everlinQ endoAVF Post-Market Study

Study Protocol: CD-0018
Version 02
06-March-2018

Sponsor: TVA Medical, Inc.
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Austin, TX 78746

PROTOCOL SIGNATURE PAGE

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to ICH Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki 21CFR 50, 56 and 812, and any local regulations.

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Clinical Site Name (Print)

_____

Site Investigator Name (Print)

_____ _____

Site Investigator Signature **Date (mm/dd/yyyy)**

everlinQ endoAVF Post-Market Protocol Summary

Title	everlinQ endoAVF Post-Market Study
Study Device	Any commercially available everlinQ endoAVF System
Study Design	Prospective, multi-center post-market study to evaluate the everlinQ endoAVF System when used to create an endovascular arteriovenous fistula (endoAVF) for patients who require vascular access for hemodialysis.
Objective	Collect data in an observational study on outcomes of endovascular fistula creation using the everlinQ endoAVF System in the post-market setting where the System is available for use.
Enrollment	Up to 200 treated patients at up to 20 sites
Follow-Up	Up to 12 months
Outcome Measures	• Adverse events • Assisted primary patency • Duration of central venous catheter exposures • Functional patency • Intervention rate • Primary patency • Procedure success • Secondary patency • Time to endovascular fistula maturation
Inclusion Criteria	**Patients must meet all inclusion criteria:** 1. Adult (age >18 years old) 2. Currently on chronic dialysis, or expected to be started on chronic dialysis within 3 months of planned endoAVF creation 3. Target vein diameter(s) for fistula creation ≥ 2.0 mm via Duplex Ultrasound or Venogram 4. Target artery diameter(s) for fistula creation ≥ 2.0 mm via Duplex Ultrasound or Arteriogram 5. Both radial and ulnar artery flow to the hand, as confirmed with Duplex Ultrasound and/or Allen's test (i.e.: palmar arch)

Exclusion Criteria	**Patients will be excluded if <u>ANY</u> of the following criteria apply:** 1. Known central venous stenosis or central vein narrowing > 50% based on imaging on the same side as the planned AVF creation 2. Absence of perforator feeding the target cannulation vein(s) via venogram 3. Occlusion or stenosis >50% of target cannulation cephalic or basilic vein 4. Target cannulation vein that is <2.5 mm in diameter 5. Significantly compromised (≥50% stenosis) flow in the treatment arm as determined by physician and imaging ***NOTE:*** patients that have ≥50% arterial stenosis may undergo a Digital Brachial Index (DBI) test, if DBI result is <.65 patient is excluded 6. Documented ejection fraction (EF) ≤35% in the last 6 months 7. Pregnant women 8. New York Heart Association (NYHA) class III or IV heart failure 9. Hypercoagulable state 10. Known bleeding diathesis 11. Documented history of drug abuse including intravenous drugs within six months of AVF creation 12. "Planned" concomitant major surgical procedure within 3 months of enrollment or previous major surgery within 30 days of enrollment 13. Known allergy to contrast dye which cannot be adequately pre-medicated 14. Known adverse effects to sedation and/or anesthesia which cannot be adequately pre-medicated 15. Evidence of active infections on the day of the index procedure 16. Estimated life expectancy < 1 year 17. Patient is not willing to provide written informed consent, is not geographically stable and/or not willing to comply with required follow-up 18. Patient with a target cannulation vein that is > 6 mm deep that would require a transposition procedure, defined as the elevation of a target cannulation vein AND the creation of a new AV fistula 19. Patient is not willing to undergo a 2nd stage procedure as defined in Section 4.5.3 of this protocol	
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ABBREVIATIONS	
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
CEC	Clinical Events Committee
CKD	Chronic kidney disease
CMS	Center for Medicare and Medicaid Services
CVC	Central venous catheter
DBI	Digital brachial index
DUS	Duplex ultrasound
EC	Ethics Committee
eCRF	Electronic case report form
endoAVF	Endovascular arteriovenous fistula
EQ VAS	EQ visual analogue scale
ESRD	End stage renal disease
FFBI	Fistula First Breakthrough Initiative
HRQOL	Health Related Quality of Life
HTN	Hypertension
ICF	Informed consent form
IFU	Instructions for Use
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
QOL	Quality of Life
RF	Radiofrequency
SADE	Serious adverse device effect
SAE	Serious adverse event
SVS	Society for Vascular Surgery
USADE	Unanticipated serious device effect
USRDS	United States Renal Data System

DEFINITIONS	
Access site for cannulation	A vascular site, as a way to reach the blood for hemodialysis.
Access site for device	A site of catheters insertion during index procedure.
Angiogram	An X-ray procedure that uses contrast agent and a camera (fluoroscopy) to assess and capture flows or blockages in arteries and veins.
Assisted Primary Patency	The interval from access placement to thrombosis or abandonment; not triggered by access circuit interventions performed in the absence of occlusion.
Bleeding Diathesis	Is a disorder that involves the tendency to hemorrhage, or bleed. Hypercoagulability causes this condition. This condition is also known as bleeding tendency or predisposition.
Chronic Kidney Disease	An unusual susceptive condition due to hypercoagulability, usually caused by a defect in coagulation. A term that includes stages such as mild, moderate and severe loss of kidney function based on the patient's level of glomerular filtration rate (GFR).
Dialysis Patient	Patient who was receiving hemodialysis at the time of enrollment.
endoAVF abandonment – terminal use of endoAVF	The endoAVF is considered abandoned if any of the following occur: • The endoAVF is occluded and patency cannot be restored by any intervention, including medical, surgical, radiological or rest through the last follow-up. • The endoAVF is deemed inadequate for dialysis (for example, it never matures or is too deep for needle access) and the associated problem cannot be corrected by any intervention, including medical, surgical, radiological or rest. • The endoAVF is ligated. An endoAVF is not considered abandoned when it is not cannulated in subjects with a successful renal transplantation or when reasons of subject preference alone preclude cannulation.
End Stage Renal Disease	Last stage of Chronic Kidney Disease. When the kidneys stop working well enough to meet the needs of daily life.
Functional Cannulation	Defined as 2-needle access of the endoAVF access circuit with performance of ≥ 2/3rds of ≥ 120-minute dialysis sessions through the endoAVF access circuit over a continuous 28-day period.
Functional Patency	The interval of time from the first 2-needle dialysis utilizing the access until access abandonment.
Hypercoagulable State	Blood clotting disorder.

