalic fistula
CRF – Case report form
CTA – Clinical trial agreement
eCRF – Electronic case report form
ESRD – End stage renal disease
FAS – Full analysis set
GLMM - Generalized linear mixed model
ICH-GCP - International Conference on Harmonization - Good Clinical Practice
IDE – Investigational device exemption

IFU – Instructions for use
IRB – Institutional review board
KDOQI – Kidney disease outcomes quality initiative
MAR – Missing at random
MMI- Medical Metrics Inc.
PG –Performance goal
PP – Per protocol
SAE – Serious adverse event
SOP – Standard operating procedure
TTFM – Transit time flow measurement
UADE – Unanticipated adverse device effect
US - Ultrasound
USA – United States

1 SCOPE AND PURPOSE

This document describes a prospective clinical study of the Laminate VasQ external support for arteriovenous fistulas. The VasQ constraints and directs the geometrical parameters of the fistula, such as the anastomosis radius of curvature as well as the vascular diameter and gradient in the vicinity of the AV fistula. These geometrical constraints direct flow and influence hemodynamics with the intent to minimize turbulence and promote laminar flow. The device is designed to improve fistula outcomes. The VasQ is intended for use as an external support for autologous vascular conduits created by means of vascular surgery, where veins are incorporated into the arterial circulation for purposes such as vascular access.

2 BACKGROUND AND RATIONALE

2.1 The clinical need

Vascular access continues to be a leading cause for hospitalization and morbidity in patients with chronic kidney disease. Appropriate care of hemodialysis patients requires constant attention to the maintenance of vascular access patency and function. An ideal access delivers a flow rate to the dialyzer adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (e.g., infection, stenosis, thrombosis, aneurysm, repeat interventions, and limb ischemia). Of available accesses, the surgically created fistula comes closest to fulfilling these criteria.

The AV fistula is created by suturing together an artery and a vein, usually in the arm below the elbow (brachio-cephalic) or above the wrist (radio-cephalic), and allowing arterial pressure to enlarge the vein to accommodate a large needle. In order to be used for dialysis, a newly created fistula must maintain patency and mature; that is, the artery and vein must undergo dilation and remodeling to accommodate the markedly increased blood flow that results from creating the AV anastomosis.

Studies over several decades consistently demonstrate that native fistula accesses have the best 4- to 5-year patency rates and require the fewest interventions compared with other access types. However, despite the clear benefits of native arteriovenous (AV) fistulas over other access methods, early failure occurs in over 40% of these fistulas. Most of these failures occur in the peri-anastomotic region.

Local flow patterns and exposure of the vein to arterial pressures and high flow trigger the onset of remodeling and intimal hyperplasia. As demonstrated in the literature, placing a venous external support has the potential to reduce wall shear stress, radial force and cyclic stretching of medial and endothelial cells, all of which might be expected to reduce intimal hyperplasia (wall thickening). In addition, control of the geometric configuration as well as hemodynamic and flow patterns also has the potential to decrease damaging turbulent flow near the anastomosis region, and hence decrease the fistula's early maturation failure rate.

2.2 The VasQ

The VasQ, an external support device for AV fistula, is implanted by the vascular surgeon during the fistula creation surgical procedure. The VasQ targets those segments of the vein which are immediately proximal and distal to the anastomosis, where flow disturbances and intimal hyperplasia are most significant and where frequent occlusions occur.

VasQ is a Nitinol implant (Figure 2-1), which incorporates a conical braided wire portion (around the vein), welded to laser cut tube (around the anastomosis). The VasQ is available in 4 dimensions so as to best comply with vessel diameters and ensure optimal fit with the fistula.

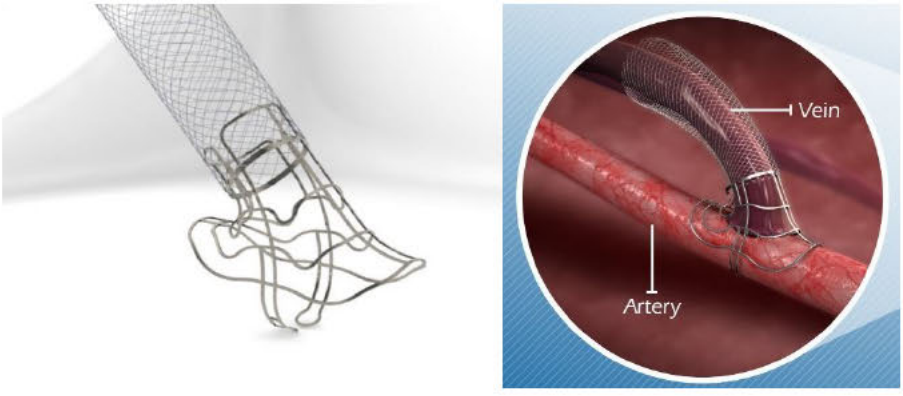


Figure 2-1: VasQ as positioned over the fistula

2.2.1 Intended use

The VasQ is intended for use as an external support for upper extremity arteriovenous fistulas created for vascular access by means of vascular surgery.

2.2.2 Accessories

An accessory to the VasQ device is the dedicated Selection Tool, which is used during the procedure to gage the artery diameter and select the best fitting VasQ model.

3 STUDY OBJECTIVES

The study is designed to clinically demonstrate safety and effectiveness of the VasQ in the following aspects:

1. Demonstrate the potential of the VasQ in meeting the specified performance goal in primary patency of AV fistulas.
2. Demonstrate the safety of the VasQ in vascular access.

4 STUDY DESIGN

4.1 Structure

This is a prospective, multi-center, single-arm, open label study enrolling patients in the US, who are referred for creation of a new AV fistula. The VasQ will be applied to the AV fistula in all patients. The primary effectiveness endpoint for this trial will be measured at 6 months and compared to a performance goal (PG). Patients will be followed up for an additional 18 months for a total of 2 years. Additionally, this trial has several secondary endpoints. 129 patients will be enrolled with upper arm fistulas + 15 patients with forearm fistulas.

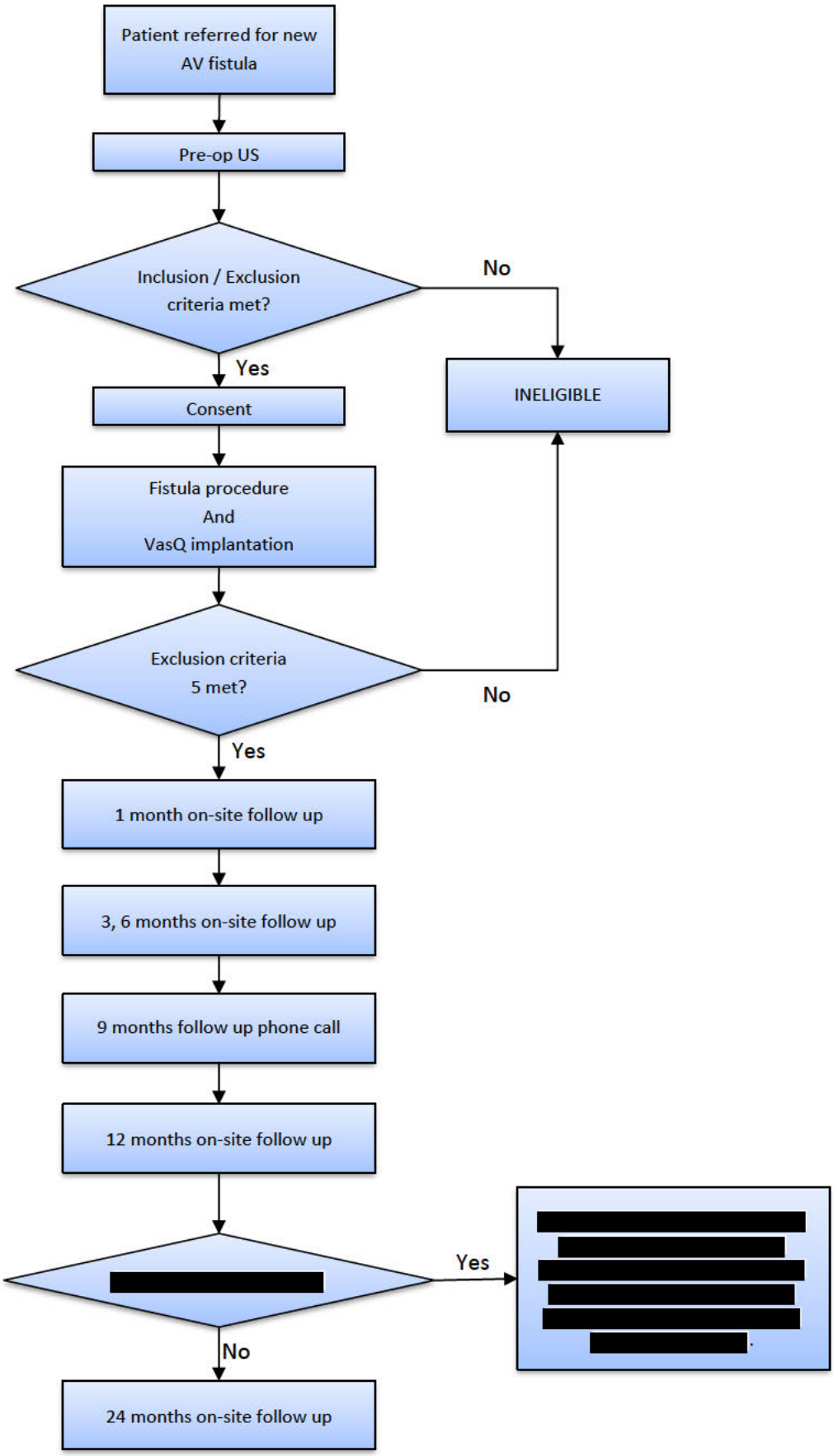
4.2 Visit schedule

Screening – per eligibility criteria
Index fistula procedure – VasQ implantation in all subjects

