BLUEGRASS VASCULAR

Clinical Investigational Protocol

Evaluation of the Surfacer® System Approach to Central Venous Access

Protocol No: BVT.Surfacer.17-01

Version 2.0, 07 Dec 2017

Study Sponsor:
Bluegrass Vascular Technologies Inc. (BVT)
12500 Network Boulevard, Suite 308
San Antonio, TX 78249

Investigational Device:
Surfacer® Inside-Out® Access Catheter System

PRINCIPAL INVESTIGATOR / SPONSOR SIGNATURE PAGE

By signing below, I confirm that I have read protocol BVT.Surfacer.17-01 v. 2.0 dated 07Dec17, and the associated study documents provided by BVT. I agree to conduct the study in accordance with the procedures outlined in this protocol, and in accordance with all applicable laws and regulations and Good Clinical Practice (GCP) guidelines.

All the information in the electronic case report forms presented to me for collection by BVT will be entered in a timely manner ensuring completeness, legibility and accuracy.

I agree to actively enroll subjects into this study per the eligibility criteria as listed in this protocol and that all information provided to me by BVT, including pre-clinical data, protocols, electronic case report forms, and any verbal and written information, will be kept strictly confidential and confined to the study staff involved in conducting the study.
In addition, no reports or information about the study or its progress will be shared with anyone not involved in the study other than BVT or the Institutional Review Boards or Independent Ethics Committees. Any such submission will indicate that the material is confidential.

The Principal Investigator (PI) may delegate one or more of the above functions to a sub-investigator or other qualified study staff. The PI retains overall responsibility for proper conduct of the study.

Principal Investigator Name:	**Title:**
Signature:	**Date:**
Co-Investigator Name:	**Title:**
Signature:	**Date:**
Co-Investigator Name:	**Title:**
Signature:	**Date:**
Sponsor Approval	
Sponsor Name:	**Title:**
Signature:	**Date:**

ABBREVIATIONS

AE	Adverse Event
BC	Brachiocephalic
cm	Centimeter
eCRF	Electronic Case Report Form
CVC	Central Venous Catheter
CVA	Central Venous Access
CV	Curriculum Vitae
ECG	Electrocardiogram
Fr	French size
IFU	Instructions for Use
IJ	Internal Jugular
IOCVA	Inside out central venous access
IVC	Inferior Vena Cava
mg	Milligram
mm	Millimeter
MRI	Magnetic Resonance Imaging
MI	Myocardial Infarction
SC	Subclavian
SVC	Superior Vena Cava
TCVO	Thoracic Central Vein Obstruction

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1.0 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Title	Surfacer® System to Facilitate Access in Venous Occlusions
Protocol Number	BVT.Surfacer.17-01
Type and Phase	Pre-Market Investigational Device Exemption (IDE) Study
Number of Sites	Three sites will participate in the study initially, with up to 10 sites overall.
Device Name	Surfacer® Inside-Out® Access Catheter System
Indication for Use	The Surfacer® Inside-Out® Access Catheter System is intended to obtain central venous access to facilitate catheter insertion into the central venous system for patients with upper body venous occlusions or other conditions that preclude central venous access by conventional methods.
Device Description	The Surfacer® Inside-Out® Access Catheter System (Surfacer® System) is designed to facilitate entry and placement of central venous access catheters within the peripheral vasculature. The Surfacer® System is comprised of four components: a Workstation (Workstation Sheath) for percutaneous access to the femoral vein; a Delivery Instrument (Surfacer Device) which contains a Needle Wire and Needle Guide which is advanced to the supraclavicular space; an Exit Target which provides fluoroscopic guidance to mark the exit point; and an Exit (Peelable) Introducer which is introduced over the Needle Wire to access the central venous system. The Surfacer® System facilitates the entry and positioning of standard access catheters by establishing a transient passage across venous occlusions. Once the access is obtained and a catheter is in place, the Surfacer® System is removed.

Study Design	This is a prospective, single-arm, multi-center, study to demonstrate the safety and efficacy of the Surfacer® System.
Study Objectives	This goal of this study is to demonstrate that the Surfacer® System, once in place, facilitates stable upper body central venous access that is suitable for any conventional catheter. Safety will be evaluated based on the overall rate of acute complications using the study device as compared to historical rates of device/procedure related safety events using conventional CVA methods. Efficacy will be evaluated by the rate of transient successful central venous accesses created by the study device.
Planned Study Duration and Number of Subjects	Total study duration is anticipated to be approximately 12 months. A total of 30 subjects is planned. 10 subjects will be enrolled initially. After review of safety data, enrollment is expected to continue to 30 subjects overall. Subjects will participate in the study as follows: • Screening/Baseline • Procedure (Surfacer System procedure and CVA catheter insertion) • Hospital Discharge • 7-days (+7) Post Procedure (assessments are to occur on Day 7, or as soon as possible thereafter)
Study Sites	A minimum of three (3) sites in the United States and Europe will participate, with a majority of the subjects being enrolled at US sites if feasible.

Primary Study Endpoints	**Primary Efficacy Endpoint:** • Rate of safe insertion and patency of CVCs created across venous occlusions. **Primary Safety Endpoints:** • Acute device safety, defined as the absence of procedural complications (hemopericardium, hemothorax, pneumothorax, blood transfusion, resuscitation, emergency post-procedural intervention, transfer to an intensive care unit, and death) at discharge and 7 days post-procedure • Overall device and procedure related anticipated adverse events compared to historical safety data from CV placement procedures.
Secondary Study Endpoints	**Secondary Efficacy Endpoint** • Surfacer System clinical utility use from insertion into the femoral vein to sub-clavicular exit assessed by the ability of the Surfacer System to facilitate central venous access placement **Secondary Safety Endpoint** • Technique conversion rate

Inclusion Criteria	1. Subjects are between 18-80 years of age. 2. Subjects have been referred for placement of central venous access catheter. 3. Subjects have limited or diminishing upper body venous access or pathology impeding standard access methods. 4. Subjects are willing and able to give written informed consent.
Exclusion Criteria	1. Subjects are contraindicated for Surfacer System use if one of the following are found (per the IFU): a. Occlusion of the right femoral vein; b. Occlusion of the iliac vein; c. Occlusion of the inferior vena cava. 2. Subjects are contraindicated for central venous access based upon the treating physician's opinion and institutional standard of care. 3. Subject has acute thrombosis within any vessel (SVC, jugular, inferior vena cava (IVC), brachiocephalic and subclavian) planned be crossed by Surfacer System. 4. Subject has tortuous anatomy which precludes a straight line from femoral venous entry to subclavian exit. 5. Subject has been diagnosed with active pericarditis or endocarditis. 6. Subject has a known or suspected pericardial effusion. 7. Subject has a known or suspected aneurysm or ectasia of ascending aorta, innominate artery, or subclavian artery. 8. Subjects who are pregnant or of childbearing potential not taking adequate contraceptive measures or nursing during the study.

1.3 Schedule of Assessments

STUDY ASSESSMENTS WILL OCCUR AS FOLLOWS:

Assessments/Interval	Screening	Baseline	Intra-Procedural	Hospital Discharge	7 Days (+7) Post Procedure[7]
Informed Consent	X				
Study Eligibility	X				
Medical History/Demographics	X				
Physical Exam including Vital Signs		X		X	X
TCVO Lesion Type Classification		X			
Procedural Complication Assessment			X	X	X
Study Device Performance			X		
Medications (Antithrombotic & Cardiovascular)		X		X	X
Clinical Laboratory Tests[1]					
Pregnancy Test[2]	X[2]				
Creatinine		X			
Coagulation Profile (APTT/PT/INR)		X		X	
CRP		X		X	
LDH/ASAT/ALAT		X		X	
Fibrinogen/D-dimer		X		X	
Exams and Tests[3]					
AP and LAT Chest X-Ray or cine-fluoroscopy		X[4]	X	X[5]	
Ultrasound or Venous Duplex Venography		X			
ECG 12-lead		X			
TTE			Only If Cardiac Events	Only If Cardiac Events	
Contrast Angiography			X		
Fluoroscopy			X		
Cone Beam CT/cardiac echo/advanced imaging modalities[6]			X		
Adverse Events			X	X	X
Protocol Deviations		X	X	X	X

[1] Laboratory tests must be completed no more than 72 hours prior to the procedure.
[2] Pregnancy test is not required if patient is male or of non child bearing potential.
[3] Ultrasound or Venous Duplex Venography must be completed no more than 7 days prior to the Screening Visit. Other Screening/Baseline tests must be completed no more than 30 days prior to the Procedure.
[4] AP and LAT chest X-ray or cine fluoroscopy will be performed prior to the index procedure to define the pattern of occlusions, to rule out acute thrombosis, and to detect pleural fluid and mediastinal widening.
[5] Post-procedural AP and LAT chest X-ray or cine fluoroscopy will be performed, ideally assessed immediately after the index procedure is complete, to check the correct placement and position of the CVA Catheter tip, rule out pleuro-pulmonary damage (pneumothorax, hemothorax, etc.), and to detect pleural fluid and mediastinal widening. If the Investigator determines that additional imaging is clinically indicated at the time of discharge (same day or next day discharge), a chest x-ray may be obtained.

[6]Cone Beam CT, cardiac echo, or similar advanced imaging modalities to be performed in subjects with Type IV TCVO lesions, and Type III TCVO lesions suspected to be characterized by unusually tortuous vessels or otherwise challenging anatomy.
[7]A +7 day visit window has been provided to allow for outpatient clinic scheduling. However - this visit is to occur on Day 7, or as soon as possible thereafter.

2.0 INTRODUCTION AND BACKGROUND

2.1 Background

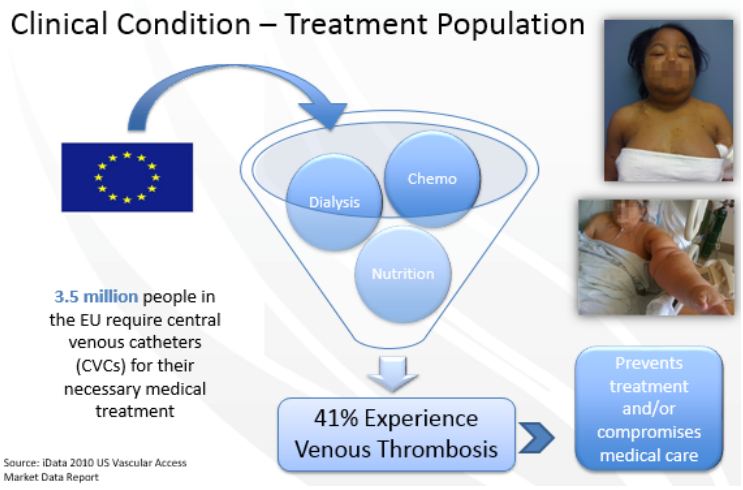
2.1.1. Central Venous Access

Central venous access (CVA) is one of the most commonly performed procedures in medicine, vital to many patients with acute and chronic illness. Indications for CVA include life-sustaining therapies such as hemodialysis, chemotherapy infusion, parenteral nutrition, hemodynamic monitoring and fluid management.[i, ii]

Central Venous Access Devices (CVADs) have become a mainstay for patients requiring intravenous (IV) administration of medications and other therapies. In fact, more than 7 million CVADs are implanted every year in patients in the United States, whilst in Europe this number is reported to be 3.5 million constituting a population dependent upon on CVADs (Figure 1).[iii, iv]

Obstruction or occlusion of CVADs due to venous thrombosis, with a reported frequency of up to 41%, is a serious problem in patients requiring repeated access or semi-permanent access. Chronic venous occlusions occur when thrombus forms around a catheter or pacing lead, and organizes into dense thrombus or fibrous tissue that permanently obliterates the vessel lumen. As a CVA is vital to the management of many chronic medical conditions, occlusion of the vein hosting the access becomes a life-threatening disease. Other risks include infection, pain, infiltration or extravasation.