DEFINITIONS	
Intervention Rate	Rate of all interventions (and specific interventions) will be reported. All interventions that occur during the index procedure and during follow-up will be reported. • Interventions to maintain or restore patency of the endoAVF, including endovascular and surgical procedures designed to address occlusive thrombosis (resulting in absence of thrill or bruit at endoAVF) and clinically significant occlusive stenosis at or near endoAVF site. • Interventions to support maturation of the arterialized vein segments, including endovascular procedures such as secondary coil embolization to facilitate flow into the target cannulation veins. • Interventions to support cannulation of the arterialized vein segments, including procedures such as a superficialization or elevation where the target cannulation vein is brought closer to the skin surface to enable cannulation, without the creation of a new AV fistula. • Any intervention to address any complications or adverse events of the access circuit.
Maturation of endoAVF	Successful hemodialysis using 2- needle cannulation **OR** Vascular accesses that is free of stenosis or thrombosis, with brachial artery flow of at least 500 ml/min and at least a 4.0 mm vein diameter as measured via duplex ultrasound.
Maturation time	The number of days between the date of AVF creation and the date of endoAVF maturation (based on primary efficacy endpoint definition of maturation).
Occlusion	The blockage of a blood vessel.
Operator	Person who conducts index procedure.
Pre-dialysis Patient	Patient who was not receiving dialysis at the time of enrollment.
Primary patency	The interval from the time of access placement until any intervention designed to maintain or re-establish patency, access thrombosis, access abandonment, or the time of measurement of patency.
Procedure duration	The sum of the venography time, endoAVF creation time, coil and closure time.
Protocol deviation	Deviation from the approved Study Protocol.
Secondary Patency	The interval from the time of access placement until access abandonment, loss to thrombosis, or the time of patency measurement including intervening manipulations (surgical or endovascular interventions) designed to re-establish functionality in thrombosed access.
Stenosis	The abnormal narrowing of the blood vessel.
Thrombosis	The formation or presence of a blood clot within a blood vessel.
Venogram	An X-ray procedure that uses contrast agent and a camera (fluoroscopy) to assess and capture flows or blockages in veins.

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1 INTRODUCTION

End Stage Renal Disease (ESRD) currently affects over 2 million people worldwide.[1] It is projected that the worldwide incidence of ESRD will increase dramatically over the next 10 years, due to the increasing incidence of an aging population, diabetes, hypertension, and obesity.[2] Currently, Renal Replacement Therapy for patients with ESRD consists of either hemodialysis or peritoneal dialysis. The rates of implementation of either hemodialysis or peritoneal dialysis vary widely per country. According to the United States Renal Data System (USRDS), in 2006 hemodialysis accounted for around 60% of Renal Replacement Therapy patients in the US, while peritoneal dialysis accounted for 6-7% of patients in the US and the remainder is kidney transplant patients.[2]

Vascular access is a critical component in the care of patients undergoing hemodialysis. The three methods of long term vascular access available to a patient requiring hemodialysis are: an autogenous arteriovenous access or native arteriovenous fistula (AVF), a prosthetic arteriovenous graft (AVG) or a tunneled dialysis catheter.[3] The AVF has been shown to be superior to AVG and superior to catheter access in terms of both mortality and morbidity.[4,5] In fact, the focus of numerous initiatives worldwide has been to increase the implementation of AVF as the preferred method of vascular access in patients requiring hemodialysis. In 1997, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines were published to highlight the importance and to promote the increased placement of AVF.[6] These guidelines and subsequent versions have stressed the importance of proactive identification of patients requiring hemodialysis, and have described procedures and quality initiatives to maximize access longevity. In 2006, the updated KDOQI Guidelines recommended that AVF be constructed in at least 65% of prevalent hemodialysis patients.[7] In addition, the AV Fistula First Breakthrough Initiative (FFBI), a coalition lead by the Center for Medicare and Medicaid Services (CMS) has set a formal goal for AVF construction of 65% in prevalent patients by 2009.[8] The Society for Vascular Surgery (SVS) has also approved and sponsored initiatives around the development and publication of reporting standards for hemodialysis access and the development of practice guidelines for hemodialysis access.[9]

An AVF is traditionally created during a surgical procedure under general anesthesia. A surgical incision is made in the forearm or upper arm, followed by identification of target arteries and veins for surgical connection. Frequently, prior to the procedure, the vessels are mapped using duplex ultrasound imaging, allowing for pre-operative vessel diameter measurement and vessel selection. Typically, the radial artery or brachial artery and the cephalic vein or basilic veins are selected. The target vessels are carefully dissected and mobilized, and the vein is transected. An arteriotomy is created, and an anastomosis is sewn between the vein and the artery. After completion, the flow is verified using palpation and ultrasound, and the incision is closed. Over the course of the following 1 - 3 months, the AVF gradually matures, that is, the vein dilates and accepts increased flow sufficient for hemodialysis.

Though there is widespread agreement that the AVF is the preferred method of vascular access, 28 – 60% of AVFs do not successfully mature and are rendered unusable for hemodialysis.[10, 12] This has unintended consequences for patients in immediate need of hemodialysis, since a tunneled dialysis catheter must often be placed. Catheters are associated with higher morbidity, mortality, and costs and are therefore considered a last resort.[11]

To improve on these results, and decrease the invasiveness of the procedure, a new tool and method for creation of an AVF has been developed, called everlinQ endoAVF System. The system uses two devices, one inserted into an artery and the other inserted into a closely-positioned vein. The devices contain magnets that bring a pair of electrodes into alignment. Radiofrequency energy is delivered to the electrodes, cutting and/or coagulating the tissue between the electrodes, creating an endovascular arteriovenous fistula (endoAVF). The procedure is facilitated using fluoroscopy and ultrasound imaging, to assist in vessel selection and to verify creation of the AVF. Because the vessels are not dissected and not mobilized, leaving the surrounding tissues intact, the vessels do not need to be sewn together with a traditional surgical technique. This proposed method may facilitate the creation of AVF, while reducing the trauma to the vessel wall potentially leading to reduction in future venous stenosis thought to arise from surgical trauma. In particular, the goal is to reduce the surgical manipulation of the blood vessels, particularly the veins in the arm, which typically exhibit intimal hyperplasia in surgical AVF. Intimal hyperplasia is believed to be a root cause of failure in surgical AVF and AVG, and this technology and method may help improve the patency and maturity of AVF in patients with ESRD.