- 1 month – [redacted]
- 3, 6 months – [redacted]
- 9 months – [redacted]
- 12 months – [redacted]
- 24 months - [redacted]

4.3 Study flow diagram

See following page for the study flow diagram.


Patient referred for new AV fistula
Pre-op US
Inclusion / Exclusion criteria met?
No
Yes
INELIGIBLE
Consent
Fistula procedure And VasQ implantation
Exclusion criteria 5 met?
No
Yes
1 month on-site follow up
3, 6 months on-site follow up
9 months follow up phone call
12 months on-site follow up
[redacted]
Yes
[redacted]
No
24 months on-site follow up

5 STUDY POPULATION

5.1 Number of patients

A total of 129 subjects will be enrolled in the main study cohort in up to 17 US sites. Individual enrollment site will be limited to 20% of the cohort (25 subjects).
15 additional subjects undergoing forearm fistula creation will be enrolled in a supplementary study cohort.

5.2 ELIGIBILITY CRITERIA

5.2.1 Inclusion criteria:

1. Main study cohort: Patients referred for creation of a new brachiocephalic fistula who consent to take part in the study and which are not indicated for a more distal fistula per treatment guidelines.
   Supplementary study cohort: Patients referred for creation of a new forearm fistula who consent to take part in the study.
2. Male and female participants.
3. Age 18-80 years.
4. Patients willing and able to attend follow up visits over a period of 24 months.

5.2.2 Exclusion criteria:

1. Patients with the planned index procedure being a revision surgery of an existing fistula.
2. Main study cohort: Target artery smaller than 2.5 mm or larger than 6 mm in inner diameter by preoperative ultrasound.
   Supplementary study cohort: Target artery smaller than 2 mm or larger than 4.1 mm in inner diameter by preoperative ultrasound.
3. Main study cohort: Target vein smaller than 2.5 mm in inner diameter by preoperative ultrasound.
   Supplementary study cohort: Target vein smaller than 2 mm in inner diameter by preoperative ultrasound.
4. Significantly stenotic target vein on the side of surgery (≥50%) as diagnosed on preoperative ultrasound. (Scan should include the area between the planned anastomosis site and the Axillary vein.)
5. Unusual anatomy or vessel dimensions (observed on pre-operative ultrasound or intraoperatively) and which preclude adequate fit of the VasQ.
6. Patients with central venous stenosis or obstruction on the side of surgery.
7. Depth of vein greater than 8 mm (on ultrasound) on side of surgery.
8. Known coagulation disorder.
9. Congestive heart failure NYHA class ≥ 3.
10. Prior steal on the side of surgery.
11. Known allergy to nitinol.

12. Life expectancy less than 30 months.
13. Patients expecting to undergo kidney transplant within 6 months of enrollment.
14. Women of child bearing age without documented current negative pregnancy test.
15. Inability to give consent and/or comply with the study follow up schedule.

5.3 Relevance to Medicare beneficiaries

The cohort eligible for participation in this study are all patients with ESRD who require vascular access for administration of dialysis. ESRD patients of any age who are receiving dialysis are all eligible for Medicare within certain timing rules. Hence it is expected that all of patients participating in this study are either already Medicare beneficiaries or are eligible to become beneficiaries within several months after enrollment into the study.

6 ENDPOINTS

6.1 Primary effectiveness endpoint

The primary effectiveness endpoint is primary patency at 6 months post AVF creation. Fistulas are defined as primarily patent[1] if they are free from any intervention up to 180 days (endovascular or surgical) to maintain or restore blood flow and demonstrate minimum flow on Doppler or palpable thrill and audible bruit or are receiving dialysis through the fistula.

- The flow criterion is adapted to a range consistent with a documented[2] interobserver and intraobserver variability, with various ultrasound systems.
- Due to the COVID-19 pandemic, patients are more prone to miss their on-site doppler examination at 6 months, but still undergo access site assessment (i.e. thrill palpation and bruit evaluations) which is a valid assessment for confirmation of patency (Shenoy et al.). Thus, patients that have bruit and thrill data indicating patency or actively receiving dialysis through the fistula at 6 months without interventions, will be considered as success.

1 = Success = Intervention free access patency at 180 days. Confirmation of fistula patency is established by meeting one of the following three conditions:

1. Artery or vein flow ≥ 500 (-50) ml/min determined by Doppler ultrasound.
   or
2. Clinical assessment of palpable Thrill and audible bruit at 6 months
   or
3. Patient is receiving dialysis through the fistula at 6 months
   Note: if patient is not receiving dialysis through the fistula at 6 months, this will not indicate failure.

0 = Failure = Access underwent intervention before 180 days
or

[1] Shenoy, Surendra, et al. "Clinical trial end points for hemodialysis vascular access: background, rationale, and definitions." Clinical Journal of the American Society of Nephrology 13.3 (2018): 490-494.
[2] Hoyt Kenneth et al. Accuracy of Volumetric Flow Rate Measurements. An In Vitro Study Using Modern Ultrasound Scanners. J Ultrasound Med 2009; 28:1511–1518

None of the following conditions are met at 180 days:

- Flow ≥ 500 (-50) ml/min
- Thrill is palpable and bruit is audible
- Patient is receiving dialysis through the fistula

6.2 Safety endpoints

6.2.1 Main safety endpoints

The main secondary endpoints in this trial are, for each subject, occurrence of the following clinically meaningful safety events at up to 6 months:

- Steal
- Infection
- Aneurysm
- Seroma

These four safety endpoints have been selected since they are the major non-thrombotic access site complications associated with fistulas. Thrombotic complications which affect maturation and patency will be covered in this trial by the primary and secondary effectiveness endpoints.
These endpoints, which are defined in Section 6.4, will be scored dichotomously for each subject as 0 (did not occur) or 1 (occurred); i.e. each subject is scored 0 or 1 on each of the four endpoints. Additionally, the cumulative number of events over all subjects will be computed. This will allow both detailed and general comparisons to the relevant literature.

6.2.2 Clinical events

AE's, including SAE's, will be coded by body system, preferred term, severity, relation to procedure, and outcome. Specifically, any noted skin erosion above the access site or complications associated with wound healing will be documented and reported.

6.3 Secondary endpoints

1. Time to primary patency cessation since the fistula creation
2. Time to assisted primary patency cessation since the creation
3. Time to primary patency cessation since the first intervention (post-intervention primary patency)
4. Time to assisted primary patency cessation since the first intervention (post -intervention assisted primary patency)
5. Time to first successful cannulation
6. Time to secondary patency cessation since the fistula creation
7. Time to secondary patency cessation since the first intervention (post intervention secondary patency)
8. Time to fistula maturation (physiological)
9. Time to 100% functional fistula dependency

10. Unassisted maturation at 3 months defined as vein diameter ≥ 5mm and blood outflow ≥ 500 (-50) mL/min by Doppler ultrasound.
11. Primary patency at 6 months post AVF creation, excluding patients who have received balloon angioplasty procedures directed at cephalic arch and central vein stenosis.
12. Time to first intervention.
13. Number of interventions (including type and outcome)
14. Rate of interventions per patient-years
15. Primary Failure, at 6 months, which is fistula permanent failure before hemodialysis suitability.
16. Target artery / target vein flow (mL/min) at 1, 3 and 6 months by Doppler blood outflow measurement.
17. Target artery /target vein diameter at 1, 3 and 6 months by Doppler measurement.
18. Target artery / target vein PSV (Peak Systolic Velocity, cm/sec)
19. Proportion of fistulas used for hemodialysis at 3 and 6 months post AVF creation.
20. Duration between fistula first use for dialysis and final abandonment

6.4 Endpoint definitions

1. Primary patency: The time of access creation or placement until any first intervention (endovascular or surgical) to maintain or restore blood flow, or first occurrence to access thrombosis.