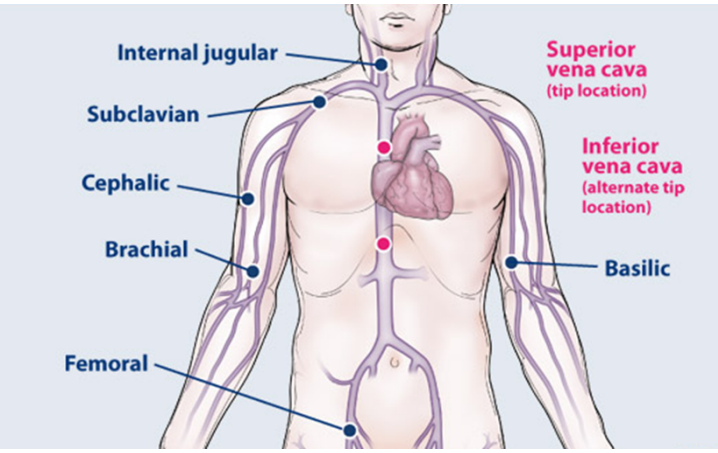
Figure 1. Conditions treated with Central Venous Access



2.1.2 Techniques for Central Venous Access

CVA is typically obtained by puncturing one of the four large upper body veins; the right or left internal jugular vein, or the right or left subclavian vein (**Figure 2**). A guidewire is introduced through the puncture needle and advanced into the central venous circulation. A plastic dilator is advanced antegrade over the wire to enlarge the channel, and then the catheter is advanced to the superior vena cava or right atrium. The tip of a CVAD is generally placed in either the lower third of the superior vena cava (SVC) or the caval atrial junction (**Figure 2**). Due to a blood-flow rate of approximately 2 liters per minute, infusates are rapidly hemodiluted and distributed in the central venous system. [v, vi]

Figure 2. Adult CVAD insertion and tip sites[vii]



Catheters are categorized into (i) non-tunneled catheters, (ii) tunneled catheters with anchoring cuff, (iii) implanted ports (iv) apheresis/dialysis catheters (tunneled and non-tunneled) and (v) PICC (peripherally inserted central catheter) **(Table 1**).[vii] They may have single or multiple lumens and can be open-ended or valved. Multiple lumen catheters are advantageous in patients undergoing stem cell transplantation or chemotherapy whereby a number of agents and blood products require simultaneous infusion. Blood products may be administered concurrently with other drugs infused through a multi-bore catheter.

Table 1: Common types of CVADs[vii]

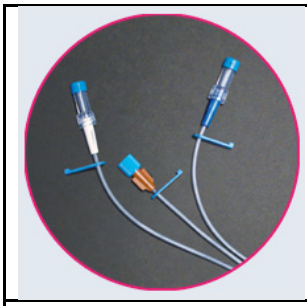
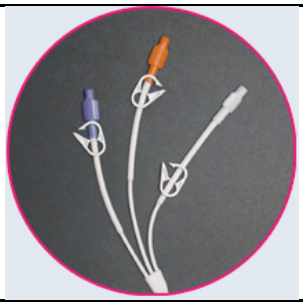
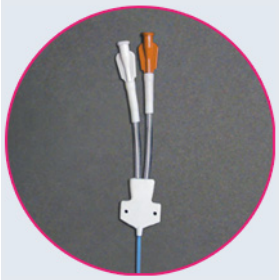
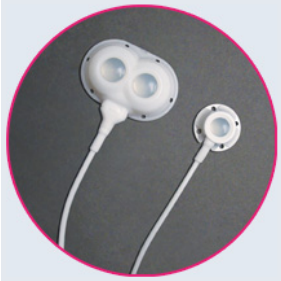
			
Non-tunneled Catheters	**Tunneled catheters**	**Peripherally inserted central catheters (PICCs)**	**Implanted ports**
Also called subclavian, percutaneous, acute-care, or short-term catheters. Typically used for days or weeks, for all types of IV therapy, to draw blood, and to monitor central venous pressure. May be placed bedside or, if necessary, in an emergency setting without sedation	Designed for long-term use and frequent venous access. Provides a more reliable IV access. Used for extended courses of antibiotics, chemotherapy, and parenteral nutrition Surgically inserted	Often used when a catheter will be needed for less than 6 months or when access to the jugular or subclavian vein is unavailable Can be used for most IV therapies and to obtain blood samples in a variety of care settings from diverse patient populations May be placed bedside or in an outpatient setting	Consists of 2 attached parts: the catheter and portal body with reservoir Long-term dwell capacity, requiring little maintenance when not in use. Useful for cyclically infused therapies, such as chemotherapy Blood draws may be done through the port Surgically inserted

Table 2 summarizes the advantages and disadvantages for each of the catheter categories. An experienced member of the Hematology Oncology team should make the decision regarding which type of catheter is most appropriate at the outset of therapy, to avoid multiple catheterizations. The decision made is based on diagnosis, length and type of therapy, patient preference, and clinical status, availability of patent veins, operator experience and previous central venous access history. For example, if an allogeneic transplant is planned a double or triple lumen skin-tunneled catheter should be inserted at the outset to ensure adequate access throughout chemotherapy and the subsequent transplant.

Table 2: Advantages and disadvantages of different catheters for CVA[viii]

Catheter type	Advantages	Disadvantages
Nontunnelled catheters	Choice of sites Easy to insert and remove Multiple lumina available	Short-term use
Skin-tunnelled catheters*	Lower infection rates than nontunnelled Long-term use	More complex insertion and removal
Ports	No external catheter Cosmetically attractive Patient can swim/bathe as normal Low maintenance Long-term use Lower infection rates than skin-tunnelled catheters	Surgical insertion and removal Less suitable for frequent repeated access
Apheresis/dialysis catheters Nontunnelled (e.g. Vascath™ Kimal) Skin-tunnelled	Permit high blood flow rates Easier to insert and remove Lower infection rates than nontunnelled devices Long-term use Good for patients with poor peripheral access who require both PBSC harvest and transplant procedure	Large bore Require flushing with concentrated heparin (for example 5000 U/ml, according to manufacturer guidelines) solution to maintain patency. Flush solution must be withdrawn prior to use Short-term use Complex insertion and removal Best inserted via internal jugular or femoral routes
PICC	Easy to insert and remove Do not require platelet support or correction of clotting prior to insertion/removal	Higher thrombosis rate particularly with polyurethane variety. Polyurethane variety required to infuse blood/platelets because has greater internal diameter than silicone variety Slower flow rates particularly in silicone/valved varieties Catheter longevity lower than with skin-tunnelled devices Incidence of malposition greater than in other types of CVC

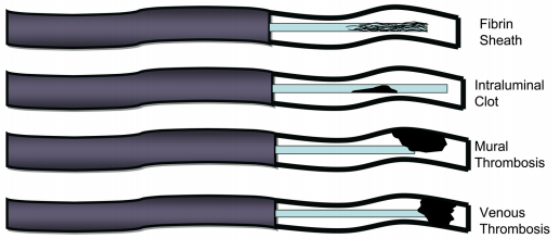
2.1.3 Conditions leading to CVA Occlusion

Catheter occlusion is the most common non-infectious complication in the long-term use of central venous access devices (CVADs). In fact, up to 25% of catheters may become occluded. [ix, x, xi] Occlusions may occur soon after insertion of a device or develop at any time during the course of intravenous (IV) therapy.

About 58% of catheter occlusions are thrombotic, resulting from formation of a thrombus within, surrounding, or at the tip of the catheter. [xii, xiii]

About 42% of catheter occlusions are due to non-thrombotic causes, including precipitates, mal-positioning, mechanical obstructions, and other factors. [xii]

Conditions leading to CVA catheter dysfunction are outlined in **Figure 3**.

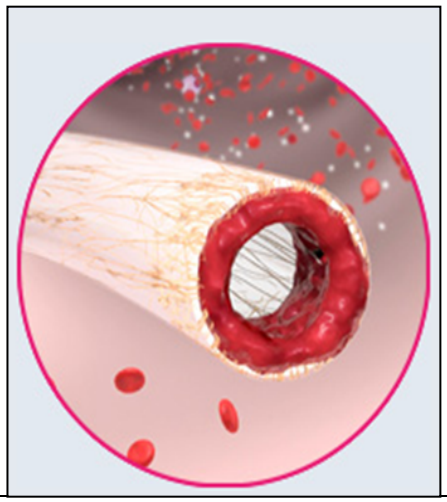
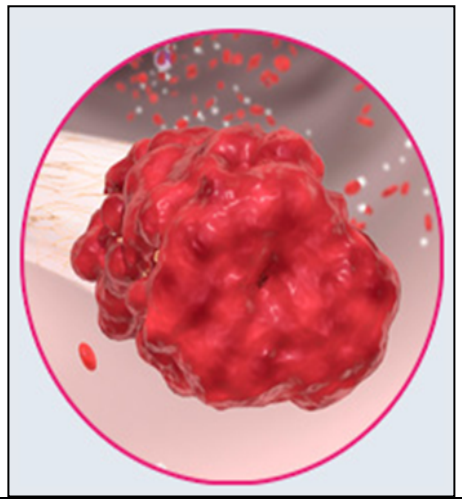
Figure 3: Conditions leading to CVA catheter dysfunction. [xiv]	
a) intraluminal or extraluminal thrombosis b) deposition of residues of lipids c) precipitation (e.g., of calcium phosphate) by simultaneous infusion of solutions with low and high pH d) angulation or folding of the catheter e) pinch-off syndrome (compression of the catheter between the clavicle and first rib, mainly during long-term use) f) intramural migration of the catheter tip.	

Catheter obstructions can be thrombotic and non-thrombotic (**Figure 4**).

All catheters, when introduced into the body, become covered with plasma proteins and fibrin. This is the body's natural attempt to protect itself against a foreign body. The fibrin starts to form a layer around the outside of the catheter within minutes of insertion, starting at either the line entry site or where the tip contacts the vein.

The concentration of proteins on the catheter surface equals the concentration in the bloodstream within 5 minutes of insertion, and a 1-mm thick layer of platelets and white blood cells adhere to these proteins within 24 hours. These absorbed blood components can allow the binding and colonization of bacteria, which can increase fibrin formation and may activate the clotting mechanism.

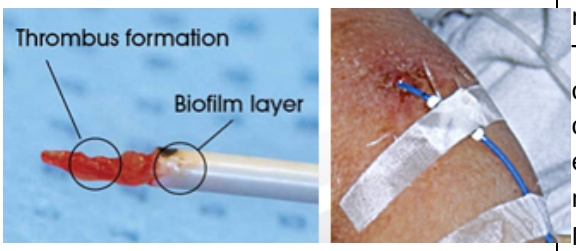
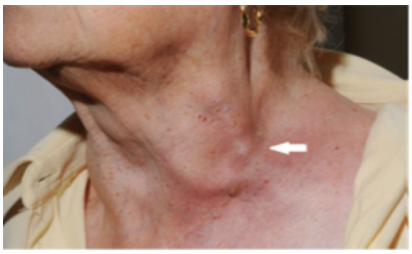
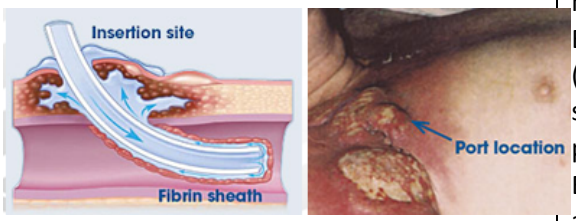
Figure 4: Intraluminal Thrombus & Fibrin Sheath Occlusions[xv, xvi]

	
Intraluminal Thrombus occurs when blood refluxes inside the catheter lumen, such refluxes may result from patient coughing, inadequate flushing after blood draws or checking for blood return, or improper use of flush syringes[xv, xvi]	**Fibrin sheath** forms when fibrin adheres to the external catheter surface, often beginning at the entry site, and may encase all or part of the catheter like a sock covering the entire opening of the catheter tip. [xv, xvi]

2.1.4 Complications of CV Catheter Occlusion

Thrombotic occlusions are associated with several complications (**Figure 5**), including:

- Risk of infection
- Pain
- Infiltration or extravasation
- Venous thrombosis

Figure 5: Complications associated with thrombotic occlusions.	
Risk of infection 	Formation of fibrin deposits and biofilm is a natural response that can start upon catheter insertion. Fibrin deposits and thrombi provide a rich culture medium for bacterial growth. Thrombus formation is linked to infection risk, caused by the interaction of fibrin, blood components, and a biofilm layer that attracts, encloses, and protects bacteria and microorganisms. Microorganisms can be released into the bloodstream as a result of aggressive flushing that shears off part of the biofilm or thrombus[xvii, xviii]
Venous thrombosis with phlebitis (jugular vein) / Pain 	Irritation to the vein from the development of a fibrin sheath on the catheter can result in thrombophlebitis denoting a twofold injury: thrombosis and inflammation. Venous thrombosis may result from formation of a thrombus between the catheter and the vessel wall, leading to complete blockage of the vein. Venous thrombosis is frequently associated with veins in the lower extremity due to the use of hypertonic or highly acidic infusion solutions.[xix]
Infiltration or extravasation 	Infiltration is the leaking of non-vesicant (non-blistering) fluids into the surrounding tissue, and may cause pain, discoloration, and swelling. Extravasation is the leaking of a vesicant (blistering) medication or solution into the surrounding tissue, resulting in more severe, painful, edema, and tissue necrosis Either infiltration or extravasation may result from a thrombotic occlusion or physical damage to the line[xx, xxi]

2.2 Study Rationale

In patients with CV occlusions, life-saving therapies such as (i.e. dialysis, chemotherapy, pacing, and nutrition) cannot be administered. The current treatment for central venous obstruction is:

to re-establish access in the current vein, or

to "try another vein"

Practice guidelines have been published by several scientific societies to address problems related to CV access. In particular, Baskin et al8 proposed an algorithm for management of occlusion and thrombosis associated with long-term indwelling central venous catheters (Figure 6).