The family of everlinQ endoAVF Systems manufactured by TVA Medical, titled the everlinQ endoAVF System (e.g., everlinQ endoAVF System, everlinQ S endoAVF System, everlinQ endoAVF 4 System, etc.). Any commercially available system (i.e., system that received CE mark) may be introduced into the study. This clinical study is being conducted to gather information on endovascular fistula creation using the everlinQ endoAVF Systems.

2 DEVICE DESCRIPTIONS

Any of the everlinQ endoAVF Systems, include a single-use disposable device that consists of two (2) flexible, magnetic catheters. One (venous) catheter contains an electrode to deliver radiofrequency (RF) energy and a second (arterial) catheter. Once the catheters are properly inserted and aligned, the magnets contained in each catheter attract to one another, approximating the vessels. RF energy is delivered to the electrode whereby the AVF is created.

For additional details regarding the device or its principle of operation, please refer to the most current Instruction for Use (IFU) for the appropriate system selected for use as described above. For clarity and consistency, the study device will remain referenced as “everlinQ endoAVF System”.

3 RISKS/BENEFITS

3.1 Benefits

The everlinQ endoAVF System may facilitate a less-invasive and more reproducible AVF procedure while minimizing surgical incisions as compared to conventional surgical AVF creation. This endovascular approach may lower the risk of procedural infections as compared to surgical AVF creation. Due to the less-invasive nature of the procedure with the everlinQ endoAVF System, the endoAVF may exhibit improved maturation and patency characteristics compared to historical maturation and patency data. In addition, patient recovery time may be decreased, and anesthesia may be minimized compared to a conventional surgical AVF procedure.

3.2 Risks

Most of the potential risks and complications associated with the everlinQ endoAVF System and procedure are similar to the risks expected for Chronic Kidney Disease (CKD) patients undergoing surgically created AVF or AVG procedures. The potential risks related to the everlinQ endoAVF Systems and procedure include but are not limited to:

- Aborted or longer procedure
- Additional procedures (interventions)
- Bleeding, hematoma (a solid swelling of clotted blood within the tissues) or hemorrhage (an escape of blood from a ruptured blood vessel)
- Bruising
- Burns
- Compartment syndrome (excessive bleeding, a hematoma that worsens and causes increased pressure in a muscle compartment within the access arm)
- Death (mostly due to CKD related complications not the everlinQ endoAVF device or procedure)
- Electrocution
- Embolism (blood clot or device piece)
- Failure to mature (AVF can never be used)
- Fever (pyrogenic reaction)
- Heart problems such as arrhythmias (abnormal beats) that can be caused due to high levels of potassium in the blood (mostly due to CKD and not the everlinQ endoAVF device or procedure)
- Increased risk of congestive heart failure (heart fails due to increased flow from AVF)
- Infection (local or in the blood (bacteremia))
- Numbness, tingling and/or coolness in the fistula extremity
- Occlusion
- Problem due to sedation or anesthesia
- Pseudoaneurysm (leaking hole in artery that forms blood clot on outside of it)
- Sepsis (systemic inflammatory reaction)
- Steal syndrome or ischemia (not enough blood flow to hand)
- Stenosis
- Swelling, irritation or pain
- Thrombosis
- Toxic or allergic reaction
- Venous hypertension (arm swelling)
- Vessel, nerve or AVF damage or rupture
- Wound problem

Cannulation risks that may occur in endo AVF are similar to the cannulation risks expected for patients undergoing surgically created AVF or AVG procedures. (e.g., fistula infiltration injury due to needle cannulation, clotting, etc.)

There may also be other potential risks related to use of the everlinQ endoAVF System and procedure that are unforeseen at this time.

3.3 Minimization of Risk

To minimize the risks, the everlinQ endoAVF Systems have undergone pre-clinical testing and clinical testing. In addition, all Investigators participating in this clinical trial will be trained on the everlinQ procedure which will contribute to minimizing risks associated with the use of the device.

Qualified physicians trained on the study protocol will also utilize the established eligibility criteria to select appropriate patients to participate in the study.