   [redacted]

   Proportion of patients (rate) with primary patency can be calculated at defined time points.
2. Secondary patency: the time of access creation or placement until access abandonment, and includes all surgical and endovascular interventions.
   Proportion of patients (rate) with secondary patency can be calculated at defined time points.
3. Primary failure: Fistula permanent failure before hemodialysis suitability.
   Proportion of patients (rate) with primary failure can be calculated at defined time points.
4. Primary assisted patency: The time of access creation or placement until any first intervention (endovascular or surgical) to restore blood flow of a thrombosed access, first occurrence to access thrombosis.
5. Maturation: Vein diameter ≥ 5mm and blood outflow ≥ 500 (-50) mL/min by Doppler ultrasound or fistula is used for dialysis.
   Proportion of patients (rate) with mature fistulas can be calculated at defined time points.

6. Time to fistula maturation (physiological): the time (in days) between the fistula placement to date of the earliest confirmation of Vein diameter ≥ 5mm and flow volume in either artery or vein (at least one of them) ≥ 500 (-50) mL/min
7. Time to 100% Functional Fistula Dependency (applicable to patients who enter the study on dialysis): The time (in days) between the fistula placement to the start date of the first 4-week period in which the fistula was the only access available for administration of dialysis.
8. Fistula used for hemodialysis: Proportion of patients (rate) dialyzed through the study fistula. The rate can be calculated at defined time points.
9. Duration between fistula first use for dialysis and final abandonment: The time interval (in days) between first study fistula use for dialysis and the last confirmed use. [redacted]
10. Steal[3] – Moderate or severe limb ischemia when graded as follows:
    1. Mild - Cool extremity with few symptoms but demonstrable by flow augmentation with fistula occlusion), no treatment needed
    2. Moderate - Moderate (intermittent ischemia only during dialysis/claudication), intervention sometimes needed
    3. Severe - Severe (ischemic pain at rest/tissue loss), intervention mandatory
11. Arteriovenous fistula aneurysm – Local outflow vein dilation to at least three times the diameter of the adjacent normal vein with a minimum aneurysm diameter of 2 cm.[4]
12. Access site infection – Infection at anastomosis site graded as follows:
    1. Resolved with antibiotic treatment
    2. Loss of AV access because of ligation, removal, and possible bypass
    3. Loss of limb
13. Seroma[3] – Collection of seroma fluid or hematoma at anastomosis site which requires treatment, graded as follows:
    1. Observed, resolved without treatment
    2. Aspirated, surgical treatment
    3. Loss of AV access
14. Device related SAEs or device integrity failures – any identified device failure and/or SAE which is judge by the investigator to be related to the device, as defined in section 8.2.5.

7 METHODS

7.1 Screening

A screening visit will take place during which patients will be evaluated according to eligibility criteria. Screening will include a pre-op ultrasound examination of access vessels and draining veins, to verify vessel dimensions and rule out stenotic veins. Screening will further include a physical

[3] Sidawy et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. J Vasc Surg 2002;35:603-10
[4] Pasklinsky, et al. Management of true aneurysms of hemodialysis access fistulas. J Vasc Surg 2011;53:1291-7

examination to check for patient eligibility for receipt of a BCF according to KDOQI guidelines[5] (including suspicion of central venous stenosis and other symptoms which are contraindications for creation of VA fistula according to practice guidelines). Women of childbearing age will be administered a pregnancy test.

7.2 Consent and enrollment

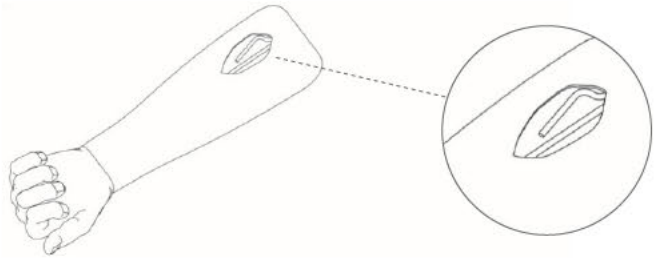
During the screening visits the patients will be introduced to the concept of the study and presented with the informed consent form (ICF). The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject prior to any protocol-dictated procedures. Subjects wishing to participate must give their written informed consent.
The subject must also give Authorization for Use and Release of Health and Research Study Information (HIPAA) in the United States and other written documentation required by local regulations and/or the reviewing IRB prior to any study-related procedures or change in treatment.
Patients who consent to participate but do not undergo surgery at all for any reason will be considered as "screen failures" and will not be considered as enrolled. Patients who are excluded intraoperatively due to unusual anatomy (exclusion criteria # 5) for whom VasQ was not implanted, will also be considered as screen failures and will not be considered as enrolled. These patients will not be followed but will be logged and the reason for screen failure will be documented and reported. Only patients which underwent the BCF procedure and had the VasQ implanted will be considered as enrolled in the study. Telephone numbers should be obtained from the patient to ensure the ability to contact them at the required follow-up times. These phone numbers should include all home numbers, work numbers, mobile phone numbers and primary physician numbers. A phone number of a relative or friend should also be requested.
During this visit, a baseline for the concomitant medications of the patients will be determined, as specified in section 11.2.

[redacted]

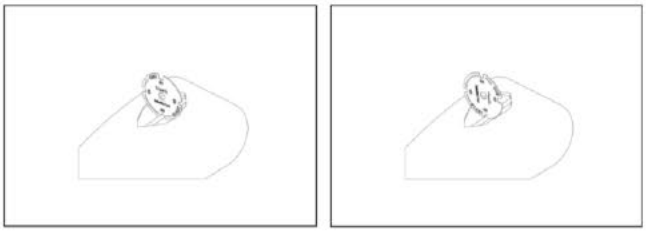
7.3 Intraoperative procedure

1. Expose the vein and the artery through a 6 cm skin incision.
2. Dissect out the artery and vein. Ensure that there is no stretching or kinking of the vein.
3. Assess whether the target vessels demonstrate any unusual anatomy or vessel dimensions which preclude adequate fit of the VasQ.

[5] National Kidney Foundation, KDOQI Clinical Practice Guidelines For Vascular Access, Update 2006



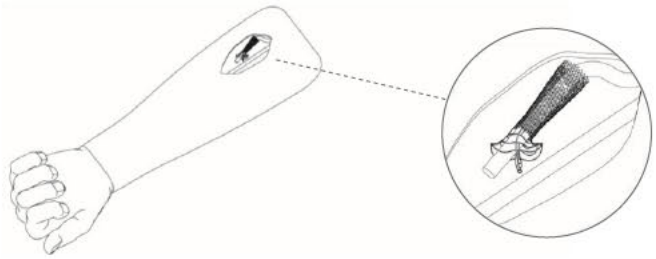
4. Use suture to close off side branches. **Do not** use metal clips.
5. Use the Laminate Model Selection Tool to gage the vessel external diameter.
6. Attempt to place the "START" notch of the Model Selection Tool over the vessel.
7. VasQ model is chosen based on the gaged vessel diameter. Identify the smallest indentation which can accommodate the vessels, by attempting first to fit the vessel into the smallest indentation marked "START" and then, one by one, attempting the larger indentations until the vessel fits in.
8. The **VasQ** model is selected according to the model number written next to the smallest indentation that accommodates the vessels. When in doubt, choose the larger model.



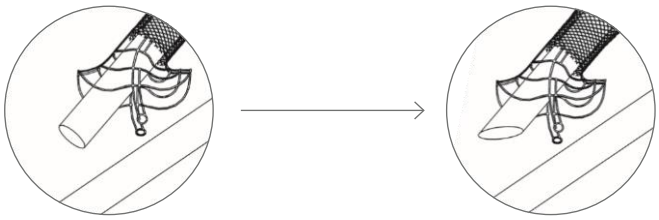
Model	Artery diameter D (mm)
4B	D ≤ 3.7
5B	3.7 < D ≤ 4.2
6B	4.2 < D ≤ 5.0
7B	5.0 < D ≤ 5.5

Model	Vessel Diameter D(mm)
1R	2.0 ≤ D ≤ 3.2
2R	3.2 < D ≤ 3.7
3R	3.7 < D ≤ 4.1

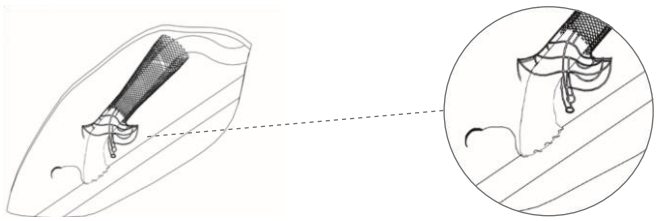
9. Thread the **VasQ** device up the vein by holding the brace, so as to leave the anastomosis suturing area conveniently free and clear.