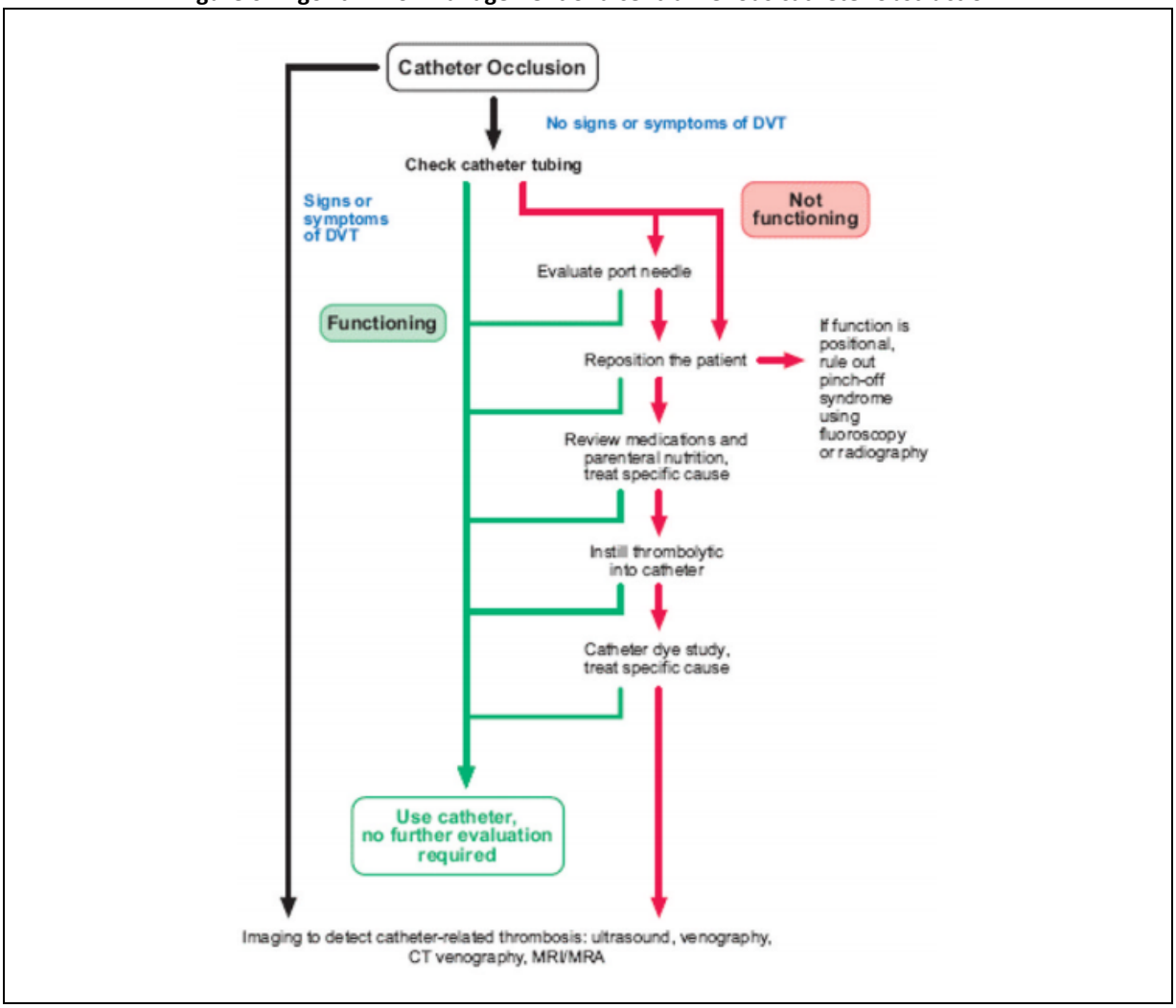
After ruling out mechanical dysfunction and medication or parenteral nutrition-related etiologies, the next step is to exclude the thrombotic obstruction. A contrast study of the catheter (sometimes referred to as a "linogram") can be used to detect an intraluminal clot or fibrin sheath.

Current recommendations include administration of a thrombolytic agent into the catheter lumen with a dwell time of at least 30 minutes and a repeated dose if needed. If catheter patency is not restored, a low dose of alteplase, a tissue plasminogen activator (tPA), can be infused over 6 to 8 hours. An ultrasound, venogram, or other diagnostic study is warranted if venous thrombosis is suspected.

If thrombolytic therapy fails to clear the catheter, a guide wire can be inserted through the catheter lumen to dislodge a thrombus at the tip of the CVC.

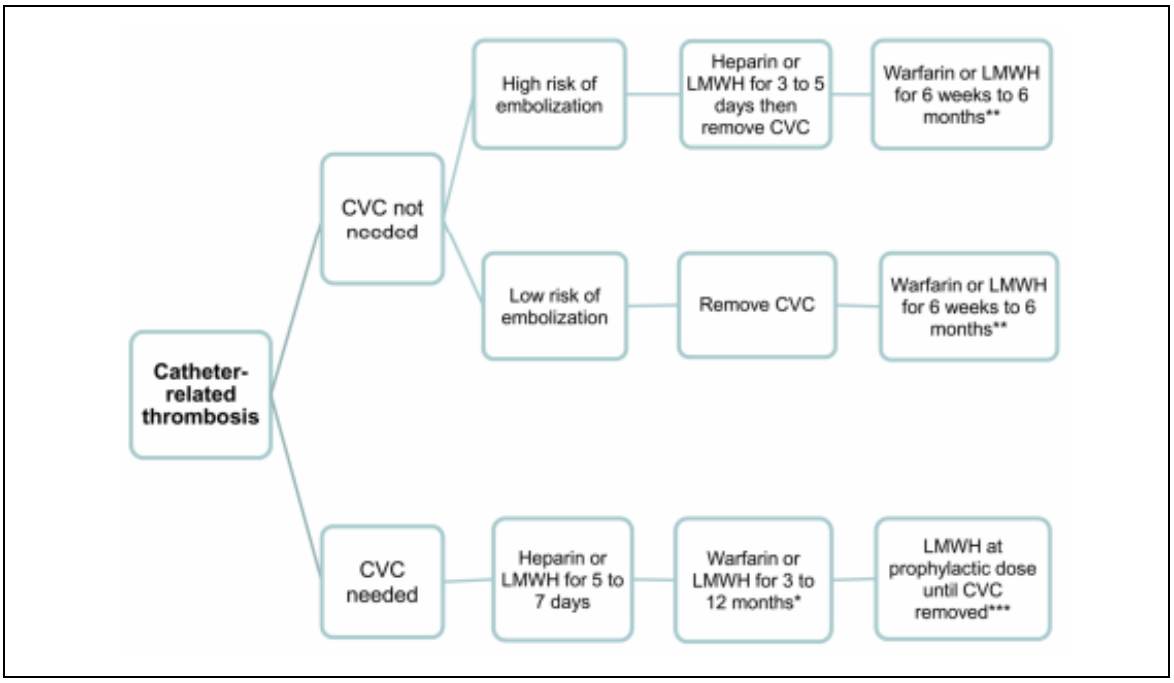
Fibrin sheath stripping has also been used for CVC occlusion that is resistant to medical management. The procedure uses femoral venous access to pass a vascular snare device to dislodge and remove the fibrin sheath. Although effective, these procedures are more invasive and are only used as a last resort.

Figure 6: Algorithm for management of a central venous catheter obstruction



Due to the lack of prospective studies, controversy continues regarding optimal management of a catheter related thrombosis (CRT). Recent guidelines suggest dividing patients with CRT into 2 categories based on whether or not they continue to need central venous access (**Figure 7**).

Figure 7: Two categories, for patients with CRT, based on whether or not they continue to need central venous access



For patients who have developed a CRT but no longer need a CVC or in whom it is no longer functioning, guidelines from the American College of Chest Physicians (ACCP) recommend to remove the catheter after 3–5 days of anticoagulation therapy. However, some believe that the CVC can be removed once a patient has been appropriately anticoagulated, as documented by an appropriate partial thromboplastin time (if unfractionated heparin is used) or anti-Xa level (if low molecular weight heparin is used).

The length of time a patient should be anticoagulated following removal of the CVC is controversial. Although some physicians advocate anticoagulation for 3 months after the CVC has been removed, others may shorten the course depending on the patient and the severity of the clot.

For the majority of patients who continue to require central venous access, the catheter can be left in place and anticoagulation therapy initiated.

Some patients develop a thrombosis that may threaten life or limb.

Alternatively, anticoagulation may be contraindicated, in which case the CVC would likely require

removal regardless of the patient's need for central venous access.

For patients that retain their catheter, current recommendations include initial anticoagulation for several days, with unfractionated heparin or low molecular weight heparin, followed by at least 3 months of anticoagulation with a vitamin K antagonist or low-molecular-weight heparin.

Low-molecular-weight heparin is preferred for cancer patients since it more effectively prevents recurrent thrombosis and because warfarin interferes with some chemotherapy regimens and is more difficult to adjust when thrombocytopenia occurs.

Thrombolytic treatment for an upper extremity DVT (deep vein thrombosis) is not recommended for initial therapy of a CRT. Additionally, if the catheter remains in place once the course of full-dose anticoagulation is complete, the American College of Chest Physicians recommends continued anticoagulation therapy at a prophylactic dose until the catheter is removed.

Clinicians who treat adults should refer to the recently updated ACCP guidelines.

2.3 Device Development

Central venous access (CVA) is one of the most commonly performed procedures in medicine and is vital to many patients suffering from both acute and chronic illnesses. It is estimated that over six million patients worldwide require central venous access for long term treatment or chronic disease management including the need for parenteral nutrition, hemodynamic monitoring and fluid management, hemodialysis for renal failure, and chemotherapy infusion.

The Surfacer System has been developed and designed to satisfy an unmet lifesaving clinical need: facilitating central venous access in patients for whom access has been lost or diminished, due to obstruction of central veins. The Surfacer System is designed to safely overcome chronic, total occlusion of the superior vena cava (SVC) or both internal jugular and subclavian veins, as well as occlusions inaccessible by conventional methods. The device is intended to enable access using the same vessel that would not be accessible, or would prove difficult to access, with conventional methods, and therefore brings potential benefits that cannot be achieved with the current standard of care.

Restoring CV access is necessary to provide life-saving therapies (dialysis, chemotherapy, pacing,

nutrition), but it is also important to avoid risks such as post-thrombotic syndrome, pulmonary embolism, and catheter infections that are known to be associated with CV thrombosis. Bluegrass approaches this problem by reversing the standard approach of recanalizing or bypassing occlusions by advancing a catheter system via the inferior vena cava to the superior vena cava and to the location of the occlusion. Once tunneled through the occlusion, the system exits the body and access catheters can be back-loaded into the body.

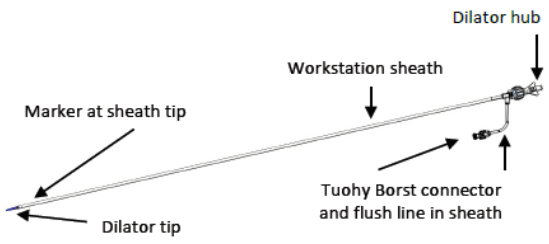
The Surfacer System is a high-impact technology for clinical practice, considering the severity of the clinical condition that this device treats and for which there are limited, if any, therapeutic options.

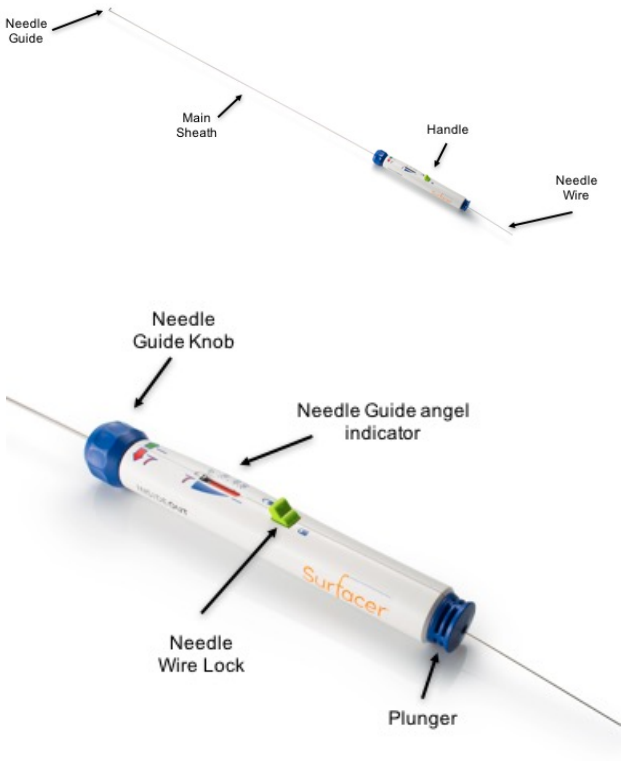
3.0 DEVICE DESCRIPTION

3.1 The Surfacer® Inside-Out® Access Catheter System

The Surfacer® Inside-Out® Access Catheter System (Surfacer® System) is designed to facilitate entry and placement of central venous access catheters within the peripheral vasculature. The Surfacer® System is comprised of four components: a Workstation (Workstation Sheath) for percutaneous access to the femoral vein; a Delivery Instrument (Surfacer Device) which contains a Needle Wire and Needle Guide which is advanced to the supraclavicular space; an Exit Target which provides fluoroscopic guidance to mark the exit point; and an Exit (Peelable) Introducer which is introduced over the Needle Wire to access the central venous system. The Surfacer® System facilitates the entry and positioning of standard access catheters by establishing a transient passage across venous occlusions. Once the access is obtained and a catheter is in place, the Surfacer® System is removed.