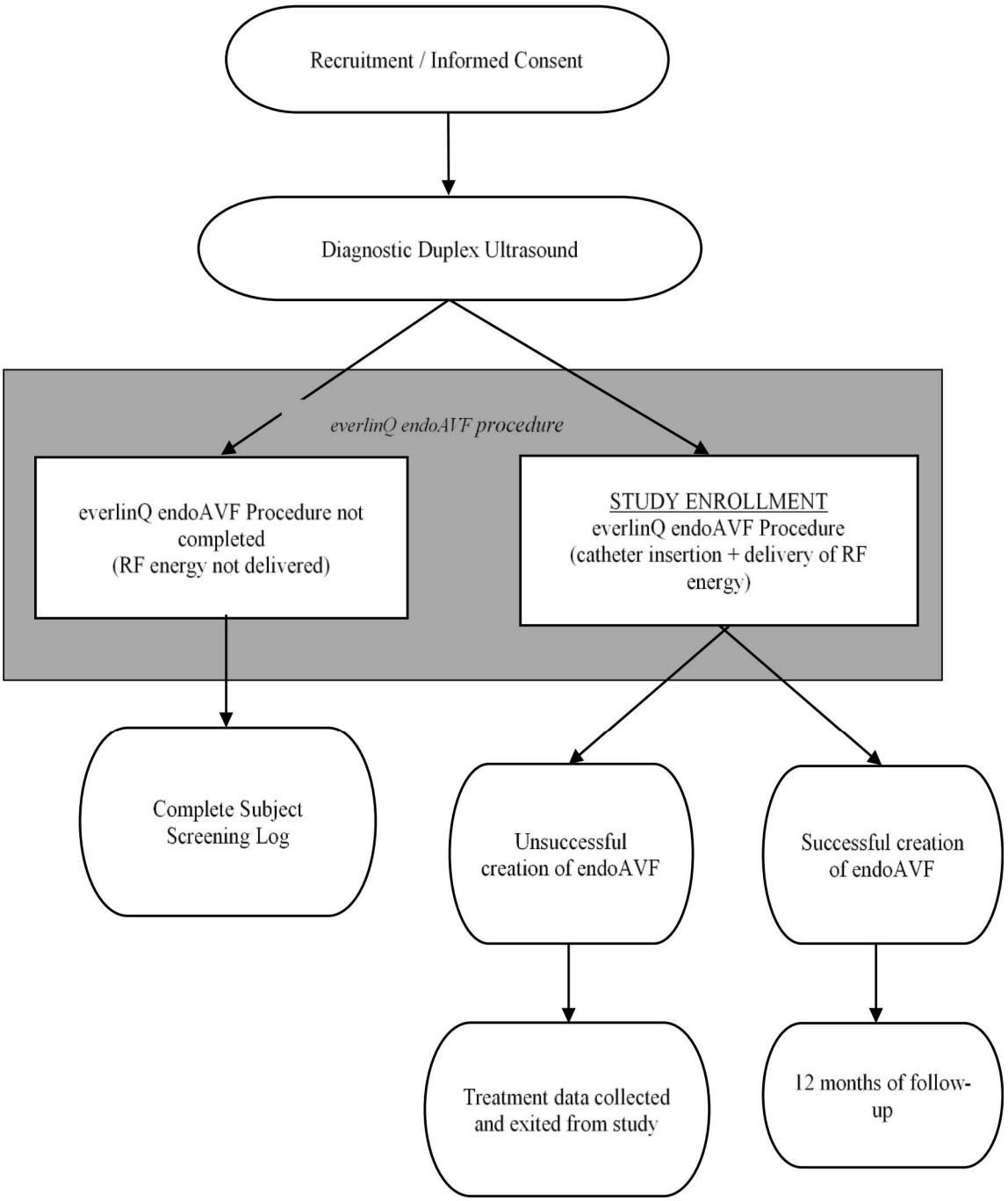
4 STUDY METHODOLOGY

4.1 Study Design

This is a prospective, multi-center study to evaluate the everlinQ endoAVF System when used to create an endoAVF for patients who require vascular access for hemodialysis. This study is a post-market study, and will be available to sites in selected regions where the product is available for use and properly registered or licensed (i.e. CE Mark, Health Canada License).

The study may have up to 20 active sites participating in order to enroll up to 200 patients that undergo endoAVF creation with the everlinQ endoAVF System. All patients who meet study inclusion criteria and no exclusion criteria will be considered a study candidate. Study candidates who undergo the everlinQ procedure (catheter insertion and delivery of RF energy) will be enrolled in the study. Study candidates who do not undergo the everlinQ procedure will be treated per physician and hospital guidelines and will not be considered enrolled in the study. All enrolled patients are expected be followed up to 12 months. Refer to Figure 1 for a flowchart overview of the study, and Table 2 for Withdrawal and Follow-Up Requirements.

Figure 1: Study Flowchart



4.2 Study Objective

Collect data in an observational study on outcomes of endovascular fistula creation using the everlinQ endoAVF System in the post-market setting where the System is available for use. Data collected in the study may support future reimbursement and publications.

4.3 Study Outcome Measures

All patients enrolled in the study and do not have a renal transplant, will be included in these outcome measurements unless otherwise noted.

Primary Patency: The interval from the time of access placement until any intervention designed to maintain or re-establish patency, access thrombosis, access abandonment, or the time of measurement of patency.

- **endoAVF abandonment definition:**

The endoAVF is considered abandoned if any of the following occur:

- The endoAVF is occluded and patency cannot be restored by any intervention, including medical, surgical, radiological or rest through the last follow up;
- The endoAVF is deemed inadequate for dialysis (for example, it never matures or is too deep for needle access) and the associated problem cannot be corrected by any intervention, including medical, surgical, radiological or rest;
- The endoAVF is ligated.

An endoAVF is not considered abandoned when it is not cannulated in subjects with a successful renal transplantation or when reasons of subject preference alone preclude cannulation.

Assisted Primary Patency: The interval from access placement to thrombosis or abandonment; not triggered by access circuit interventions performed in the absence of occlusion.

Secondary Patency: The interval from the time of access placement until access abandonment, loss to thrombosis, or the time of patency measurement including intervening manipulations (surgical or endovascular interventions) designed to re-establish functionality in thrombosed access.

Functional Patency: The interval of time from the first 2-needle dialysis utilizing the access until access abandonment.

Procedure Success: The successful creation of an endoAVF with blood flow confirmed intraoperatively by fistulography or by duplex ultrasound postoperatively.

Time to Endovascular Fistula (endoAVF) Maturation (Vascular Access Usability): Total time (number of days) from successful endoAVF creation to one of the following:

- Successful hemodialysis using 2 needle cannulation ***OR***
- Vascular accesses that is free of stenosis or thrombosis, with brachial artery flow of at least 500 ml/min and at least a 4.0 mm vein diameter as measured via duplex ultrasound.

Time to Cannulation: The time (number of days) from the index procedure (successful endoAVF creation) to the first use of the endoAVF for cannulation will be reported.

Number of Patients Who Met Functional Cannulation: Functional Cannulation is defined as 2-needle access of the endoAVF access circuit with performance of ≥ 2/3rds of ≥ 120 minute dialysis sessions through the endoAVF access circuit over a continuous 28-day period.

Central Venous Catheter (CVC) Exposure: CVC exposure will be analyzed at the follow-up time points, presenting the number/percent of patients reporting CVC use and the number/percent reporting dialysis access through other means, as well as the number/percent of subjects not yet on dialysis.

Adverse Events: Rate of serious procedure or device related Adverse Events (AEs) throughout the study period. The relevant events and rates of occurrence will be analyzed with a time component, to analyze procedural AEs and post-procedural AEs.