10. Cut the cephalic vein, in preparation for an end-to side anastomosis. Trim the vein at an approximate angle of 50 Degrees.

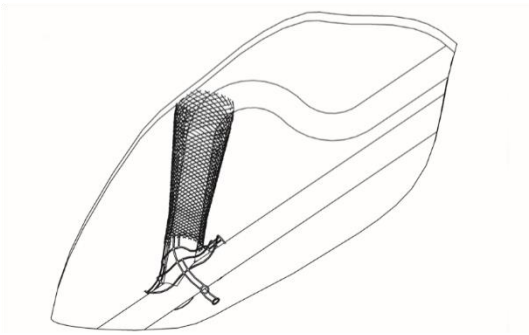


11. Perform an arteriotomy in the artery (5-7mm) and anastomose the cephalic vein to the artery in your routine manner. The area of anastomosis has to be free of fatty tissue.



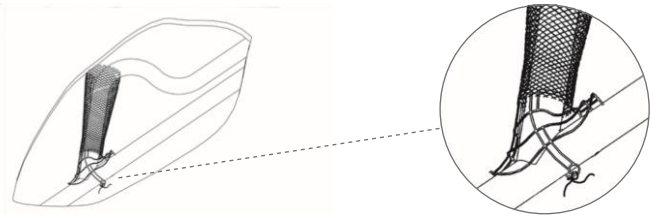
12. Perfuse the fistula and examine it for adequate flow and lack of leaks.
13. If available, use TTFM[6] to verify that venous outflow is greater than 200 ml/min.

Slide the **VasQ** along the vein onto the anastomosis.



14. Use a suture to knot two eyelets of the device brace and secure it around the artery.

[6] Transit Time Flow Measurement



15. Verify once more with TTFM that venous outflow is greater than 200 ml/min.
16. Before closing the surgical incision, photograph in close up the fistula with the device, without including in the photo any patient identifiers. The photos will be uploaded to the eCRF.
17. Close the surgical incision in a routine fashion.
18. Record any medication administered during the surgical procedure.

7.4 Discharge

Physical assessment of the fistula will be performed before discharging the patient from the hospital according to the following guidelines:

- If the surgical procedure required an in-patient hospitalization, a physical assessment of the fistula will be performed at time of discharge.
- If the surgical procedure does not require an in-patient hospitalization, a physical assessment of the fistula will be performed at the end of the surgical procedure.
- The physical assessment includes:
  - Palpation for thrill.
  - Listening for bruit by stethoscope.
  - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).

7.5 1 Month ±7 days follow-up

Fistula will be assessed for patency and maturation. The following examinations will be performed:

- Doppler US:
  - [redacted]
  - A de-identified DICOM file of the US scan will be uploaded to a central system provided by Medical Metrics Inc. (MMI). Instructions for submitting images to MMI are provided in the Image Transfer Protocol and section 11.3.

- Physical examination including:
  - Palpation for thrill.
  - Listening for bruit by stethoscope.
  - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).
- Dialysis status (start/stop dates, dialysis access, flows, number and length of weekly sessions).
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Adverse events / Serious Adverse Events will be recorded in accordance with section 8.
- Concomitant medications update will be recorded (in accordance with section 11.2.
- A de-identified UB-04 form of the index surgery and any fistula intervention will be collected and uploaded to the eCRF.

7.6 3 Months ± 14 days follow-up

Fistula will be assessed for patency and maturation. The following examinations will be performed:

- Doppler US:
  - [redacted]
  - [redacted]
  - [redacted]
  - A de-identified DICOM file of the US scan will be uploaded to a central system provided by Medical Metrics Inc. (MMI). Instructions for submitting images to MMI are provided in the Image Transfer Protocol and section 11.3.
- Physical examination including:
  - Palpation for thrill.
  - Listening for bruit by stethoscope.
  - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).
- Dialysis status (start/stop dates, dialysis access, flows, number and length of weekly sessions).
- Adverse events / Serious Adverse Events will be recorded in accordance with section 8.
- Concomitant medications update will be recorded in accordance with section 11.2.
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Serious Adverse events will be recorded.

- A de-identified UB-04 form of any fistula intervention will be collected and uploaded to the eCRF.

7.7 6 Months ± 14 days follow-up – primary endpoint assessment

Fistula will be assessed for patency and maturation. The following examinations will be performed:

- Doppler US:
  - [redacted]
  - [redacted]
  - [redacted]
  - A de-identified DICOM file of the US scan will be uploaded to a central system provided by Medical Metrics Inc. (MMI). Instructions for submitting images to MMI are provided in the Image Transfer Protocol and section 11.3.
- Physical examination including:
  - Palpation for thrill.
  - Listening for bruit by stethoscope.
  - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).
- Dialysis status (start/stop dates, dialysis access, flows, number and length of weekly sessions).
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Adverse events / Serious Adverse Events will be recorded in accordance with section 8.
- Concomitant medications update will be recorded in accordance with section 11.2.
- Serious Adverse events will be recorded.
- A de-identified UB-04 form of any fistula intervention will be collected and uploaded to the eCRF.

7.8 9 Months - ± 14 days follow-up (by phone call)

- Dialysis status (start/stop dates, dialysis access, number and length of weekly sessions).
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Serious Adverse events will be recorded.

7.9 12 Months ± 14 days follow-up

Fistula will be assessed for maturation and patency. The following examinations will be performed:

- Doppler US:

- [redacted]
- [redacted]
- [redacted]
    - A de-identified DICOM file of the US scan will be uploaded to a central system provided by Medical Metrics Inc. (MMI). Instructions for submitting images to MMI are provided in the Image Transfer Protocol and section 11.3.
- Physical examination including:
    - Palpation for thrill.
    - Listening for bruit by stethoscope.
    - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).
- X-ray imaging of the arm to determine VasQ integrity. [redacted]
- Dialysis status (start/stop dates, dialysis access, flows, number and length of weekly sessions).
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Adverse events / Serious Adverse Events will be recorded in accordance with section 8.
- Concomitant medications update will be recorded in accordance with section 11.2.
- A de-identified UB-04 form of any fistula intervention will be and uploaded to the eCRF.

7.10 24 Months - ± 1 month follow-up

Fistula will be assessed for maturation and patency. The following examinations will be performed:

- Doppler US:
    - [redacted]
    - [redacted]

- [redacted]
  - A de-identified DICOM file of the US scan will be uploaded to a central system provided by Medical Metrics Inc. (MMI). Instructions for submitting images to MMI are provided in the Image Transfer Protocol and section 11.3.
- Physical examination including:
  - Palpation for thrill.
  - Listening for bruit by stethoscope.
  - Documentation of non-thrombotic access events: steal, infection, aneurysm, and seroma (per definitions in section 6.4).
- [redacted]
- Dialysis status (start/stop dates, dialysis access, number and length of weekly sessions).
- Document any access intervention (type, date, purpose [initiating vs. maintenance of dialysis], outcome).
- Adverse events / Serious Adverse Events will be recorded in accordance with section 8.
- Concomitant medications update will be recorded in accordance with section 11.2.
- A de-identified UB-04 form of any fistula intervention will be collected and uploaded to the eCRF.

After the 24 months visit patients will be followed with the routine follow up as customary with vascular access patients.