Table 3: Device Components

	**A) Surfacer Workstation Sheath:** The Workstation Sheath provides access to the peripheral venous system via the femoral vein. The Workstation Sheath provides a lumen for the Surfacer Device, preventing injury when it is advanced.



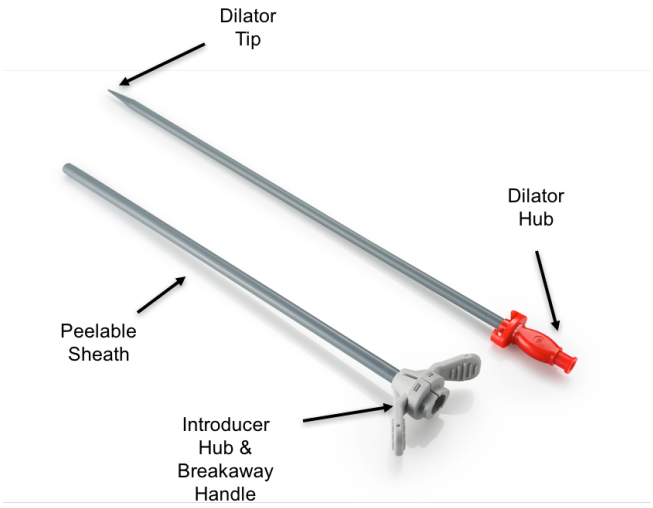
B) Surfacer Device:

The Surfacer Device consists of a Main Sheath, Needle Guide, Needle Wire, and a Handle:

- The **Main Sheath** is 8F and has a 95 cm effective length. The Main Sheath provides access to the peripheral venous system via the femoral vein. The Main Sheath has a lumen for the Needle Guide.
- The **Needle Guide** is 3F and extends 10 mm from the main sheath. The Needle Guide provides access to the peripheral venous system via the femoral vein. It has a lumen for the Needle Wire. The Needle Guide passes though the Main Sheath.
- The **Needle Wire** is 1F and 180 cm long. The Needle Wire is advanced through the Needle Guide to the percutaneous exit location at the supraclavicular space.
- The **Handle** incorporates a rotating knob to position the Needle Guide and to to advance and retract the needle wire.

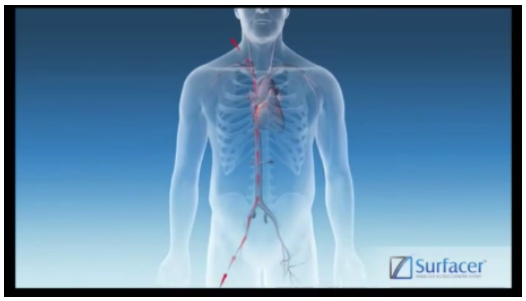
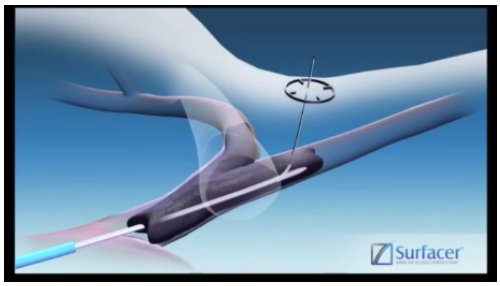
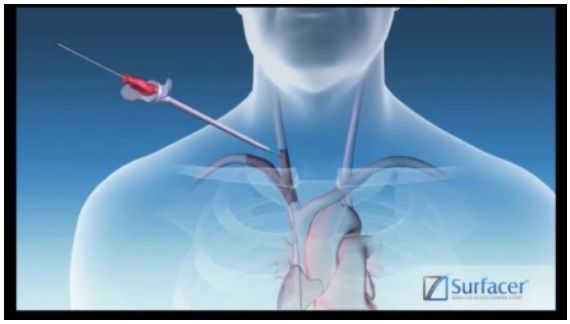
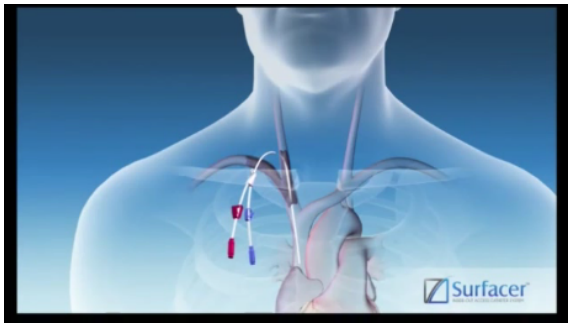
C) Exit Target:

The Exit Target is a radiopaque marker use to locate the desired Needle Wire exit location on the patient's skin (the supraclavicular space) using fluoroscopic imaging.

	**D) Peelable Introducer:** The Peelable Introducer provides percutaneous access to the venous system and permits insertion of the CVA catheter. The Peelable Introducer has a split sheath, valve and dilator. The Peelable Introducer is 16F x 20 cm long.

The Surfacer System catheter is delivered through the femoral vein and the superior vena cava (SVC) into the peripheral venous system and to the occlusion.

Figure 8: Schematic of Surfacer System procedure

 a) The Surfacer System is introduced via a femoral vein approach. The catheter "Workstation Sheath" component is navigated along the illustrated path to the desired upper body veins location just proximal to the occlusion.	 b) The catheter "Surfacer Device" component, is passed through the "Workstation Sheath", and penetrates the occlusion. The Needle Guide is oriented to the "Exit Target" (radiopaque ring marker) by fluoroscopy. A "Needle Wire" exists the Needle Guide by the side of the catheter and is advanced toward the supraclavicular space where the Exit Target has been placed and perforates the skin.
 c) The "Peelable Introducer" is delivered over the Needle Wire and advanced to the SVC to facilitate the introduction of a new Central Venous Catheter into the vein.	 d) A new Central Venous catheter is then positioned into the Central Venous system and access is restored.

3.2 Indication for Use/Intended Use

The Surfacer® Inside-Out® Access Catheter System is intended to obtain central venous access to facilitate catheter insertion into the central venous system for patients with upper body venous occlusions or other conditions that preclude central venous access by conventional methods.

3.3 Principles and Mode of Operation

The Surfacer System uses the same principle technique as conventional CVA procedures, by tunneling through or bypassing the occlusion, but does this in the reverse direction, from the inside to the outside. With the Surfacer System, the Surfacer Device is percutaneously introduced into the right femoral vein. It is advanced up the inferior vena cava, via the superior vena cava (SVC), to the location of the occlusion. When the occlusion has been visualized under fluoroscopy, a needle wire is oriented to advance through or to bypass the occlusion and to exit to a pre-determined external target. A new central venous catheter is then back-loaded into the Peelable Introducer and positioned below the occlusion. Placement of the central venous catheter below the venous occlusion restores central venous access.

Prepare the right femoral and right sub-clavicular area for sterile percutaneous access. Administer conscious sedation and local anesthesia according to hospital protocol. Follow standard access procedures to gain access into the femoral vein using .035" x 150-180 cm J-tip exchange guidewire.

Advance the Workstation Sheath and dilator over the exchange wire to the venous occlusion. Once the location of the Workstation Sheath is in the occlusion as confirmed by injecting a small bolus of contrast, place an Exit Target to the exit point supraclavicular and proceed with insertion of the Surfacer Device through the Workstation Sheath. Once positioning is confirmed the Handle can be used to advance the Needle wire out of the needle guide and exit the skin. For Type III and Type IV occlusions, inject a small bolus of 5-10cc of contrast through Workstation sidearm to exclude extravasation of contrast under fluoroscopy into the pleural or pericardial space. If visualization cannot be confirmed a 4 or 5F sheath could be back loaded over the Needle wire and injection of contrast could be performed under a gently pull back to opacify the tract of exit is free from extravasation. Once confirmed, the Peelable Introducer can now be back loaded over the exiting wire and access can be confirmed by fluoroscopy. Upon completion of the procedure, a desired CVA catheter can be exchanged or introduced adjacent to the Peelable Introducer.

3.4 Contraindications

The Surfacer System is contraindicated for patients with an occlusion of the right femoral vein, iliac vein

or inferior vena cava, or acute thrombosis within a vessel to be crossed by the Surfacer System. Special precautions may be required for patients with coagulation disorders and patients on anti-coagulation therapy.

The Surfacer System is not intended for use in the coronary or cerebral vasculature.

This device is not to be used in the arterial system.

3.5 Device Training

BVT intends to implement the current commercial device training program under way in Europe, and will train Principal Investigators and study staff using this training program. A detailed description of Surfacer System preparation and use is provided in the Instructions for Use. Principal Investigators must be familiar with the Indications for Use (IFU), Contraindications, Warnings, Precautions, and Implantation Procedure as described in the IFU prior to use of the Surfacer System. Training documents and the IFU will be provided with the study manual.

4.0 REPORT OF PRIOR INVESTIGATIONS

4.1 Clinical Data Overview

The Inside-Out procedure (IOCVA) using modifications of commercially available devices (Elayi 2011[xxii]; Gurley 2012[xxiii]) has been reported to be used in 124 cases with no or low adverse event occurrences, and life-saving benefits to patients with few therapeutic options for central venous access due to upper body venous occlusions.

The Surfacer System has also been investigated in an approved clinical study of 12 patients with two or more total upper body venous occlusions where there were no serious adverse events, 100% technical success in inserting the device, and 100% success in achieving central venous access in all patients evaluated.

A comparison of the successful outcomes in the Bluegrass Vascular clinical study (N=12), with the outcomes of two previously reported studies (N=124) utilizing the same procedure and similar technology provides evidence of procedural safety and effectiveness in patients with chronic total

venous occlusions. See **Table 4**, Clinical Outcomes of IOCVA system, below.

Table 4: Summary of Clinical Outcomes using the IOCVA Method Surfacer System

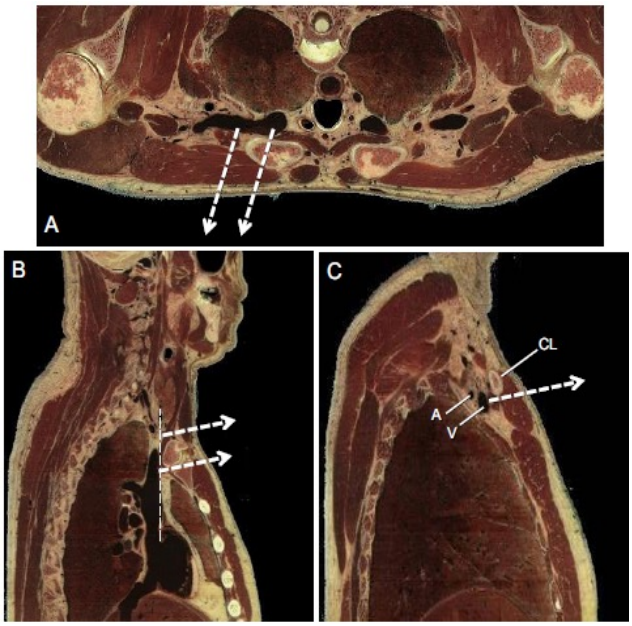
Procedure	IOCVA Method Pacing leads placement (Elayi 2011xxiv) N=8	Investigator Experience IOCVA Methods (Gurley 2012xxv) N=116	BVT Surfacer System GEN1 FIH Study (Ebner 2013) N=12
Fluoroscopy time (min)	39 ± 43	2.4 ± 1.2 (type I) 5.4±7.8 (type II) 10.3±11.8 (type III) 15.6±2.4 (type IV)	7.4 ± 2.8
Technical success	100%	100%	100%
Repeated procedures	0%	1 procedure in 47 pts (67%) 2 procedures in 12 pts (17%) 3 procedures in 6 pts (9%) 4 or more procedures (7%)	2 procedures in 1 patient (8.3%)
Procedural complications	Not reported	1 pocket hematoma due to excessive OAC (0.8%, 1/116)	1 exit site hematoma resolved with manual compression treatment (1/12 patients, 8.3%,)
Overall success rate	100% (136 out of 136 patients)		
Overall complication rate	1.47% (2 out of 136 patients)		

The studies presented, when compared with the success and safety data on standard access procedures in patients with obstructed central veins (presented in section 2.1 of the protocol), provides assurance that the overall benefits of the Surfacer® Inside-Out® Access Catheter System potentially exceeds the potential risks in the clinical setting. Additionally, the device offers a safe and effective alternative to physicians and patients with venous occlusions, for whom limited options exist to deliver life-saving therapies.