Intervention Rate: The percentage of patients requiring intervention will be calculated at 3, 6 and 12 months follow-up visits post index procedure. The rate of interventions that occurred during the index procedure and during short term follow-up will also be calculated.

The endoAVF-related interventions include:

- Interventions to maintain or restore patency of the endoAVF, including endovascular and surgical procedures designed to address occlusive thrombosis (resulting in absence of thrill or bruit at endoAVF) and clinically significant occlusive stenosis at or near endoAVF site.
- Interventions to support maturation of the arterialized vein segments, including endovascular procedures such as secondary coil embolization to facilitate flow into the target cannulation veins.
- Interventions to support cannulation of the arterialized vein segments, including procedures such as a superficialization or elevation where the target cannulation vein is brought closer to the skin surface to enable cannulation, without the creation of a new AV fistula.
- Any intervention to address any complications or adverse events of the access circuit.

Note: Any additional procedure performed at the time of the index procedure to address an adverse event will require a Post-Procedure Intervention eCRF to be completed.

Note: Diagnostic fistulagram, angiogram or duplex ultrasound will not be considered an intervention for the purpose of this study.

4.4 Site Selection

Investigational sites selected to participate in this clinical study will be dependent on the Investigator at the site having the necessary resources to fulfill the clinical research requirements outlined in the protocol. These resources include adequate patient population, facilities and support staff to perform the clinical evaluation according to all applicable requirements. Sites must reside in a region or country where the System is available for use and properly registered or licensed (i.e. CE Mark, Health Canada License).

4.5 Study Population

Candidates for this trial are patients being evaluated for placement of vascular access for chronic hemodialysis. Only patients meeting all of the inclusion and none of the exclusion criteria who signed the Informed Consent Form (ICF) may be considered for participation.

4.5.1 Inclusion Criteria

1. Adult (age >18 years old)
2. Currently on chronic dialysis or expected to be started on chronic dialysis within 3 months of planned endoAVF creation. Target treatment vein diameter(s) for fistula creation ≥ 2.0 mm as measured via Duplex Ultrasound or Venogram
3. Target treatment artery diameter(s) for fistula creation ≥ 2.0 mm as measured via Duplex Ultrasound of Arteriogram
4. Both radial and ulnar artery flow to the hand, as confirmed with Duplex Ultrasound and/or Allen's test (i.e.: palmar arch)

4.5.2 Exclusion Criteria

1. Known central venous stenosis or central vein narrowing > 50% based on imaging on the same side as the planned AVF creation
2. Absence of perforator feeding the target cannulation vein(s) via Venogram
3. Occlusion or stenosis >50% of target cannulation cephalic or basilic vein
4. Target cannulation vein that is <2.5 mm in diameter
5. Significantly compromised (≥50% stenosis) flow in the treatment arm as determined by physician and imaging
   NOTE: patients that have ≥50% arterial stenosis may undergo a Digital Brachial Index (DBI) test, if DBI result is <.65 patient is excluded
6. Documented ejection fraction (EF) ≤35% in the last 6 months
7. Pregnant women
8. New York Heart Association (NYHA) class III or IV heart failure
9. Hypercoagulable state
10. Known bleeding diathesis
11. Documented history of drug abuse including intravenous drugs within six months of AVF creation
12. "Planned" concomitant major surgical procedure within 6 months of enrollment or previous major surgery within 30 days of enrollment
13. Known allergy to contrast dye which cannot be adequately pre-medicated
14. Known adverse effects to sedation and/or anesthesia which cannot be adequately pre-medicated
15. Evidence of active infections on the day of the index procedure
16. Estimated life expectancy < 1 year
17. Patient is not willing to provide written informed consent, is not geographically stable and/or not willing to comply with required follow-up
18. Patient with a target cannulation vein that is > 6 mm deep that would require a transposition procedure, defined as the elevation of a target cannulation vein AND the creation of a new AV fistula
19. Patient is not willing to undergo a 2nd stage procedure as defined in Section 4.5.3 of this protocol

4.5.3 2nd-Stage Procedure

Study patients may require secondary procedure(s), also known as 2nd-stage procedures. These are procedures that are performed AFTER the endoAVF index procedure. Such procedures are considered interventions and require completion of the Post-Procedure Intervention eCRF. These procedures may include but are not limited to the following:

- Procedures to support maturation of the arterialized vein segments (i.e. secondary coil embolization);
- Procedures to support cannulation of the arterialized vein segments (i.e. elevation or superficialization of a target cannulation vein);
- Procedures to maintain or restore patency of the AVF (i.e. balloon angioplasty).

5 STUDY SCREENING AND FOLLOW-UP PROCEDURES

Patients are required to undergo a thorough screening evaluation prior to the index procedure and return for evaluations according to the study follow-up schedule. Table 5-1: Schedule of Study Procedures outlines the required testing and follow-up required for each study interval. Study data will be collected on electronic case report forms (eCRFs) provided by the Sponsor.

Table 5-1: Schedule of Study Procedures

Assessment	Screening	Index Procedure	Post Index Procedure				
			0-10 Days *Visit 1*	1 Month *Visit 2*	3 Month *Visit 3*	6 Month *Visit 4*	12 Month *Visit 5*
Compliance Window	-60 days	day 0	0-10 days	21-45 days	Anniversary date +14 days		
Informed Consent	**X**						
History, Physical Exam, Pregnancy Test	**X**						
Blood Pressure	**X**	**X**	**X**	**X**	**X**	**X**	**X**
HTN Medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**
DUS Evaluation	**X**	**X**[1]	**X**	**X**	**X**	**X**	**X**
Angio/Venography		**X**					
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**
Allen's Test /Palmar Arch	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Dialysis Access Data				**X**[2]	**X**[2]	**X**[2]	**X**[2]
QOL Questionnaire	**X**				**X**	**X**	**X**

[1] Recommended post-procedure to confirm absence of bleeding or hematoma formation
[2] All efforts by the site must be undertaken to provide this data to the sponsor, minimally over a continuous 28-day period.