Table 7-1: Main Study Data Elements Per Visit

	Screening	Intra-operative	1 month	3 months	6 months	9 months	12 months	24 months
Physical examination for appropriateness for BCF according to KDOQI guidelines	✓							

	Screening	Intra-operative	1 month	3 months	6 months	9 months	12 months	24 months
Doppler US of proximal veins and access vessel dimensions	✓		✓	✓	✓		✓	✓
Anatomic adequacy per exclusion criteria #5		✓						
Fistula inflow and outflow			✓ By Doppler	✓ By Doppler	✓ By Doppler		✓ By Doppler	✓ By Doppler
Arterial/venous stenosis/obstruction/ dilation			✓ By Doppler	✓ By Doppler	✓ By Doppler		✓ By Doppler	✓ By Doppler
Outflow vein diameter			✓ By Doppler	✓ By Doppler	✓ By Doppler		✓ By Doppler	✓ By Doppler
Fistula patency			✓	✓	✓		✓	✓
Fistula maturation			✓	✓	✓		✓	✓
X-ray imaging of the arm							✓*	✓
Fistula interventions			✓	✓	✓	✓	✓	✓
Serious adverse events		✓	✓	✓	✓	✓	✓	✓
Adverse Events		✓	✓	✓	✓	✓	✓	✓
Dialysis status	✓		✓	✓	✓	✓	✓	✓
Steal			✓	✓	✓		✓	✓
Infection			✓	✓	✓		✓	✓
Aneurysm			✓	✓	✓		✓	✓
Seroma			✓	✓	✓		✓	✓
Concomitant Medications	✓	✓	✓	✓	✓		✓	✓
Collection of de-identified UB-04			✓ For index surgery and any fistula intervention	✓ For any fistula intervention	✓ For any fistula intervention		✓ For any fistula intervention	✓ For any fistula intervention

* If any previously unknown loss of integrity is detected on Xray imaging at the 12 months visit, additional follow up will be performed every 3 months, including clinical evaluation and Doppler ultrasound

7.11 Special COVID-19 pandemic instructions

1. In the event an on-site visit is not possible due to hospital restrictions or subject refusal to attend visit:
   a. Conduct a phone visit (preferably using video with participation of investigator and subject). Use the relevant study follow-up worksheets to document the data. Please insert a note on the worksheet that the visit was performed by phone and not on-site.
   b. Review the subject's medical record in detail to identify any adverse events, diagnostic fistulogram, interventions on the study fistula, placement of additional accesses, etc.
   c. If dialysis records are not accessible in the EMR, please call the dialysis unit and collect the study required data. Please document the call in a dated and signed note.
   d. Upload obtained data into the EDC using the Unscheduled Visit forms - Access site Assessment and Dialysis.
   e. Report a protocol deviation of the follow-up visit out of window (if relevant) and Phone visit in EDC and record this in the protocol deviation log. Please add a comment in the comment field explaining that the deviation was caused by the restrictions related to COVID-19.
2. Once restrictions are lifted, the requirement for completing missing on-site visits based on subject status and progress in the study will be assessed.
3. End of Study should not be declared if X-Ray is missing even if all other data is available. The subject should return for X-Ray imaging as soon as possible before exiting the study.

8 ADVERSE EVENTS

8.1 Follow-up

Throughout the course of the study adverse events will be followed and recorded as follows:

- All Adverse Events (AEs) will be followed from date of informed consent until the date of the "1 month" visit and recorded in the CRF (excluding events as detailed in section 8.4).
- Assessment of occurrence and severity of the following non-thrombotic access adverse events (per definitions in section 6.4): steal, infection, aneurysm, and seroma will be recorded during each on-site follow-up visit (1, 3, 6, 12, 24 Months visits).
- All other fistula related adverse events will be recorded in each on-site follow-up visit (1, 3, 6, 12, 24 Months visits).
- Serious adverse events (SAEs) will be followed throughout the duration of the study from date of informed consent until date of "24 months" visit or "End of study".

8.2 Adverse events definitions

8.2.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

8.2.2 Serious Adverse Event (SAE)

Adverse event that resulted in any of the following:

1) Death,
2) A life-threatening illness or injury - any AE that places the Subject, in the view of the reporter, at immediate risk of death from the AE as it occurred (it does not include an AE that, had it occurred in a more severe form, might have caused death),
3) A permanent impairment of a body structure or a body function - any AE that results in a substantial disruption of the Subject's ability to conduct normal life functions,
4) In-patient hospitalization or prolonged existing hospitalization,
5) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or
6) Fetal distress, fetal death or a congenital abnormality or birth defect.

8.2.3 Unanticipated Adverse Device Effect (UADE)

SAE related to the use of an investigational medical device which by its nature, incidence, severity or outcome is not anticipated.

As required by 21 CFR §812.46(b)(2), if the Sponsor determines that an UADE presents an unreasonable risk to study Subjects, the Sponsor will terminate the investigation within 5 working days of the unreasonable risk determination.

8.2.4 Severity

Definitions for classification of severity are:

Mild - Symptoms are barely noticeable or do not make the Subject uncomfortable. The AE does not influence performance or functioning.

Moderate - Symptoms are of sufficient severity to make the Subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.

Severe - Symptoms are of sufficient severity to cause the Subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

Note: A "severe" AE is not the same as an "SAE" (serious adverse event), which is defined above.

8.2.5 Relationship to study device

The Investigator will determine whether the Subject's symptom or problem is most likely unrelated to the study treatment or is possibly/probably/definitely related to the study device.

8.3 Procedures for reporting serious adverse events

All Serious Adverse Events (SAEs) that occur after the time of informed consent and before the Subject's "24 months" visit date (study exit) must be reported by the investigators to the sponsor. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports). The Sponsor shall evaluate all SAEs and determine and document in writing whether they meet the definition of an Unanticipated Serious Adverse Device Effect (USADE). These shall be reported to all participating investigators, the regulatory authorities, and IRBs as required by national regulations. In the event of an SAE, the Investigator must:

1) Notify sponsor within 24 hours of the Investigator's awareness of the event by completing the relevant data in the eCRF and/or contacting the CRO representative or Sponsor representative at the number listed on the front page of this protocol.
2) Obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the Subject.
3) Provide sponsor with a complete, written detailed description, including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement from the Investigator as to whether or not the event was related to the use of the investigational device.
4) Promptly inform the governing IRB/EC of the event, if it is device-related. For other SAEs, notify the governing IRB/EC as required by the IRB/EC, local regulations, and the governing health authorities.

8.4 Events that do not need to be reported

Common medical events (as determined by the investigator) such as colds, influenza, elective minor outpatient procedures such as colonoscopy, minor trauma and musculoskeletal discomforts do not need to be reported as adverse events unless they result in a hospital visit. Events related to pre-existing non-kidney failure ailments such as arthritis, gout, gastrointestinal reflux disorder (GIRD) do not need to be reported as adverse events unless they result in a hospital visit. Events related to the administration of dialysis do not need to be reported. Occurrence and level of any stenosis in the vascular access will be recorded by Doppler US during on-site follow-up visits, and should not be reported separately as an AE, unless clinically significant (i.e. requires an intervention).

8.5 Potential / anticipated adverse events

Systemic complications and adverse events are documented in the literature and expected to occur with ESRD patients:

1) Death
2) Cardiac failure
3) Fluid overload
4) Pneumonia
5) Anemia
6) Gastrointestinal bleeding
7) Musculoskeletal pain

8) Abnormal glucose level (Hyperglycemia/Hypoglycemia)
9) Hypertension
10) Alteration of mental state
11) Pruritus

Arteriovenous fistula site complications and adverse events are documented in the literature and expected to occur in patients with AVF include (but not limited to):

1) Post operative bleeding from surgical site
2) Surgical wound dehiscence
3) Bleeding / Hematoma / Seroma / Pseudo aneurysm
4) Infection
5) Aneurysm
6) Stenosis
7) Occlusion / Thrombosis
8) Arm swelling
9) Edema
10) Cold arm / Hypoesthesia / Hand ischemia / Steal syndrome
11) Access revision / intervention
12) Pain in the access arm

An anticipated event related to the VasQ device:

1) Damage to blood vessels or surrounding tissue due to device fracture

9 RISK BENEFIT CONSIDERATIONS

The VasQ is used as an adjunct to standard of care end-to-side fistula. It does not interfere in any way with the anastomosis creation and with acceptable surgical paradigms. In clinical use to date (>50 patients) the VasQ device has not been associated with device related adverse events. The potential benefits of the VasQ are in shaping fistula geometry and supporting the venous wall so as to regulate flow regime, mitigating turbulence, and mitigating intimal hyperplasia. Thus the VasQ is designed to enhance fistula patency.

The VasQ should be implanted by trained professional vascular surgeons. Care should be taken to use the VasQ according to the IFU. The VasQ model should be carefully selected according to instructions for use. There is some risk of VasQ interfering with side branch ligations, however this can be mitigated with training and careful attention to instructions, mainly avoidance of metal clips in ligation of side branches.

Potentially, if incorrectly placed or incorrectly sized, the VasQ can lead to fistula failure which in turn can necessitate additional intervention. This risk can be significantly mitigated by careful model selection, avoidance of metal clips, and careful compliance with the IFU.

Additional potential adverse effects associated with the VasQ may include the complications reported for conventional fistula placement procedure and ESRD patients such as: infection, bleeding, aneurysms, hand ischemia, cardiac failure, need for repeat intervention, or death.
In summary, while the potential benefits in mitigating venous disease and regulating flow regime are promising, the risks are mainly due to those associated with any vascular access surgery and the adjunct use of the VasQ to standard fistula creation adds minimal risk which can be mitigated with careful training and compliance with IFU.
Other risks associated with ESRD and/or vascular access surgery apply to these patients, but are not expected to be influenced by use of the VasQ.