4.2 Anatomical Studies

All current methods of transvenous lead placement require puncture of a central vein from outside the body. IOCVA is a new concept that reverses the approach by directing a needle outward from within the body. IOCVA can be performed safely because there are consistent anatomic relationships adjacent to the thoracic central veins (**Figure 9**). Soft tissues, clavicle, and skin bind the central veins anteriorly. A needle directed anteriorly will not encounter arteries, nerves, or pleura, which lie posterior and lateral to the central veins. Evaluation of visible human thorax slices illustrates that the path of the Inside-Out puncturing needle is free from critical structures including lungs, hilar vessels and arteries, as showed in **Figure 9** below.

Figure 9: Gross anatomy study of the human thorax – Visible Human



A: Gross anatomy of the human thorax in the horizontal plane. A needle directed anteriorly from the posterior aspect of the clavicle encounters fat, muscle, and skin. This applies to either a subclavian or supraclavicular exit path.

B: Gross anatomy of the human thorax in the sagittal plane. Vertical line marks the posterior aspect of the head of the clavicle. A needle directed anteriorly from this point encounters fat, muscle, and skin. Critical structures, including lung, hilar vessels, and arteries, remain posterior to this line.

C: Sagittal plane view (lateral to panel B) showing the positions of the subclavian artery (A), subclavian vein (V), and clavicle (CL) at a typical point of subclavian venous access. Critical structures remain behind the posterior aspect of the clavicle.

4.3 Proof of Concept Study (Elayi 2011)

Elayi CS, Allen CL, Leung S, Lusher S, Morales GX, Wiisanen M, Aikat S, Kakavand B, Shah JS, Moliterno DJ, Gurley JC.
Inside-out access: a new method of lead placement for patients with central venous occlusions.
Heart Rhythm. 2011 Jun;8(6):851-7

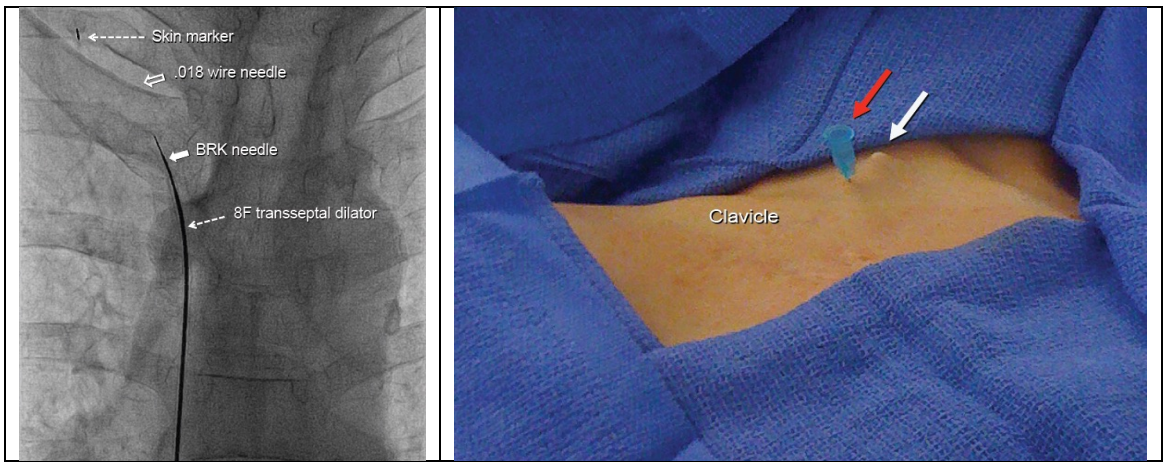
This study described the experience of using the Inside-Out central venous access method to place pacemaker and defibrillator leads in 8 patients with upper body central venous occlusions that could not be crossed with conventional methods. IOCVA can be performed safely because there are consistent anatomic relationships adjacent to the thoracic central vein.

This study demonstrates that the inside-out central venous access can be successfully and safely applied to establish central venous access in patients with chronic, total SVC and subclavian vein occlusions that cannot be recanalized with currently available technology.

Eight patients were treated using off-the-shelf devices, physician modified for use in an IOCVA approach. All patients were referred for clinically indicated permanent pacemaker or defibrillator implantation in accordance with practice guidelinesxxvi. Additionally, all patients had chronic SVC, brachiocephalic, and/or subclavian vein occlusions that prevented a standard prepectoral transvenous approach to device implantation. The occlusions consisted of long segments of densely fibrotic lumen obliteration that could not be recanalized by conventional interventional techniques using a variety of guidewires, catheters, and dilators.

Occlusions were resistant to aggressive probing with 0.035-inch, stiff-shaft hydrophilic wires and supporting catheters. Probing was attempted from at least one direction and, in some cases, from both sides of the occlusion. None of the patients had collateral venous channels suitable for lead placement. An attempt at inside-out central venous access was offered after explanation of potential risks, including the possibility of risks not yet known for the procedure.

Figure 10: Images from pacing leads using IOCVA insertion methodology



All procedures were performed in a setting that was capable of managing major complications.

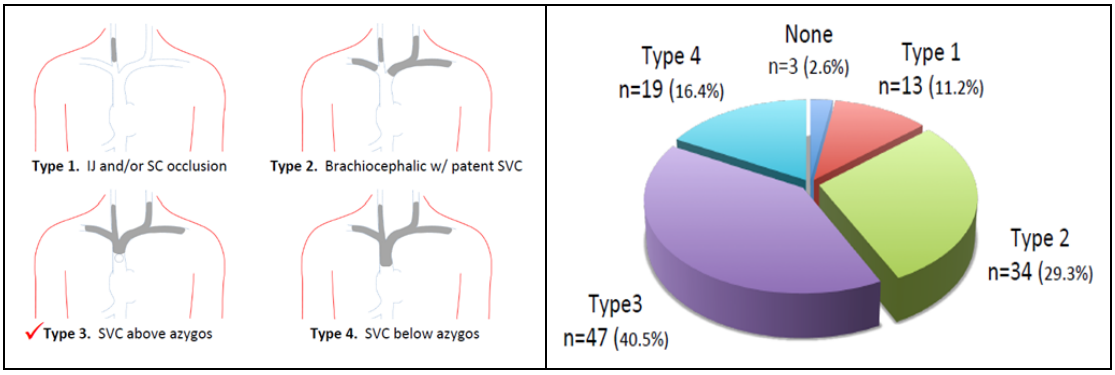
No clinical complications occurred except a for a small pocket hematoma that resolved without intervention.

4.4 Investigator Experience, Gurley (2012)

John C Gurley, MD
Inside-out Central Venous Access - Presentation (University of Kentucky May 9, 2012)
Heart Rhythm Society 2012, May 9-12, Boston MA

Dr. John C. Gurley, MD presented the results of 116 procedures utilizing the Inside-Out® technique for a variety of procedures involving upper body venous obstructions. Gurley used off-the-shelf devices (modified) to provide central venous access for patients with Type 1 to Type 4 venous occlusions (**Figure 11**).

Figure 11: Type and Distribution of Treated Occlusions

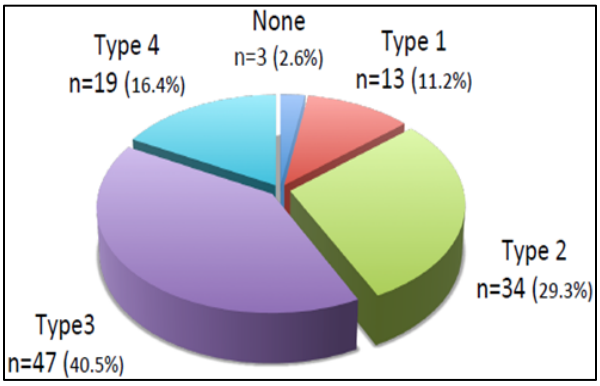


Dr. Gurley reported successful results with this approach over multiple subsequent inside-out procedures as follows:

- One procedure in 47 patients (67% procedures)
- Two procedures in 12 patients (17% procedures)
- Three procedures in 6 patients (9% procedures)
- Four or more procedures (8% procedures)

The rates of procedural entry sites used prior to attempting the IOCVA procedure are summarized in **Figure 12** below.

Figure 12: Entry Sites

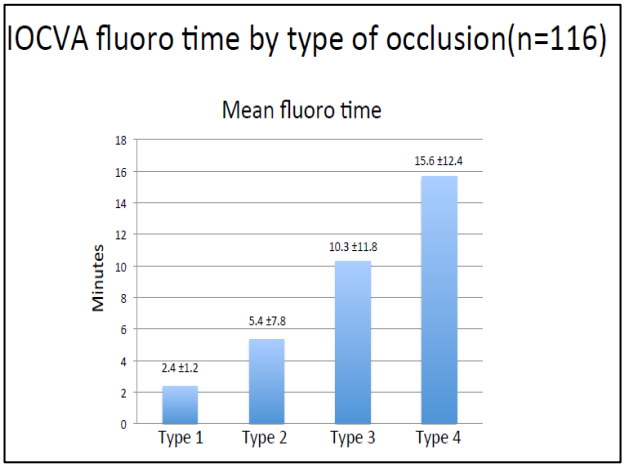


The technological differences of the Surfacer® System (a device designed specifically for this procedure) are such that a minimal clinical impact may be expected as compared with the Gurley procedure. These differences were addressed in a clinical study (protocol ID CR-4001) conducted by Bluegrass Vascular Technologies, Inc. The interim results of this study have been published (Ebner 2013).[xxvii]

In total, 116 IOCVA procedures were successfully completed by Dr. Gurley, with no complications or technical failures, and with one adverse event due to a delayed pocket hematoma associated with excessive anticoagulation. The IOCVA mean fluoroscopy time by type of occlusion is shown in Figure 13.

Of these 116 procedures, 83.6% (97 procedures) were associated with successful right supraclavicular exits utilizing the equivalent technology, in the same anatomy and for the same clinical effect as Surfacer Inside-Out Access Catheter System.

Figure 13: IOVCA Fluoroscopy Time by Occlusion Type



Results from Dr. Gurley's investigations provided evidence of the feasibility and safety of the inside-out approach using modified commercially available components and procedural steps that are equivalent to those utilized by the Surfacer® System.

4.5. Surfacer® System FIH Evaluation (Ebner, 2013)

Adrian Ebner, MD; Santiago Gallo, MD; Carlos Cetraro, RT(R); John Gurley, MD; and Laura Minarsch, CVT, RT(R)
Inside-Out Upper Body Venous Access: The first-in-human experiences with a novel approach using the Surfacer Inside-out Access Catheter System
Endovascular Today June 2013

The study published by Ebner et. al. represents the final report of a clinical investigation performed by Bluegrass Vascular, study CR4001, using the Surfacer System GEN1. More details on study CR4001 are provided in the next paragraph.

Severe renal dysfunction and venous occlusive disease are major causes of morbidity, mortality, and increased medical costs, especially within the dialysis population. The long-term risks of central venous access include occlusion, which can occur within days of catheter placement and is a common problem in patients requiring repeated access or semi-permanent access. Central venous occlusion can deprive patients of vital therapies such as hemodialysis, cardiac pacing, chemotherapy, and drug infusion.

Because simple central venous occlusions force providers to sacrifice secondary veins, patients often endure the morbidity of venous hypertension and the mortality risk of an access crisis. Central venous occlusive disease is entirely iatrogenic, highly destructive, and vastly underappreciated by the general medical community.

As part of a safety and feasibility study, 12 patients (ranging from 27-63 years of age) consented and were treated with the Surfacer IOCVA System. All patients presented with severe renal dysfunction and compromised upper venous occlusive disease. They also required hemodialysis and had two or more occluded upper body venous access points; one patient was diabetic. The study was performed at the Italian Hospital in Asuncion, Paraguay. Patients underwent the following tests:

- routine chest radiography and electrocardiography (ECG)
- venous duplex venography

Patients were sedated with intravenous midazolam plus fentanyl. All patients had creatinine levels averaging 10.0.

Average procedure time was 32.8 ± 16.9 minutes (**Table 5**) and decreased with increased operator experience (**Figure 14**).

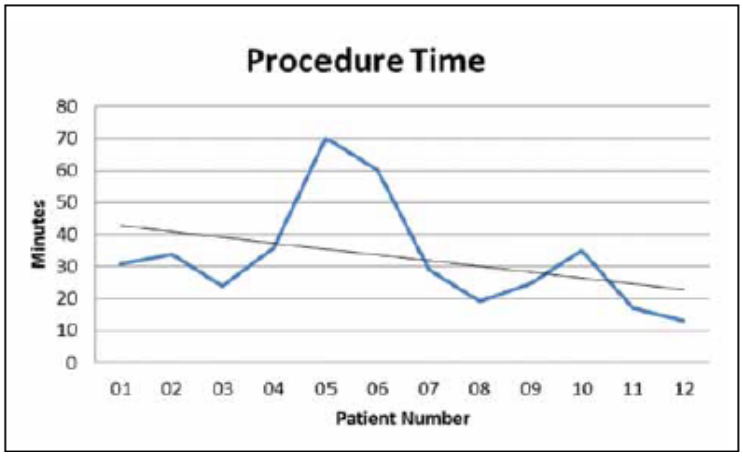
Average amount of contrast used was approximately 16 ml.