5.1 Informed Consent

Prior to any non-standard-of-care procedures, the patient must sign the Informed Consent Form (ICF) approved by the Ethics Committee (EC). All patients will be informed in detail about the nature of the clinical investigation, as well as its risks, potential benefits, and any anticipated discomforts. The Investigator or assigned designee must administer the ICF to each prospective study patient, and obtain the patient's signature or a legally authorized representative signature along with the date of consent. Proper informed consent should be obtained in accordance with local/country guidelines as needed.

5.2 Screening Evaluation

All patients considered for enrollment must undergo a thorough screening evaluation prior to the scheduled vascular access creation procedure. The screening evaluation includes:

- Collection of demographic data;
- A medical history and physical exam;
- A duplex ultrasound and optional angiography/venography assessment;
- Pregnancy test (if of child bearing potential (urine or blood))

There will be a final determination of the patient's study eligibility due to vascular anatomy made at the time of the index procedure and thus, there may be some consented patients who are determined to be ineligible to participate in the study thus who will not undergo the everlinQ endoAVF procedure. All patients that sign the study ICF and do not undergo the everlinQ procedure will be considered screen failures.

The status of all patients screened should be captured on the study Subject Screening Log for tracking and reporting purposes.

5.2.1 Duplex Ultrasound

A duplex ultrasound (DUS) assessment of the flow rates and inner diameters of the arteries and veins of the target vessels must be performed per the study Duplex Ultrasound Guidelines. Sites should ensure that only DUS operators who are trained on the protocol and DUS guidelines are performing these tests.

5.3 Medications

There are no required medications in the study however, it is recommended that an antiplatelet medication be administered as a loading dose prior to the study procedure and continue daily for at least 1-month post study procedure.

A Medication Log (eCRF) will be completed and maintained from Screening through 12 month follow up on the use of Hypertension Medications.

5.3.1 Intra-Procedure

All patients must receive adequate anticoagulation according to hospital standard practice. It is recommended that an activated clotting time (ACT) test be administered after the initial dose of anticoagulant therapy to verify an ACT $\geq$ 225 seconds prior to the insertion of the study device.

5.3.2 Study Procedure

If a study candidate presents for the index procedure with any medical condition that precludes treatment, the procedure should be delayed until the infection or medical condition is treated and resolved.

The everlinQ endoAVF System should be used per package labeling and the most current Instruction for Use (IFU) for the system selected. Procedural steps for the everlinQ procedure are outlined in the specific IFU and supporting training materials. All elements of the procedure are consistent with other endovascular procedures.

Only about 10cc of diluted contrast agent is required for the entire everlinQ procedure which is similar to other AVF interventions performed on pre-dialysis patients. Alternatively, CO_2 contrast can be used for venography/angiography as determined by the treating physician.

5.3.3 Post-Treatment

After the treatment with the everlinQ endoAVF system, the arterial and venous puncture sites should be closed per standard hospital procedures, and it is recommended that manual compression is held for 20 minutes.

Note: TVA Medical does not recommend the use of arterial closure devices to obtain hemostasis in subjects treated with the everlinQ system.

5.4 Follow-Up Visits

All enrolled patients that undergo a successful endoAVF creation will return for follow-up at 0-10 days post index procedure, then again at 21-45 days, 3, 6, and 12 months post index procedure. Refer to Table 1 for required testing at each follow-up visit.

5.4.1 Dialysis Access Data

Once hemodialysis is first initiated via the endoAVF (1 or 2- needle cannulation), detailed dialysis access data will be collected until 2/3 of the dialysis sessions are successfully performed using the endoAVF with 2- needle cannulation for over a continuous 28-day period.

5.5 Unscheduled Visit

In addition to scheduled follow-up visits, the patient should be instructed to contact the Investigator at any time during the follow-up period if he/she has questions or concerns relating to the procedure or the vascular access. If the patient returns to the clinic for evaluation related to his/her participation in the study between scheduled follow-up visits (i.e., not a study required visit):

- No adverse events noted during unscheduled visit – no forms need to be completed.
- Adverse event noted – The Adverse Event (AE) eCRF is required to be completed for each event.
- Intervention to maintain or restore patency of the fistula, to support maturation of the arterialized vein segments, or to support cannulation of the arterialized vein segments – the Post-Procedure Intervention eCRF must be completed.

The patient will still be required to return for the next scheduled follow-up visit if the unscheduled visit is out of the compliance follow-up window.

If the patient is treated by a health-care professional other than the Investigator for treatment-related complications, the Investigator must request copies of the medical records and, if necessary, complete the appropriate eCRFs.

5.6 Lost to follow-up

If an enrolled patient fails to comply with follow-up evaluations and misses two (2) consecutive follow-up visits with failure of all contact attempts, the patient may then be considered lost to follow-up and exited from the study. Please contact TVA Medical to discuss any patients who

may be lost to follow-up, prior to exiting the patient from the study. Data collected prior to the study exit will be included in the analysis. All missed follow-up visits must be documented on a Protocol Deviation eCRF.

5.7 Patient Withdrawal from the Study

Patients can voluntarily withdraw from the study at any time for any reason; the reason for withdrawal will be documented on the End of Study eCRF. All available data at the time of withdrawal (if any) will be used for analysis. Table 5-2: Withdrawal and Follow-Up Requirements summarizes the required actions and follow-up for patients who may have to be withdrawn from the study for varied reasons.

Table 5-2: Withdrawal and Follow-Up Requirements

If	Action Item
ICF was signed and the study catheter was not inserted.	The patient is not considered enrolled. Complete the Subject Screening Log as a screen failure.
The study catheter was inserted but RF energy was not delivered and therefore, the patient did not undergo endoAVF procedure (e.g., index procedure was aborted or converted to other surgical methods for AVF creation).	The patient is not considered enrolled. Complete the Subject Screening Log as a screen failure.
The study catheter was inserted and RF energy was delivered but the endoAVF was not created, with or without a reportable adverse event(s).	Patient is considered enrolled. Follow patient until protocol reportable AE resolves. Collect all baseline-procedure and adverse event data and exit the patient (end date = date of AE resolution).
The study catheter was inserted and RF energy was delivered and endoAVF was successfully created.	Patient is considered enrolled. Follow all required visits per Study Protocol.
endoAVF was successfully created (patient enrolled) and there is a permanent loss or abandonment of the endoAVF	Patient participation ends. Complete Follow up forms as appropriate until loss of endoAVF, then complete an End of Study eCRF.