10 STATISTICAL CONSIDERATIONS

10.1 Design considerations

This is a single-arm study where device effectiveness will be tested by comparing study outcome to a pre-specified performance goal (PG). Safety will be evaluated by descriptive comparisons of specific procedure-related AEs between those observed in this study and those of a large study conducted at the Mayo Clinic. The following two sections explain our approach to assessing safety and effectiveness in this trial.

10.2 Safety

Fistulas, being the gold standard vascular access for decades, have a long history of well-established safety. Data exists for the four non-thrombotic safety events relevant: Steal, Infection, Aneurysm, Seroma. In this section we present safety data available from the literature, which we believe is appropriate for comparison to the safety endpoints observed under this study.

10.2.1 Historical safety data

A search of the literature yielded two papers with data on non-thrombotic complications up to a period of 6 months. Based on these papers, SOC fistula safety can be estimated, whose rates with respect to the steal, infection, aneurysm, and seroma are presented in Table 10-1 below:

Table 10-1: Safety data from literature

Paper	Country	N	Steal (%)	Infection (%)	Aneurysm (%)	Seroma (%)	Overall rate#
Schinstock et al. Outcomes of Arteriovenous Fistula Creation after the Fistula First Initiative. Clin J Am Soc Nephrol 6: 1996–2002, 2011	USA	293	5.1	7.5	2.4	1.4	7.5 - 16.4
Dunlop et al. Vascular access: experience with the brachiocephalic fistula. Annals of the Royal College of Surgeons of England (1986) vol. 68	Scotland	77	6.5	2.6	3.9	NR*	6.5 – 13.0

*NR=Not reported

#Assuming no subject experienced more than one AE (which we know is not the case) the rate for experiencing any AE is the sum of the rates. Assuming every subject experienced all of the AEs (which we know is not the case) the rate experiencing any AE is the largest percentage reported

Note that:

- The study done in 1986 reports relatively similar rates to the most recent study. The SOC in this indication has changed little in 40 years so that we can expect older data to be as valid for comparison as newer.
- The Schinstock et al study was done in the Mayo Clinic in the US and included nearly 300 patients. For this reason, we propose it as the main comparison to the data to be collected in our own study.
- Importantly, AE rates are reported separately for the each of the four AEs allowing for a detailed comparison of new treatment to the SOC
- The rates reported in the above table overlap so that the average number of AEs for subjects who had these AEs is more than one. Neither of the papers provides an overall rate of subjects who experienced any of the four AEs.

Several additional papers which report data on one or more of the four complications are provided in Table 10-2 in support of the safety values to which the study observed data can be compared. Overall, it can be observed that values for all 4 events converge around single digit incidence rate for each event.

Table 10-2: Additional safety data from the literature

Paper	Steal (%)	Infection (%)	Aneurysm (%)	Seroma (%)
Huber et al. Access-related hand ischemia and the Hemodialysis Fistula Maturation Study. J Vasc Surg 2016;-:1-9	4-7	-	-	-
Al Jaishi, Master's thesis dissertation, University of Western Ontario, 2013 http://ir.lib.uwo.ca/cgi/viewcontent.cgi?article=2734&context=etd	5-10	-	-	-
Padberg et al. Complications of arteriovenous hemodialysis access: Recognition and management. J Vasc Surg 2008;48:55S-80S	0.25-1.8	0.56-5	-	0.48-4.2
Pasklinsky et al. Management of true aneurysms of hemodialysis access fistulas. J Vasc Surg 2011;53:1291-7.	4-9	-	5-7	-
Fitzgerald et al. Outcomes of Upper Arm Arteriovenous Fistulas for Maintenance Hemodialysis Access. Arch Surg. 2004;139:201-208	1.1	1.1	1.1	-
Huijbregts et al. Hemodialysis Arteriovenous Fistula Patency Revisited: Results of a Prospective, Multicenter Initiative. Clin J Am Soc Nephrol. 2008 May; 3(3): 714–719.	0.7	2.8	-	-
Lew et al. Hemodialysis vascular access construction in the upper extremity: a review. J Vasc Access 2015; 16 (2): 87-92	2	2	0	-

Paper	Steal (%)	Infection (%)	Aneurysm (%)	Seroma (%)
Oliver et al. Comparison of transposed brachiobasilic fistulas to upper arm grafts and brachiocephalic fistulas. Kidney International, Vol. 60 (2001), pp. 1532–1539	11	2	-	0

10.2.2 Methodology for assessing safety

Laminate believes that the most appropriate way for assessing safety in the current study is to compare the rates for each type of AE obtained in the study with those reported in the literature. Such a multidimensional comparison will provide a more complete picture of the VasQ's safety profile than comparing an overall rate combining AEs with different clinical implications.
Given the four comparisons, we feel it is most appropriate they be done descriptively. First, because statistical testing would involve 4 separate tests, along with associated issues of Type I Error and power (for success in all 4). Second, as noted, neither study provides overall, non-overlapping rates for these four non-thrombotic AEs, nor can this be obtained from the more detailed data presented in the articles (and shown in the preceding section). For this reason a statistical comparison of overall AEs rate cannot be done.
It is important to add that a descriptive comparison of each of the 4 rates between the current trial and Schinstock et al. is meaningful given that the precision of each of the (relatively small) rates is 2% to 4%; i.e. given the small AE rates involved, the planned N for our study of 116 evaluable patients will provide good precision that, in turn, will provide a meaningful comparison between our rates and those reported by Schinstock et al. In addition, even the upper bound higher rate (16.4%) has a precision of 4%. Precision is here defined as the half width of the two sided, 95% confidence interval computed using the Exact Binomial method.
Consequently, we propose evaluating safety in our trial by presenting the 4 AEs listed along with associated two-sided, 95%, Exact Binomial confidence interval to those presented in Schinstock et al.
In conclusion, we feel that the most appropriate safety assessment for the VasQ is by:

- Evaluating each of the four AEs of interest separately
- Presenting safety data with two-sided 95% confidence intervals of high precision; i.e. that are relatively narrow at ± 3% to 4%

10.3 Effectiveness vs. performance goal

The study is a single-arm trial whose results will be compared to a performance goal (PG). The AVF fistula procedure for vascular access, to which Laminate's results will be compared, is mature as it has been the standard of care in this indication for over 40 years. Moreover, the expected outcomes of this procedure with respect to our primary endpoint are well documented. Consequently, in this trial it is appropriate to specify a PG to which device performance will be compared.
The PG for primary patency rate in this trial is based on rates observed in the relevant literature. The following section describes the review of the literature done.

Two sources of data will be used for [redacted] analyses:

- Main study cohort: N 129 U.S. subjects (primary analysis)
- Supplementary study cohort: N = 15 U.S. subjects ([redacted] secondary analysis is performed on data combining Main and Supplementary cohorts; 15 + 129 = 144)

10.3.1 Literature review

Laminate has performed a systematic literature review in order to arrive at a PG for the primary endpoint of Primary Patency.
The literature review included the following steps:

- Identification of search criteria.
- Performing said search in Pubmed.
- Assessing each resulting abstracts.
- Selection of papers for full text appraisal.
- Appraisal of full text documents according to specified criteria.
- Selection of documents to be included in analysis.

Papers published over the last 10 years were searched on March 8, 2016.
The search terms have been selected so as to focus on arteriovenous fistula patients and various possible wordings for patency appraisal:

(((((((((("Arteriovenous fistula"[Title]) OR "Arteriovenous fistulae"[Title]) OR "Arteriovenous fistulas"[Title]) OR "AV fistula"[Title]) OR "AV fistulae"[Title]) OR "AV fistulas"[Title])))
AND ((("primary patency") OR "primary failure"[Title/Abstract])))
AND
((("vascular access"[Title/Abstract]) OR "hemodialysis access"[Title/Abstract]))
Filters: 10 years, Humans, English

This search resulted in 40 papers. 40 abstracts were reviewed in order to select papers for full text analysis. Papers were omitted if they related only to specific populations, focused on alternative specific surgical techniques, specific age groups, salvage procedures, etc. 13 papers were selected for detailed data analysis.
Papers were selected to be included if they had provided 6 months post AVF placement Primary Patency data for a patient population similar to the one defined in this protocol. Five papers including data from 966 patients were included for PG calculations (Table 10-3).