All twelve patients received a central venous access catheter, which remained in place and was confirmed to be functional and patent at 14-days post-procedure.

Table 5: Procedural Results

Subject No.	Procedure Time (min)	Fluoroscopy Time (min)	Contrast Volume (mL)
1	31	10.4	20
2	34	10.5	20
3	24	10.3	20
4	36	9.3	20
5	70	10.4	25
6	60	9.5	10
7	29	4	10
8	19	4.6	10
9	25	5.3	20
10	35	4.8	10
11	17	4.4	15
12	13	5.7	10
Average	**32.8**	**7.4**	**15.8**
Standard deviation	**16.9**	**2.8**	**5.6**

Figure 14: Surfacer Inside-Out Access Catheter FIH Procedure Times



Results show that this novel approach provides safe and effective percutaneous central venous access, despite chronic occlusion of the SVC. Inside-out central venous access should be explored further as a new option for patients with upper body venous occlusive disease.

Clinical relevance: The patients in the clinical trial of the Bluegrass Inside-out System were treated in accordance with the standard of care at the hospital, international guidelines and recommendations. The procedures are consistent with those described in the published guidelines and articles discussed in this LRR. The absence of complications in this consecutive series of hemodialysis patients with compromised upper venous occlusive disease, demonstrates the safety and efficacy of the Surfacer System technology.

4.6 Regulatory Status

The Surfacer System has been CE Marked and is commercially available in Europe. The Surfacer System is an investigational device in the United States.

5.0 BENEFIT/RISK ANALYSIS

5. 1 Importance of CVA

Central venous access is vital to many patients with acute and chronic illness, being one of the most commonly performed procedures in medicine. Hemodialysis, fluid management, chemotherapy infusion and parenteral nutrition are examples of life-sustaining therapies that would not be possible

without CVA.

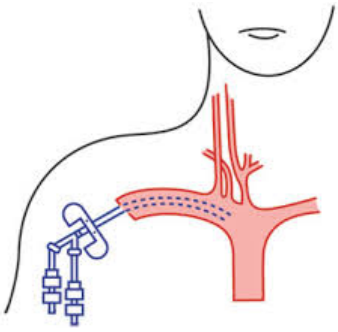
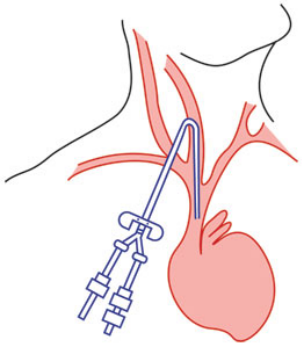
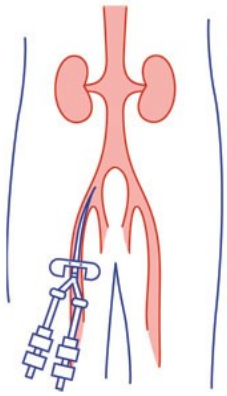
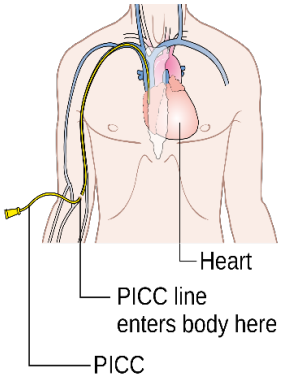
The indications for long-term venous access are widening and include the following:

- Cancer chemotherapy
- Long-term antibiotic therapy (e.g. infected prosthetic joints, bacterial endocarditis, cystic fibrosis)
- Parenteral nutrition (e.g., short bowel syndrome) hemodialysis
- Repeated blood transfusions
- Repeated venesection

The aim of CVA therapy is to position the catheter in a large vein to allow adequate dilution of infused products; reduced pain on injection; delay in the development of thrombosis; and aspirate blood. There is increasing use of long-term central venous access devices, both in and out of hospital. Despite the apparent similarity between short and long-term access devices, there are important differences in design, usage and patterns of complication that are relatively specific to longer-term venous access.

Central venous catheters or CVCs are commonly inserted via the internal jugular, external jugular, subclavian, or femoral veins (**Table 8**).

Table 8: CVA Access Sites

	
Subclavian Access	**Jugular Access**
	
Femoral Access	**Peripheral Inserted Central Catheter (PICC)**

Catheter-related vein thrombosis is a recurrent problem with longer-term venous access devices. It is thought that thrombus starts at the site of the venipuncture and then migrates along the catheter to eventually occlude the tip. Such thrombus can be seen on ultrasound floating around the catheter within the vessel lumen, or as a ghost after catheter removal. Thrombus creates an obstruction to infusion of fluids and withdrawal of blood, and there is a strong link between thrombus and infection.

In a literature review conducted by Bluegrass Vascular Technologies, Acute Risks of mechanical complications during the CVA insertion procedure include arterial puncture, malposition, local hematoma, pneumothorax, hemothorax, air embolism, arrhythmias, accidental removal and failure of catheterization. Similarly, other mechanical complications are vessel perforation, atrial perforation and catheter malfunctions (Karkee, 2010)[xxviii]. Table 9 displays safety rates for CVA insertion procedures via

subclavian and femoral routes.

Reported rates of arterial puncture are in the range of 1.3% - 4.2% for subclavian access, 2.2% -7.5% for jugular access, and 2.4% - 4.3% for femoral access. The percentage of misplacement is between 0% - 3% in subclavian access, between 0% - 2.2% in jugular access, 0% in femoral access. In the articles analyzed the percentage of pneumothorax and hemothorax are reported respectively in a range of 0% - 3% and 0.04% in subclavian approach, 0% for both pneumothorax and hemothorax for the jugular and femoral access, 33% for both pneumothorax and hemothorax for the translumbar access. Mechanical complications are common in venous catheter insertion. The values reported are 6.5% for subclavian access, 5.8% for jugular access, between 3.6% and 14.3% for femoral access and between 8% and 21% for Translumbar access. The risk of Hematoma with the subclavian approach is 7.5%; jugular approach is between 1.0% - 12%; femoral approach is between 0% - 7.2%; and translumbar or transhepatic is between 0% - 4.5% (**Table 9**).

Long Term Risks after the placement of the CVA catheter include complications related to the permanence of the catheter such as infections, deep venous thrombosis, catheter colonization, and thrombotic complications. These complications are common for all types of Central Venous Access. Typical rates of infection are reported in a range of 0.4% - 29.3% for the subclavian access, 0.76 - 40% for the jugular access, 0.6% - 40.5% for the femoral access and 9.5% - 28% for the translumbar access. Thrombotic complications are reported for each access site examined, with values between 0.8% - 4.5% for the subclavian access, 4.3% - 22.7% for the jugular access, 2.4% - 12.7% for the femoral access and 3.2% - 33% for the translumbar access. Deep venous thrombosis values are reported in a range of 5.8% - 6.5% for the subclavian access, 0.5% - 12.8% for the jugular access, 0.5% - 8.9% for the femoral access and 16.7% for the translumbar access. Typical rates of catheter colonization are reported in a range of 1.4% - 4.9% for the subclavian access, 4.6% - 25.2% for the jugular access, 7.2% - 40.5% for the femoral access and 8% – 33.3% for the translumbar access.

In summary, although femoral vein cannulation has been reported as easier than subclavian or jugular, this vascular access type is associated with higher risk of mechanical complications and catheter colonization/infection compared to jugular and subclavian access.

Translumbar access sites are associated with the highest risk of complications compared to jugular, subclavian and transfemoral accesses. Indeed, the inferior vena cava access is preferred only when other accesses are occluded. Immediate hazards of translumbar access include retroperitoneal bleeding and inadvertent puncture of the right renal artery. Delayed complications include catheter migration and dislodgment, spontaneous retroperitoneal hemorrhage, and IVC stenosis progressing to chronic occlusion. Catheter erosion into the right ureter (ureteral fistula) has also been reported. Translumbar central venous catheters should be used only for patients with no other option.

Table 9. Safety rates for Standard CVA Insertion Procedures

SUBCLAVIAN		Arterial Puncture		Misplacement		Pneumo-thorax		Hematoma		Hemothorax		Mechanical complications**	
Author	**Year**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**
Alexandrou E.	2014	2383	1.3%	2383	2.4%	2383	0.4%		-	2383	0.04%		-
Karkee D.V.	2010	203	3%	203	3%	203	0.5%		-		-	203	6.5%
Biffi R.	2009	-	-	136	0%	136	0%		-		-		-
Bertogli S	1996	424	4.2%		-	424	1.4%	424	7.5%		-		-
Smith H.O.	1995	133	3.8%		-	133	3%		-		-		-
FEMORAL		**Arterial Puncture**		**Misplacement**		**Pneumo-thorax**		**Hematoma**		**Hemothorax**		**Mechanical complications****	
Author	**Year**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**	**Pts**	**%**
Hingwala J.	2014		-		-		-		-		-		-
Alexandrou E.	2014	163	4.3%	163	0%	163	0%		-	163	0		-
Yeral M.	2013		-		-		-	45	0%		-		-
Parienti J.J.	2008		-		-		-	370	1.1%		-		-
Lorente L.	2008		-		-		-		-		-	184	7.61%
Al-Hwiesh, A.K.	2007											14	14.3%
Montagnac R.	1997		-		-		-		-		-	55	3.63%
Bertoglio S.	1996	41	2.4%		-	41	0%	41	7.2%		-		-

**Mechanical complications include arterial puncture, malposition, local haematoma, pneumothorax, haemothorax, air embolism, arrhythmias, accidental removal and failure of catheterization. Similarly, other mechanical complications are vessel perforation, atrial perforation and catheter malfunctions (Karkee, 2010).
Note: complication or data not analysed/mentioned in the articles are indicated with a dash (-).

5.2 Limitations of Available Treatments

Usually, when venous occlusion or thrombus fibrin formation occurs, the occluded vessel is difficult to access or deemed no longer patent or usable for long-term central venous access. Consequently, another access is required. Conventional methods for CVA in the presence of central venous occlusion have significant limitations, as described in **Table 10**.

Table 10: Conventional methods for central venous occlusion

Options	Therapeutic approach for CVA	Issues
Other upper body veins	When confronted with occlusion of a central vein, physicians usually utilize one of the remaining upper body veins (jugular and subclavian). The process can continue until all four central veins have been obliterated.	Loss of all four upper body central veins creates an access crisis leaving the patient without a central venous lifeline. When all four upper body central veins become occluded; physicians are forced to utilize alternative approaches that are much less desirable.
Femoral Veins Access	The femoral veins are utilized for long-term CVA when upper body sites are no longer available. Femoral veins are attractive secondary targets because they are relatively easy to access and, in most communities, the only option for central venous access when upper body sites have been exhausted.	Femoral venous catheters have poor stability due to leg movement, as well as high rates of infectious and thrombotic complications. Catheter migration, kinking and retraction are unique and common problems that result from leg movement. It is clear that the femoral veins are poorly suited to long-term central venous access. The use of femoral veins for long-term access can quickly lead to occlusions that eliminate a future route of temporary central venous access, further compounding the problem of lost central venous access.
Inferior Vena Cava access	Translumbar puncture of the inferior vena cava (IVC) is available in some tertiary care centers, but this procedure is technically challenging and carries significant risks. Translumbar central venous catheters should be used only for patients with no other option	Immediate hazards of translumbar access include retroperitoneal bleeding and inadvertent puncture of the right renal artery. Delayed complications include catheter migration and dislodgment, spontaneous retroperitoneal hemorrhage, and IVC stenosis progressing to chronic occlusion. Catheter erosion into the right ureter (ureteral fistula) has been reported.
Transhepatic access	Direct puncture of the liver can provide access to the inferior vena cava and right atrium via a hepatic vein. Due to poor catheter performance and	Transhepatic access is associated with substantial risks, and experience with the procedure is still limited. Serious complications include liver laceration, intra-peritoneal bleeding, and procedure-related death. Catheter instability due to respiratory

Options	Therapeutic approach for CVA	Issues
	very substantial hazards, transhepatic puncture for long-term central venous access should only be considered as a last resort	movement is a major problem. Catheter mobility also causes kinking, perforation, and related malfunctions that require catheter removal. Early thrombosis occurs much more frequently with transhepatic than with upper body catheters
Atrial access	Atrial access or surgical placement of catheters directly into the right atrium, has been described in a few patients who required life-sustaining nutritional support and had no alternative for vascular access. Isolated case reports describe right thoracotomy, median sternotomy, and video-assisted thoracic surgery to place catheters in the right atrium or the right atrial appendage.	Delayed complications of surgically-placed central venous catheters include catheter migration, dislodgment, infection, bleeding and pleural effusion. Thoracic surgery for placement central venous catheters is highly invasive and not easily repeated.
Occluded vessel recanalization	Recanalization of the occluded vessel, with placement of a new Central Venous Catheter, may allow recovery of the lost central venous access without involvement of other veins. Scientific literature describes this method as **"sharp recanalization"**: the distal sharp tip of a catheter is forced to cross the occluding thrombus. A fluoroscopic target is placed on the other side of the occlusion, requiring a second skin entry point. After the thrombus is crossed, a loop is introduced to catch and pull a new Central Venous Catheter inside the vessel.	The sharp recanalization procedure is complex and not standardized. It often requires new transcutaneous accesses both from the femoral vein and from the occluded vein, more distally than the previous access location. There is no single device that has been developed to perform this procedure, although the Outback and Rosh-Uchida catheters have been used "off label" to perform the procedure.