5.8 End of Study

The End of Study eCRF is required to be completed whenever a patient exits the study. This includes patients enrolled in the study who:

- Complete the study protocol, after 12 months of follow up
- Voluntarily withdraw from the study
- Withdrawn by the study Investigator
- Met the definition of endoAVF abandonment (see Section 4.3)
- Lost to follow-up
- Deceased
- Other reason(s) for exiting the study

6 ADVERSE EVENTS

An Adverse event (AE) will be defined as any adverse medical change (i.e., *de novo* or increased severity in a preexisting condition) from the patient's baseline condition that occurs during the course of the clinical study, after starting treatment, whether considered treatment-related or not. "Treatment" includes all commercially-approved products administered according to the study protocol and specific Instruction for use (IFU) documents.

Any pre-planned procedures (refer to Section 4.5.3- 2nd-Stage Procedures), or additional interventions, will not be considered AEs for this study. In addition, normally expected symptoms caused by the treatment that do not prolong or affect patient discharge, or are managed with observation alone and do not require intervention (e.g., medical, endovascular, surgical) are not considered an AE for this study.

These may include but are not limited to:

- Transient arterial spasm resolving spontaneously OR with medication only
- Minor discomfort or bruise at the arterial access site
- Small amount of bleeding at point of arterial access
- Transient numbness, tingling or coolness that resolved within 4 weeks post index procedure
- Bruising at the AVF creation site
- Side effects of standard-of-care medications
- Hematoma at the arterial and/or venous access site(s) and did not require endovascular or surgical intervention nor adversely affected discharge.

Only AEs that are relevant to index procedure, study device, access site or the endoAVF will be collected in the study. For example, if the subject has knee replacement or undergoes a hysterectomy, these events will be considered as non-study related and will not be required to be recorded via Adverse Event eCRF.

Table 6-1: Adverse Event Type

AE Type	Definition

Serious Adverse Event (SAE)	AE that:
	• led to death,
	• led to serious deterioration in the health of the patient, that either resulted in:
	  ○ a life-threatening illness or injury, or
	  ○ a permanent impairment of a body structure or a body function, or
	  ○ in-patient or prolonged hospitalization, or
	  ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
	• led to fetal distress, fetal death or a congenital abnormality or birth defect

Adverse Device Effect (ADE)	AE related to the use of study device. ***NOTE:*** *This definition includes **adverse events** resulting from insufficient or inadequate IFU, deployment, installation, operation, or any malfunction of the study device. In addition to **any event** resulting from use error or from intentional misuse of the study device.*

Serious ADE (SADE)	ADE that has resulted in any of the consequences characteristic of a SAE.
Unanticipated SADE (USADE)	USADE which by its nature, incidence, severity or outcome *has not* been identified in the current version of the study protocol, IFU, or other study documentation.

6.1 Relationship to Device or Procedure

The Investigator will also evaluate the relationship of the adverse event to the everlinQ endoAVF System or procedure according to the following definitions:

Definite (YES): The AE follows a reasonable timing from treatment (or attempted treatment) with the device and the possibilities of factors other than the device or the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded. This includes an AE that occurs during the index (endoAVF creation) procedure.

Probable (YES): The AE follows a reasonable timing from treatment (or attempted treatment) with the device and the probability of device or procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment may be possible.

Unlikely (NO): The AE follows an unlikely timing relationship from treatment (or attempted treatment) or is more likely due to other factors and there is no definitive information suggesting that it was related to the device or procedure.

Not Related (NO): The AE has no timing relationship from treatment (or attempted treatment) or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

The Investigator will evaluate the relationship to the everlinQ device portion of the procedure using the yes/no definitions above. The everlinQ device portion of the procedure only includes insertion, deployment and removal of the everlinQ catheters.

All reported adverse events will be reviewed and adjudicated by an independent Clinical Events Committee (CEC).

7 DATA ANALYSIS

The study will be observational in nature and will not involve the formulation or statistical testing of study hypotheses.

Variables that are categorical in nature (such as gender) will be summarized by frequencies and percentages while those that are continuous in nature (such as age) will be summarized by the mean, standard deviation, minimum and maximum values. Continuous variables that appear not to be normal in distribution will also be described by the median value.

Variables involving time (such as primary patency) will be analyzed using the Kaplan-Meier product limit approach. This approach yields cumulative probabilities of having an endoAVF for a given period of time without the occurrence of some specified terminal event, such as endoAVF thrombosis. The analysis requires both a time variable and a variable indicating whether or not the event of interest has occurred. Results of these analyses will be presented both graphically and in tabular form.

8 REGULATORY OBLIGATIONS

8.1 Responsibilities of the EC/EC Approval

Each site must obtain EC approval and any other regulatory agency's approval as required by local or country guidelines prior to study initiation. A copy of the approval notification and the approved study specific patient informed consent must also be kept on file at the site and a copy provided to Sponsor prior to the enrollment of patients. If applicable, written EC approval of any patient's information materials or any advertisement must also be attained prior to their use.

8.2 Sponsor Obligations

The Sponsor must assume responsibilities that are not limited to the following:

- Provide the Investigator with the necessary information (protocol and IFU) and training required to conduct the investigational study
- Inform study Investigators of any new information
- Conduct an evaluation of any USADE and report the result of such evaluation to all reviewing ECs and all participating Investigators within 10 working days of first receiving notice of the event.

8.3 Clinical Events Committee (CEC) Obligations

The CEC will be an independent group of physicians experienced in vascular access that will be responsible for the review and adjudication of the adverse events.

8.4 Investigator Obligations

Upon signing the Study Agreement, the Investigator agrees to assume the following responsibilities, to keep the required records, and to file the required reports in a timely manner.

The Investigator agrees to:

- Conduct the investigation in compliance with the signed agreement, study protocol, and applicable regulations. Changes to the protocol will only be made after approval by the sponsor and the reviewing EC, or when necessary to protect the safety, rights or welfare of a patient.
- Conduct the investigation in compliance with the EC and other applicable Regulatory agencies.
- Personally, conduct or supervise the investigation.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.
- Protect the rights, safety and welfare of research patients. All patients must be informed that the device is being used for investigational purposes.
- Assure initial and continuing review of the investigation by an EC.