Table 10-3: Papers selected for PG calculations

Paper	Geography	N	Primary Patency rate (%)
Lee et al. Comparison of Survival of Upper Arm Arteriovenous Fistulas and Grafts after Failed Forearm Fistula. J Am Soc Nephrol 18: 1936–1941, 2007	USA	59	50
Chiulli et al. Superior Patency of Upper Arm Arteriovenous Fistulae in High Risk Patients. J Surg Res. 2011 September ; 170(1): 157–164	USA	44	61
Field et al. Primary patency rates of AV fistulae and the effect of patient variables. J Vasc Access 2008; 9: 45-50	United Kingdom	79	57
Schinstock et al. Outcomes of Arteriovenous Fistula Creation after the Fistula First Initiative. Clin J Am Soc Nephrol 6: 1996–2002, 2011	USA	293	50
Huijbregts et al. Hemodialysis Arteriovenous Fistula Patency Revisited: Results of a Prospective, Multicenter Initiative. Clin J Am Soc Nephrol. 2008 May; 3(3): 714–719	Netherlands	491	57

Table 10-4: Cohort data from papers used for PG calculations

Paper	Cohort	Age (Y)	Gender (Male %)	Ethnicity Caucasian %	Diabetes	BMI
Lee et al.	Retrospective review of new elbow fistulas after failed primary fistulas placed during 2000-2004	56	61%	83% black	54%	36% > 30 kg/m
Chiulli et al.	Retrospective review of new elbow fistulas placed during 2004-2009	65.8	97.7%	75%	47.7%	28.2
Field et al.	Retrospective review of new elbow fistulas placed during 2003-2007	61	34.2%	94%	43.1%	Not reported
Schinstock et al.	Retrospective review of new fistulas placed during 2006-2008	65.1	65.2%	88.1%	43.3%	29.8
Huijbregts et al.	Prospectively enrolled during 2004-2005 All hemodialysis patients or patients who had chronic renal failure and required a new permanent vascular access.	64.6	62%	78%	33%	25.1

10.3.2 PG calculations

The studies enumerated in the above table report outcomes for Primary Patency for a total number of 966 subjects, whose outcomes are relatively homogeneous (SD = 4.9%; range: 50%-61%) compared to our experience in many other indications where outcomes, even in mature technologies, are typically much more variable. Additionally, the largest studies reported here, encompassing N = 293 and N = 491, were conducted in the US and Netherlands respectively and demonstrated an even narrower range of 50% to 57% respectively.

Taken together, the total N of these studies, coupled with AV fistula creation being a very mature technology demonstrating Primary Patency Rate outcomes that are similar over a wide range of studies in a number of countries over the past 10 years, indicates that the Primary Patency Rate calculated based on these trials is appropriate for use as an PG for our device, which aims to improve upon the relatively homogeneous outcomes reported.

To account for both the variation of subjects between studies and that in percentage of Primary Patency, we applied a statistical model to compute the mean and two-sided 95% confidence interval. The model applied was the generalized linear mixed model (GLMM) with a random effect and a binomial distribution, and the estimation method was maximum likelihood based on the Gauss-Hermite quadrature integral approximation. Study ("paper" in the code below) was included in the model as a random effect. The model was applied using PROC GLIMMIX in SAS® V9.4 using the following SAS® code:

Generalized linear mixed model syntax:

```
proc glimmix data = papers method = quad;
     class paper;
     model success/n =  / solution cl dist=binomial;
     estimate 'intercept' intercept 1  / cl ilink;
     random intercept/ subject=paper;
run;
```

Applying this model yielded a mean of 54.7% and a two sided 95% CI of [49.5% to 59.7%]. We therefore specify as our PG for Primary Patency at 6 months, the study's primary endpoint, as 55.0%.

10.4 Sample size justification

Presentation of sample size in this trial is based on the observed Primary Patency rate meeting a PG of 55% (see Section 10.1). Based on limited historical information on the use of VasQ our conservative estimate of device performance is a Primary Patency rate of 70%. A sample of N = 116 evaluable subjects will provide 90% power to demonstrate VasQ meeting the PG. To account for an approximate 10% dropout rate, 129 subjects will participate in this trial. Power computations are based on Exact Binomial computations with a two-sided Alpha = 0.05, designed to demonstrate that the lower

bound of the 95% Exact Binomial confidence interval about observed Primary Patency is above the 55% PG.
In summary, N = 129 subjects will be included in this trial to provide 90% power to demonstrate that the VasQ meets its PG.

10.5 Analysis sets

10.5.1 Safety

The safety population will consist of all subjects for whom the study device was implanted.

10.5.2 Full analysis set: Primary Effectiveness Analysis

The full analysis set for the primary effectiveness analysis (FAS_primary) will, consistent with ICH Guideline E9, include all subjects (with brachiocephalic fistulas) for whom the study device was implanted and for whom there is at least one post-procedure Primary Patency measurement. [redacted]

Handling of missing data: Patients occluded prior to 6 months will be scored as failures even if missing subsequent observations. Patients with missing primary patency at 6 months, but with observed primary patency at later visits (without undergoing interventions) will be considered Success.
Because MI assumes missing at random (MAR), we will conduct sensitivity analyses to assess the sensitivity of our results to alternative assumptions of missingness (see below).
Subjects who died or underwent transplant before 6 months, and were non-occluded at that time of the event, will be excluded from the FAS and reported separately. If such subjects were occluded at or before the time of the event (death or transplant), they will be considered failures and included in FAS for the purpose of the primary analysis.

10.5.3 Full analysis set: [redacted] Secondary Effectiveness Analysis

The full analysis set for the [redacted] secondary analysis (FAS_secondary), will consist of the main and supplementary cohort subjects who meet the criteria described in the preceding section for FAS_primary. [redacted]

10.5.4 Per protocol

The per protocol (PP) analysis set will consist of all subjects with valid Primary Patency measurements at 6 months and with no major protocol violations.
Handling of missing data: Only observed data will be used in the PP analysis set.

10.5.5 Functionality dialysis sets

The functionality endpoints are relevant only for patients with specific dialysis status as applicable per the endpoint. Therefore, the following subsets of patients will be defined to analyze dialysis functionality endpoints.
Ongoing Dialysis Subset

This subset will include patients already on hemodialysis at study entry (index procedure).

Any Dialysis Subset

This subset will include patients who are either already on dialysis at study entry or started hemodialysis during the study. For patients who started the dialysis during the study, the start date will be determined as the earliest date reported among all dialysis sections.

This subset will be used to analyze "Fistula use for dialysis" and "Duration between Fistula First Use for Dialysis and final abandonment" endpoints.

10.6 Statistical analysis

10.6.1 Overview

The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum and number of subjects for continuous data, or in tables listing count and percentage for categorical data where appropriate. Data listing by subject will be provided.

All statistical analyses will be performed and data appendixes will be created using the SAS® system, Version 9.2 or higher. The effects of noncompliance, dropouts, and possible covariates such as age, gender, and center, will be assessed to determine the impact on the general applicability of results from this study.

Safety and subject disposition analyses will be done on the safety analysis set. Primary effectiveness analyses will be done on FAS_primary and PP. Secondary [redacted] will be tested on FAS_secondary and PP. Primary and secondary [redacted] endpoints will be assessed hierarchically, so that the latter will be tested only if the former's null was rejected.

10.6.2 Subject disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized, including the number of subjects in each analysis set.

A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

10.6.3 Primary effectiveness analysis

The primary effectiveness endpoint, Primary Patency at 6 months post procedure, will be tested in the FAS_primary using the following hypotheses:

- H_0: $(\text{Primary Patency Rate})_{observed} \leq 55.0\%$
- H_1: $(\text{Primary Patency Rate})_{observed} > 55.0\%$

Hypotheses will be tested using a two-sided, 95% Exact Binomial confidence interval about the observed 6-month Primary Patency rate. We will declare success on this endpoint if the lower limit of the confidence interval is above 55.0%. Note that if there will be missing values and MI will be applied, we will apply Exact Binomial computations to each of the multiple data sets, then use SAS® PROC MIANALYZE to obtain a P-value for the combined results.

10.6.4 [redacted] Secondary Analysis

The [redacted] secondary effectiveness endpoint, Primary Patency at 6 months post procedure, will be tested in the FAS_secondary using the following hypotheses:

- H_0: $(\text{Primary Patency Rate})_{observed} \leq 55.0\%$
- H_1: $(\text{Primary Patency Rate})_{observed} > 55.0\%$

Testing will be done only if the null of the primary hypothesis in the preceding section will have been rejected (i.e. hierarchical testing). The statistical method used for testing will be identical to that of the primary hypothesis.