5.3 Clinical Considerations

Upper body veins are always preferred for long-term central venous access. Devices placed via upper body veins provide the best combination of patient comfort and mobility, device stability, accessibility, and infection risk. When the upper body central veins are lost, the remaining alternatives are undesirable for anything but emergency, temporary access. Central venous catheterization can be obtained with access from sites other than the jugular or subclavian veins, but with major short and long-term complication rates. Advantages and disadvantages of the available access routes are summarized in **Table 11**.

Table 11: Advantages and disadvantages of different routes for CVA

CV Catheter Insertion Route	Advantages	Disadvantages
Arm veins (cephalic, basilic)	Simple to access, veins visible and palpable No vital organs close Patient comfort	Failure to achieve central position High incidence of thrombosis Low maximum infusion rates
Internal jugular	Simple to insert Direct route to central veins High flow rate, low risk of thrombosis Lower risk of pneumothorax	Patient discomfort Higher rate of late complications, especially infection Tunnelling more difficult to chest wall
Subclavian axillary	Less patient discomfort Lower risk of long-term complications	Curved insertion route Difficult to access Acute complications - pneumothorax, haemothorax, nerve damage
Femoral	High flow, good for dialysis Easy insertion	Higher rate of infection and thrombosis Poor stability: migration, kinking, retraction Patient discomfort Difficult in obese patients
Inferior Vena Cava (Translumbar)	Last option procedure	Technically challenging Procedural risks: retroperitoneal bleeding, renal artery puncture Migration, Dislodgement, Occlusion

5.4 Surfacer System Potential Benefits

As described in **Table 11**, the innovative approach of the Surfacer System brings advantages to patients that no longer have adequate access or who cannot achieve CVC using conventional approaches to central venous catheterization.

The potential benefits of the Surfacer System IOCVA approach include but are not limited to the following:

- **Reduction of Insertion Risk**
  Reversing the path to venous access is intended to avoid or reduce risks of damage or involvement of other anatomical structures, such as arterial puncture (with edema or serious bleeding), lung injury (i.e. pneumothorax or hemothorax) or nerve damage.

- **Ease of Procedure**
  The aiming features using the Exit Target, specifically developed for fluoroscopy, allow precise needle positioning and accurate delivery to the skin surface. The simplicity of the procedure, which requires placing the ring at planned CVC exit, makes it attractive and suitable for clinical application in the larger treatment population.

- **Ability to Cross Occlusions**
  The Surfacer System may be able to create central venous access in subjects with prior multiple occlusions or who have no other options.

- **Ability to Spare Other Vessels**
  The Surfacer System may be able to utilize a previously occluded vessel and spares /salvages other vessels for physiological circulation and other access requirements. In emergent situations, this could be a lifesaving benefit to patients who have few or no other options for venous access.

THE SURFACER SYSTEM APPROACH HAS DEMONSTRATED THE FOLLOWING BENEFITS:

- low patient risk
- quick and safe procedure
- **solution for Central Thoracic Veno-Occlusive Diseases** in no option cases, with the potential to achieve repeated access from a single point
- success in patients with no upper body access
- preserve jugular vein access

5.5 Surfacer System Potential Risks

Potential risks associated with using the Surfacer System are considered to be similar those associated with routine interventional procedures and with the patient's underlying condition. List of Potential Risks and Definitions can be found in Appendix A.

These potential risks include, but are not limited to:

- Pain
- Infection
- Bleeding
- Adverse tissue reaction; allergic reaction
- Cardiovascular sequelae including: perforation, tamponade, spasm or effusion
- Lymphatic system sequelae
- Pulmonary sequelae including: pneumothorax, pulmonary embolism
- Vascular sequelae including vasospasm, vessel perforation, dissection, or aneurysm
- Unintended embolization or thrombosis
- Arrhythmias
- Neurologic sequelae including stroke; transient ischemic attack; nerve injury
- Arteriovenous Fistula
- Death
- Surfacer System component failure or malfunction

5.6 Benefit/Risk Statement

The Surfacer System is intended to provide a solution in patients with an upper body venous occlusion or other thrombotic fibrin occlusive pathology impeding standard access methods, including contraindication to use of remaining veins.

The Surfacer System is designed to allow Central Venous Catheterization utilizing an inside-out approach. This approach brings benefits to patients with CV occlusion, in whom alternate access options (conventional access methods) are not feasible or are associated with high risk and morbidity.

This new reversed approach brings expected benefits to patients in whom alternate access options are not feasible or associated with high risks. Expected benefits include: reduction of insertion risk; ease of

procedure thanks to the use of a visible exit target, enabling precise aiming of the needle; ability to overcome occlusions in subjects with limited or no other options; and ability to spare other vessels.

The Surfacer System approach to CVA catheterization provides visual and placement (steering) benefits that cannot be achieved with conventional approaches in patients with central vein occlusions. Additionally, the Surfacer System device provides access to occluded veins, using the same vessel that was lost for CVA. Preclinical verification and validation of the Surfacer System and clinical experiences demonstrate safety and effectiveness of the Surfacer System procedure.

The Surfacer System is not associated with long-term risks, because the device is for temporary use. However, the Surfacer System allows CVA catheters to be successfully placed for short-term and long-term use. Therefore, it is important to analyze and compare the immediate procedural risks of other conventional approaches in patients with central vein occlusions in order to determine the risk reduction that is achieved with the Surfacer System approach.

The Inside-Out approach, based on reversing the path to venous access, has shown the capability to avoid or reduce the reported clinical risks of damage or involvement of other anatomical structures, such as arterial puncture (with edema or even serious bleeding), lung injury (i.e. pneumothorax or hemothorax) or nerve damage. No such events were observed in a large series of over 124 patients who underwent this procedure as well as the 12 patients in the first in human study.

The scientific literature and human clinical experience finds that the Surfacer System provides stable, upper body central venous access that is suitable for any conventional catheter. Therefore, based on the current evidence and testing, the benefits of use of the Surfacer System outweigh the risks in the defined patient populations.

Central venous occlusions place patients at significant clinical risks, including:

- Cerebral edema, which puts patients at risk for chronic memory loss, learning deficiency, and possible MS linkage
- Current standard of care "outside-in" approach increases the risk of significant puncture, rips and tears to arteries, lungs, and other critical systems
- Increased infection risk once jugular veins are obliterated and access is shifted to the use subclavian and femoral access sites

6.0 STUDY DESIGN

This study has been designed as a prospectively enrolled, single-arm, multicenter study to demonstrate the safety and efficacy of the BVT Surfacer System in patients who require central venous access.
A total of 30 subjects is planned at a minimum of three (3) sites. Ten subjects will be enrolled initially. After safety data review, enrollment is expected continue to 30 subjects overall with no more than 10 subjects enrolled at a single site.

Enrolled subjects will undergo the Surfacer System procedure, then exit the study after follow-up at hospital discharge and 7-days post procedure. BVT will utilize an Independent Data Monitoring Committee (IDMC) to review the study's safety data during the conduct of the study and at study closure.

6.1 ASA Guidelines

The study, designed in conformance with the standard of care for central venous access, as defined by the American Society of Anesthesiologists Task Force on Central Venous Access. Anesthesiology, 2012 Mar; 116(3):539-73.[xxix] These guidelines define central venous access as placement of a catheter such that the catheter is inserted into a venous great vessel. The venous great vessels include the superior vena cava, inferior vena cava, brachiocephalic veins, internal jugular veins, subclavian veins, iliac veins, and common femoral veins.

6.2 Subject Selection and Participation

The study population include patients who are candidates for vascular access with limited or diminishing upper body venous access or pathology impeding standard access methods (see Inclusion Criteria #3,

section 6.3.1).

Subjects who provide informed consent will undergo screening and baseline assessments. Subjects who successfully pass the inclusion and exclusion criteria will undergo the Surfacer System procedure, with subsequent follow-up assessments at hospital discharge and 7 days post procedure.

6.3 Study Eligibility Criteria

To qualify for study participation, subjects must meet all of the Inclusion Criteria and none of the Exclusion Criteria.

6.3.1 Inclusion Criteria

1. Subjects are between 18-80 years of age.
2. Subjects referred for placement of a central venous access catheter.
3. Subjects have limited or diminishing upper body venous access or pathology impeding standard access methods.
4. Subjects are willing and able to give written informed consent.

6.3.2 Exclusion Criteria

1. Subjects are contraindicated for Surfacer System use if one of the following are found (per the IFU):
   a. Occlusion of the right femoral vein;
   b. Occlusion of the right iliac vein;
   c. Occlusion of the inferior vena cava.
2. Subjects contraindicated for central venous access based upon the treating physician's opinion and institutional standard of care.
3. Subject has acute thrombosis within any vessel (SVC, jugular, inferior vena cava (IVC), brachiocephalic and subclavian) planned be crossed by Surfacer System.
4. Subject has tortuous anatomy which precludes a straight line from femoral venous entry to subclavian exit.
5. Subject has been diagnosed with active pericarditis or endocarditis.
6. Subject has a known or suspected pericardial effusion.
7. Subject has a known or suspected aneurysm or ectasia of ascending aorta, innominate artery, or subclavian artery.

8. Subjects who are pregnant or of childbearing potential not taking adequate contraceptive measures or nursing during the study.

6.4 Study Endpoints

6.4.1 Primary Efficacy Endpoint

- Rate of safe insertion and patency of CVCs created across venous occlusions.

6.4.2 Primary Safety Endpoints

- Acute device safety, defined as the absence of procedural complications (hemopericardium, hemothorax, pneumothorax, blood transfusion, resuscitation, emergency post-procedural intervention, transfer to an intensive care unit, and death) at discharge and 7 days post procedure.
- Overall device and procedure related anticipated adverse events compared to historical safety data from CV placement procedures.

6.4.3 Secondary Efficacy Endpoint

- Surfacer System advancement from femoral vein to sub-clavicular exit to facilitate CVC placement assessed by the ability of the Surfacer System to facilitate central venous access placement.

6.4.4 Secondary Safety Endpoint

- Technique Conversion rate.

7.0 STUDY PROCEDURES

7.1 Informed Consent

Potential subjects will be provided with study information and given an opportunity to ask questions about the study and treatment options. If the individual agrees to participate; they will complete a written informed consent, be assigned a unique study identifier, and undergo screening and baseline assessments. Study identifier will include the site number and a sequential subject ID number (i.e. 05-04).

7.2 Screening and Baseline Assessments

Screening and Baseline assessments will include the following:

- Inclusion and Exclusion Criteria

- Medical history with demographics
- Physical exam with vital signs
- TCVO Lesion Type Determination
- Medications (antithrombotic and cardiovascular)
- Pregnancy test (not required if patient is male or non-child bearing potential)
- Clinical laboratory tests including coagulation profile (APTT, PT, INR), CRP, LDH, ASAT, ALAT, fibrinogen, D-dimer
- Ultrasound or venous duplex venography of upper body veins (SVC, jugular, inferior vena cava (IVC), brachiocephalic and subclavian) to rule out acute thrombosis within a vein to be crossed by the Surfacer System
- AP and LAT chest x-ray or cine fluoroscopy will be performed prior to the procedure to define the pattern of occlusion and to rule out acute thrombosis
- 12-lead ECG

7.2.1 Screen Failures

If the Principal Investigator determines that the subject is not an acceptable study candidate at any time during screening and the collection of baseline study data, up to the point of enrollment, the subject will be documented as a Screen Failure and no further study data will be collected. The reason and cause for Screen Failure will be documented.

7.3 Subject Enrollment

A subject will be considered “enrolled” in the study when they have completed informed consent, are qualified per all study screening requirements and component of the investigational study device is inserted into the subject.

Once a subject has been exposed to the study device, even if the Investigator is unable to complete the Surfacer treatment, the study subject will be considered part of the intent-to-treat population and will be followed up to 7 days post-procedure, or until any adverse events are resolved.

See Section 8.0 for description of analysis populations and statistical considerations.