8.4.1 Investigator's Documents

The following documents will be provided to the study Sponsor by the Investigator prior to initiation of the study.

- A signed and dated Study Agreement.
- Current (within one year) curriculum vitae of the Principal Investigator and all Co-Investigators.
- A copy of the approval letter by the EC for the study protocol and the ICF.

8.5 Records and Reports

All records and reports pertaining to this protocol are subject to inspection by regulatory agencies and must be retained for at least two years after the date on which the study is terminated or completed or for two years after the date that the records are no longer required for the purpose of supporting an application to regulatory agencies for commercial approval of the therapy/claims, or per local regulations, whichever is later.

8.5.1 Investigator's Reports

The Investigator is responsible for the preparation and submission of the reports listed in Table 8-1: Investigator Reports.

Table 8-1: Investigator Reports

Report	Submitted To	Description
Unanticipated Serious Adverse Device Events and Serious Adverse Device Effects	Sponsor & EC	The Investigator's report on any unanticipated serious adverse device event (USADE) or serious adverse device effect (SADE) must be submitted within 10 working days after the Investigator first learns of the event.
Deviations from study protocol		All deviations must be documented on a Protocol Deviation Form.
Serious Adverse Events	Sponsor	The Investigator's report on any Serious Adverse Events (SAEs) must be submitted within 10 working days after the Investigator first learns of the event
Withdrawal of EC approval		The Investigator must report a withdrawal of reviewing EC approval within 5 working days.

8.5.2 Sponsor's Reports

Sponsor is responsible for the preparation and submission of the reports listed in Table 8-2: Sponsor Reports.

Table 8-2: Sponsor Reports

Report	Submitted To	Description
Unanticipated Serious Adverse Device Effects (USADE)	EC & Investigators	Sponsor will report on any unanticipated serious adverse device effect evaluation within 10 working days after receiving notice of the effect.
Notification of Termination or Completion		Notification will be made within 30 working days of completion or termination of the investigation.

8.6 Site Training

Sponsor representative(s) will be responsible for site personnel training to ensure that all site personnel have a thorough understanding of the protocol, case report forms and associated study requirements.

A Sponsor's representative(s) will meet with the Investigator at each study site prior to the enrollment of patients for the purpose of reviewing and discussing the protocol and supporting documentation to assure total understanding of the requirements involved in performing the clinical evaluation.

8.7 Protocol Deviations

A Protocol Deviation eCRF must be completed for each deviation from the study protocol that occurred at the site (e.g., failure to obtain informed consent, enrolling a patient who does not meet inclusion/exclusion criteria, not performing required testing, repeatedly missed DUS measurements, missed follow-up visits, etc.).

8.8 Site Non-Compliance

Repeated serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations is noted, the Sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations.

8.9 Electronic Case Report Form (eCRF) Completion

All required clinical data for this study will be collected in web-based eCRFs. All data collected in the study must be supported by source documentation. Source documentation may include, but not necessarily be limited to: patient medical record notes, patient history questionnaires, physical examination forms, DUS data, radiology reports, operative summaries or other documentation that is pertinent to the patient's participation in the study. In addition to existing patient records, eCRF worksheets for the study may be used to directly record study data and serve as source documentation.

8.10 Monitoring Procedures

The Sponsor or a Sponsor representative will monitor the progress of the study as required by GCP. The study data will also be monitored. The Sponsor will request the source documents to be submitted in de-identified manner (patient's name and other personal identifiers must be removed and replaced with the study patient identification (ID) number). These source documents may include but not limited to:

- Admission, procedural and discharge reports/notes
- Any documentation relevant to SAE and procedure and device-related AEs

Monitoring will be performed by qualified and appropriately trained monitors onsite and/or remotely. The monitors may be Sponsor's employees or Sponsor's representatives.

On-site visits may be performed as needed based on enrollment, data integrity and site compliance (e.g. repeated and serious non-compliance by the site, such as significant number of data queries at the site, etc.). Each remote and on-site monitoring visit will be documented.

REFERENCES

1. "ESRD 2005 – A Worldwide Overview" Wolfgang Meichelboeck, 4th International Congress of the Vascular Access Society, Berlin, Germany, 2005. www.vascularaccesssociety.com
2. United States Renal Data System (USRDS) 2008 Annual Report.
3. Sidway, A.N. et al. Recommended standards for reports dealing with arteriovenous hemodialysis access. J. *Vasc. Surgery* Vol 35(3): 603-610 March 2002.
4. Xue, J.L. et al. The association of initial hemodialysis type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Disease* Nov;42(5): 1013-9, 2003.
5. Dhingra, R.K. Type of vascular access and mortality in U.S. hemodialysis patients *Kid Int* Vol 60: 1443-1451, 2001.
6. National Kidney Foundation. KDOQI guidelines. http://www.kidney.org/professionals/KDOQI/ guideline_upHD_PD_VA/index.htm. Accessed: Aug 30, 2009.
7. National Kidney Foundation KDOQI 2006 Vascular Access Guidelines. *Am J Kidney Disease* 2006:48(suppl 1):S177-322.
8. Fistula First National Vascular Access Improvements Initiative. Available at: http://www.fistulafirst.org/. Accessed August 30, 2009.
9. Sidway A.N. et al. The Society for Vascular Surgery: Clinical practice guidelines for surgical placement and maintenance of arteriovenous hemodialysis access. *J Vasc Surgery* Vol 48(5S): 2S-25S, 2008.
10. Asif, Roy-Chaudhury, Beathard, G. Early Arteriovenous Fistula Failure: A Logical Perspective of How and Why to Intervene. *Clin J Am Soc Nephrol* 1: 332–339, 2006.
11. Schwab, J., Beathard, G. The hemodialysis catheter conundrum: Hate living with them, but can't live without them. *Kidney International* Vol 56:1-17, 1999.
12. Dember, L., Beck, G., Allon, M., et al. Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis: A Randomized Controlled Trial. JAMA 299(18):2164-2171, 2008.