10.6.5 Safety analyses

Safety analyses will be conducted on the safety analysis set. The main safety analyses will compare descriptively between AE rates for Steal, Infection, Aneurysm and Seroma as described in section 10.2.2. That is, we will present point estimates along with Exact Binomial, two-sided, 95% confidence intervals for each of these events separately for both our study and Schinstock et al.
Additionally, descriptive statistics will be provided, with SAE's and AE's coded by body system, preferred term, arm, severity, relation to procedure by arm and outcome. Rate of freedom from major device-related adverse events will be provided along with associated two-sided 95% Exact Binomial confidence intervals.
In addition to the dichotomously scored endpoints we will also present frequency and percent for grade for steal (mild; moderate; severe), infection (resolved with antibiotic; loss of AV; loss of limb) and seroma (resolved without treatment; aspirated, surgical treatment; loss of AV access).

10.6.6 Secondary endpoints

Secondary endpoints will be considered exploratory and will be presented descriptively, along with associated 95% confidence intervals. The analysis sets for each endpoint are as follows:

1. Time to primary patency cessation since the fistula creation - *FAS primary and FAS secondary analysis sets*
2. Time to assisted primary patency cessation since the creation - *FAS primary and FAS secondary analysis sets*
3. Time to primary patency cessation since the first intervention (post-intervention primary patency) - *FAS primary and FAS secondary analysis sets*
4. Time to assisted primary patency cessation since the first intervention (post -intervention assisted primary patency) - *FAS primary and FAS secondary analysis sets*
5. Time to first successful cannulation – *Ongoing dialysis subset*
6. Time to secondary patency cessation since the fistula creation - *FAS primary and FAS secondary analysis sets*
7. Time to secondary patency cessation since the first intervention (post intervention secondary patency) - *FAS primary and FAS secondary analysis sets*
8. Time to fistula maturation (physiological) - *FAS primary and FAS secondary analysis sets*
9. Time to 100% functional fistula dependency – *Ongoing dialysis subset*
10. Unassisted maturation at 3 months defined as vein diameter ≥ 5mm and blood outflow ≥ 500 (-50) mL/min by Doppler ultrasound - *FAS primary and FAS secondary analysis sets*.

11. Primary patency at 6 months post AVF creation, excluding patients who have received balloon angioplasty procedures directed at cephalic arch and central vein stenosis *FAS primary and FAS secondary analysis sets*.
12. Time to first intervention - *FAS primary and FAS secondary analysis sets*
13. Number of interventions (including type and outcome) - *FAS primary and FAS secondary analysis sets*
14. Rate of interventions per patient-years - *FAS primary and FAS secondary analysis sets*
15. Primary Failure, at 6 months, which is fistula permanent failure before hemodialysis suitability - *FAS primary and FAS secondary analysis sets*
16. Target artery / target vein flow (mL/min) at 1, 3 and 6 months by Doppler blood outflow measurement - *FAS primary and FAS secondary analysis sets*
17. Target artery /target vein diameter at 1, 3 and 6 months by Doppler measurement - *FAS primary and FAS secondary analysis sets*.
18. Target artery / target vein PSV (Peak Systolic Velocity, cm/sec) - *FAS primary and FAS secondary analysis sets*
19. Proportion of fistulas used for hemodialysis at 3 and 6 months post AVF creation - *Any dialysis subset*.
20. Duration between fistula first use for dialysis and final abandonment – *any dialysis subset*

10.6.7 Sensitivity analyses

To assess the robustness of our results we will explore the effect of alternative imputations of missing data on the primary analysis. These include:

1) Best Case:
   All missing 6-month data are coded success (Primary Patency = 1).
2) Worst Case:
   All missing 6-month data (including those patients for whom there is no post-procedure Primary Patency measurement) are coded failure (Primary Patency = 0).
3) Tipping Point:
   Worst case imputations will be applied sequentially to missing cases until that point where the result becomes non-significant.

10.6.8 Covariate analyses

Covariate analyses for the dichotomous primary endpoint will be done using logistic regression, where the dependent variable is subject's score on the endpoint and independent variable is the covariate.

For the above we will be comparing device performance between levels defined on the covariate (e.g. male vs. female for the Gender covariate). It should be noted that much of the pertinent information will likely be obtained from descriptive statistics since this trial is not powered to demonstrate subgroup differences.

The following covariates will be tested:

- Gender
- Age
- Ethnicity
- Whether or not had previous fistula failure
- Dialysis status
- Diabetes
- Hypertension
- BMI
- Baseline artery/vein diameter

10.6.9 Poolability analyses

10.6.9.1 Poolability Analysis: Main vs. Supplementary Cohort

Poolability between the main and supplementary cohorts, with respect to the primary patency rate, will be checked on the FAS secondary analysis set. The poolability will be tested using logistic regression for observed data only. [redacted]

10.6.9.2 Site poolability analysis

Descriptive statistics for primary patency rate will be provided by site. Site poolability will be tested by logistic regression [redacted]

10.6.10 Interim analysis

There is no planned interim analysis.

11 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

11.1 Data collection

Electronic CRFs (eCRFs) using data capture will be utilized. Site staff will enter the information required by the protocol onto eCRFs using a validated software/database that conforms to FDA requirements for electronic data capture. All data fields will be completed. However, if data are not available (i.e., missed visit, etc.), the site will receive instruction regarding electronic documentation. As data are entered, automated cross-check programs will search for any data discrepancies in the

eCRFs. Appropriate error messages will be generated, allowing for the modification or verification of the entered data. Queries will generally be sent to the investigational site using an electronic data query system that includes an automated audit trail of the corrections.
Monitoring personnel of sponsor or its designee, will review the eCRFs for completeness and accuracy and will instruct site personnel to make any corrections or additions. The Investigator, or designee, will certify that the data are complete and accurate by applying an electronic signature to the eCRF. Any subsequent alterations, corrections, or additions will be reviewed and electronically signed by the Investigator prior to database lock.

11.2 Concomitant Medications

Concomitant medication will be recorded throughout the duration of the study. A baseline medication regimen for each patient will be determined during the screening visit, and subsequent changes will be recorded during each on-site follow-up visit (refer to Table 7-1 for procedures timeline). The baseline medication regimen will include all medications prescribed for the purpose of treating chronic conditions. During on-site follow-up visits the following will be recorded:

- Changes to the regimens of all medications listed in the baseline (e.g. dosage, frequency). Regimen changes will be recorded in the EDC in the following manner:

1. Enter an *end date* for the old regimen
2. Open a new medication record for the change in regimen
    - Medications administered to treat AE's/SAE's, in accordance with the AE reporting as described in sections 8.1 and 8.4.
    - New medications prescribed to treat chronic conditions.

11.3 Imaging and Core Lab

The following images will be collected and uploaded to MMI (Core lab service provider):

- Ultrasound DICOMS
- X-Ray DICOMS
- All DICOMS from endovascular procedures (Intervention / diagnostic)

Ultrasound scans will be conducted according to ultrasound instructions document (CL007).
X-Ray will be conducted according to X-Ray acquisition guidelines (CD-CA-0040, previously CL008).
All images will be transferred to MMI for storage and evaluation in accordance with the Image Transfer Protocol and will be stored in a validated, electronic database consistent with 21 CFR Part 11. Access to images and associated study data will be restricted to authorized personnel only.

11.4 Site qualification

A site visit will be performed by sponsor or designee prior to the start of the study to review the protocol in detail, to ensure the availability of appropriate trial personnel, adequate resources and to assess their ability to properly conduct the study according to ICH-GCP guidelines and local requirements.

11.5 Study monitoring and source data verification

The sponsor or designee will monitor the study to meet monitoring Standard Operating Procedures (SOPs), ICH-GCP guidelines, and applicable regulatory requirements and to ensure that study initiation, conduct, and closure are adequate.

11.6 Publication

The Sponsor and investigators plan to publish the outcomes of this study. Publication in writing and/or orally will take place after completion of the 6 months data collection and analysis or sooner if the study is terminated. Publication arrangements are detailed in the CTAs.

12 CLINICAL EVENTS COMMITTEE AND DATA SAFETY MONITORING BOARD

An independent clinical events/data safety committee will be formed to review abstracted clinical data and determine when the safety endpoints (steal, infection, aneurysm, seroma) have been met according to protocol definitions. The committee will comprise 3 physicians, who will not participate in the enrollment or treatment of subjects in this trial. In addition to the above listed safety endpoint components, all events of fistula failure and/or intervention will be reviewed by the committee and assessed for device relatedness. Any such event will trigger the accumulation of a portfolio of pertinent documents from the hospital admission. These documents will be collected and copies distributed to members of the CEC Committee. The interpretation of the event as classified and adjudicated by the clinical events committee will be used in the safety analysis.
In addition, the committee will review the progress of the trial following the enrollment of subjects and as requested on an ad hoc basis, to ensure that subject safety is not being compromised.