7.4 Intra-Procedural Assessments

During the Surfacer System procedure, the following data will be collected:

- Continuous ECG monitoring
- Contrast angiography (venography) to confirm occlusions.
- Fluoroscopy will be performed to confirm catheter tip position (catheter tip position must be visible on fluoro).
- Cone beam CT, intracardial echo, or other advanced imaging guidance to verify placement. Investigator must be able to clearly identify the level of occlusion. With Type IV occlusions, the Investigator must be able to definitively identify the remnant of SVC; if this cannot be accomplished by angiography, the operator should not proceed without advanced imaging guidance such as cone beam CT or intracardiac echo. Advanced imaging should also be utilized for some Type III TCVO lesions characterized by unusually tortuous vessels or otherwise challenging anatomy.
- AP and LAT chest x ray or cine-fluoroscopy will be performed post procedure to check the correct placement and position of the CVA Catheter tip, rule out pleuro-pulmonary damage (pneumothorax, hemothorax, etc.), and to detect pleural fluid and mediastinal widening.
- TTE (optional, only if cardiac events)
- Study Device Performance
- Adverse Events
- Protocol Deviations

7.5 Discharge/Post Procedure Assessments

Subjects will be carefully monitored with follow-up at hospital discharge and 7-days post procedure. At hospital discharge, the following assessments will be conducted and documented:

- Physical exam including vital signs
- Medications (antithrombotic and cardiovascular)
- Clinical laboratory tests including coagulation profile (APTT, PT, INR), CRP, LDH, ASAT, ALAT, fibrinogen, D-dimer
- AP and LAT chest x ray or cine-fluoroscopy, ideally assessed immediately after the index procedure is complete. If the Investigator determines that additional imaging is clinically indicated at the time of discharge (same day or next day discharge), a chest x-ray may be obtained.
- TTE (optional, only if symptomatic cardiac events)
- Adverse Events

- Protocol Deviations

At 7 Days (+ 7) post procedure, the following assessments will be conducted and documented. Although a generous visit window has been provided to allow for clinic visit scheduling, these assessments are to occur on Day 7 post procedure, or as soon as possible thereafter:

- Physical exam including vital signs
- Medications (antithrombotic and cardiovascular)
- Adverse Events
- Protocol Deviations

7.6 Subject Withdrawal

Subject study participation is voluntary and subjects may withdraw from the study at any time without penalty or compromise to their medical care. Additionally, a subject may be withdrawn from the study at any time at the discretion of the Principal Investigator, if the Principal Investigator believes that continuation in the study could result in unnecessary risks or jeopardize the subject's health and welfare.

The reason for withdrawal will be documented at the time of study withdrawal. All study data collected up to the point of withdrawal will be included in the data analysis and maintained as part of the study documentation.

7.7 Study Completion

Once a subject has undergone all required study assessments, they will have completed the study.

All study data collected through study completion will be included in the data analysis and maintained as part of the study documentation.

7.8 Study Discontinuation

The study may be discontinued at any time by BVT or applicable regulatory agency. If the study is discontinued before study activities have been completed, all study data collected up to the point of discontinuation shall remain the property of the BVT and will be subject to all applicable patient and data privacy requirements.

8.0 STATISTICAL CONSIDERATIONS

8.1 Introduction

This is a prospective, single-arm, multi-center study to demonstrate the safety and efficacy of the Surfacer® System. Clinical data will be obtained from up to 30 subjects treated with the Bluegrass Vascular Technologies Surfacer System device at a minimum of three (3) sites.

No site will enroll more than 10 subjects. The study population will include patients who are candidates for vascular access with limited or diminishing upper body venous access or pathology impeding standard access methods. Patients who provide consent will be enrolled and undergo the procedure with follow-up at hospital discharge and 7 days post-procedure. Total study duration is anticipated to be 12 months. The study objectives and analytical methods to be used are described herein.

8.2 Study Endpoints

8.2.1 Primary Endpoints

Primary Efficacy Endpoint:

- Rate of safe insertion and patency of CVCs created across venous occlusions.

Primary Safety Endpoints:

- Acute device safety, defined as the absence of procedural complications (hemopericardium, hemothorax, pneumothorax, blood transfusion, resuscitation, emergency post-procedural intervention, transfer to an intensive care unit, and death) at discharge and 7 days post procedure.
- Overall device and procedure related anticipated adverse events compared to historical safety data from CV placement procedures.

8.2.2 Sample Size Justification

A statistically powered sample size calculation is not applicable given the objective of this study. Therefore, the sample size is intended to provide sufficient data to assess basic safety and potential for effectiveness with an acceptable level of outcome evaluation certainty, while not overexposing the target population to the risks associated with an investigational device. The selection of at least 30 subjects is consistent with the range of 10-40 subjects cited as typical for such studies in recent FDA Clinical Investigator Training materials:

http://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM378265.pdf, (Slide 10 of 43 at the above link, Nov. 2013).

Table 12 provides the projected width of the confidence interval for a continuous and for a binary endpoint.

Table 12. Expected results for confidence intervals for continuous and binary endpoints

Sample Size	Continuous endpoint	Binary endpoint
	Width of 95% CI	Clopper-Pearson 95% CI
n = 30	+/- 0.37 x SD	+/- 18.7%

With 30 subjects, the Maximum Clopper-Pearson Exact 95% Confidence Interval for the binary outcome will range from 31.3% to 68.7%, assuming an observed percentage of 50% (Listing 1). As the observed rate increases, the confidence interval will narrow. For example, with 30 subjects and an observed rate of 90% (27 out of 30 successes), the Clopper-Pearson Exact 95% Confidence Interval would range from 73.5% to 97.9%. Note that due to the exact nature of the Clopper-Pearson Confidence Interval, the range will not be symmetric the more the observed rate deviates from 50%.

Listing 1. PASS 13 Output for a Binary Outcome Evaluation

Confidence Intervals for One Proportion
Numeric Results for Two-Sided Confidence Intervals for One Proportion
Confidence Interval Formula: Exact (Clopper-Pearson)

Confidence Level	Sample Size (N)	Target Width	Actual (P)	Proportion Limit	Proportion Limit	Lower P= 0.5	Upper	Width If
0.950	30	0.244	0.900	0.735	0.979	0.374		

References:
Fleiss, J. L., Levin, B., Paik, M.C. 2003. Statistical Methods for Rates and Proportions. Third Edition. John Wiley & Sons. New York.
Newcombe, R. G. 1998. 'Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. Statistics in Medicine, 17, pp. 857-872.

8.2.1 Secondary Endpoints

Secondary Efficacy Endpoint:

- Surfacer System clinical utility use from insertion into the femoral vein to sub-clavicular exit assessed by the ability of the Surfacer System to facilitate central venous access placement.

Secondary Safety Endpoint:

- Technique Conversion Rate

8.3 Statistical Analysis

8.3.1 Data Reporting Convention

Descriptive statistics will be utilized to summarize the demographic and baseline data. For continuous endpoints, descriptive statistics will be presented including the number of subjects with the measurement, mean, standard deviation, median, minimum and maximum. For categorical endpoints, descriptive statistics will include the number with the event or characteristic, the number evaluated, the percentage presented, and 95% exact binomial confidence interval. A critical two–sided alpha level of 0.05 will be carried out for all statistical evaluations.

8.3.2 Assumption Verification

As a routine function, visual inspection and statistical tests will be used during analysis to determine if the study variables are consistent with the assumptions of statistical tests proposed. For continuous outcome variables, visual examination of data symmetry will be initially performed with test of normality to be done by Shapiro-Wilks test or an equivalent, and equal variance assumptions will be tested with Folded F-test or an equivalent. For categorical variables, exact tests will be performed to limit assumptions regarding testing where possible.

8.3.3 Pooling of Study Sites

Data collected across different study sites will be pooled. The justification for pooling data

across sites is made on a clinical basis.[1] A common protocol has been used across different sites with the intention of pooling the data for analysis. Enrollment will be balanced between sites, with no more than 10 subjects enrolled at a single site overall. Every effort will be made to promote consistency in study execution at each site.

8.3.4 Analysis Populations

Enrolled Population:

Study results will be analyzed and reported for all enrolled patients who sign the informed consent, complete the screening procedures are eligible and enrolled in the study.

Intent-to-treat (ITT) Population:

The ITT safety subject population comprises all enrolled subjects in whom Surfacer System usage was attempted (i.e. the first step in the Instructions for Use of the Surfacer System was performed), regardless of whether or not the procedure was completed with the successful placement of a CVC.

Per Protocol Population:

The per protocol (PP) population will include all enrolled subjects in whom the Surfacer System procedure was completed, with a CVC implanted completely and correctly (i.e. the last step in the Instructions for Use of the Surfacer System was performed).

All primary and additional endpoints will be evaluated in both the intent to treat (ITT) and Per Protocol analysis sets. The intent to treat analysis will be considered primary.

8.3.5 Primary Endpoint Analysis

Descriptive statistics reported for both primary safety and efficacy endpoints will be summarized using number with the event or characteristic, the number evaluated, frequencies, percentages and two-sided exact 95% confidence intervals, or time to event analysis, as appropriate. Fisher's exact test will be carried out for independent proportions comparison. A

[1] Meinert, C. (1986). Clinical Trials: Design, Conduct, and Analysis. Oxford University Press, New York.

critical two–sided alpha level of 0.05 will be used for all statistical evaluations. The primary endpoint study outcomes will be evaluated in the ITT population.

8.3.6 Secondary Endpoints Analysis

For continuous secondary endpoints, descriptive statistics will be presented including the number of subjects with the measurement, mean, standard deviation, median, minimum and maximum. For categorical endpoints, descriptive statistics will include the number with the event or characteristic, the number evaluated, the percentage presented, and 95% exact binomial confidence interval.

8.3.7 Multiplicity

No multiplicity adjustment will be required.

8.3.8 Safety Evaluations and Analyses

Adverse Events will be categorized by serious and non-serious, device or procedure-related and non-device or non-procedure related, and anticipated and unanticipated.

The frequency of each event will be summarized by seriousness, severity and by relationship to the device. Since some subjects may report the same event several times, the occurrence of the highest severity case of the event will be used for the purpose of analysis.

The rates of adverse events will be presented with associated 95% confidence intervals. No statistical hypothesis test will be made. At periodic intervals during study conduct, clinical evaluation of adverse events will be performed by the IDMC.

8.3.9 Missing, Unused & Spurious Data

Every effort must be taken by the Principal Investigators and designated site personnel to ensure that all data required on every CRF is obtained and recorded. Missing data is documented as “ND” (“Not Determined”) on the CRF.

Additionally, BVT minimize the incidence of missing data through appropriate management of the clinical investigation, proper screening of study participants as well as thorough training of investigators, monitors and study coordinators.

The analysis of the endpoints will be performed with and without missing data using the Last Observation Carried Forward (LOCF) as main missing data imputation technique.

If appropriate, a set of additional missing data imputation methods will be employed to determine the impact of missing or incomplete data on the study conclusions.

8.3.10 Interim Analysis

No formal interim analysis will be performed.

8.3.11 Subgroup Analysis

No subgroup analysis will be performed.

9.0 SAFETY

Safety monitoring will be performed by the Principal Investigator during the conduct of this study. An Adverse Events (AE) will be recorded and assessed from the time of enrolment through study completion or early withdrawal. All AEs will be followed by the Principal Investigator until resolution or stabilization.

9.1 Adverse Event Classification

9.1.1 Adverse Event

An AE is any undesirable clinical event experienced by a subject participating in a study.

The intensity of an AE will be classified as one of the following:

Mild: transient, does not interfere with the subject's daily activities and does not require therapeutic measures

Moderate: Interferes with the subject's daily activities and requires simple therapeutic measure

Severe: Intolerable experiences that interrupt the subject's daily activities and requires substantial therapeutic measures including surgical intervention or hospitalization

The relationship of the AE to the investigational device will be categorized as one of the following:

Not related: No clinical evidence supporting a causal relationship

Related: Clinical evidence supports a definite and certain causal relationship

9.1.2 Anticipated Adverse Events

A list of AEs which may be anticipated, resulting from use of the study device, are defined in Instructions for Use (IFU) of the investigational device and in Section 5.5 of this protocol.

9.1.3 Serious Adverse Event/Unanticipated Adverse Device Effect

A Serious Adverse Event (SAE) is an AE that meets one of the following criteria:

- fatal
- life threatening
- results in an unanticipated or prolonged hospitalization
- results in a significant and persistent disability/incapacity
- results in a congenital anomaly or birth defect

An unanticipated adverse device effect (UADE) is any SAE as defined above that is caused by or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, degree of incidence in this protocol.

Additionally, a UADE includes any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

9.1.4 SAE/UADE Reporting

BVT will be notified of an SAE/UADE the SAE/UADE Report Form. This form must be completed by the Principal Investigator or designee, then faxed or scanned and emailed to BVT. The SAE/UADE Report Form, fax number, and email are provided in the study manual.

Initial notification of the SAE/UADE may occur by telephone, but must always be followed by submitting the SAE Report Form by the close of the next business day.

9.1.5 UADE Regulatory Requirements

If it is determined that an UADE occurred, BVT will report the results of the evaluation to the Independent Data Monitoring Committee (IDMC), the FDA, and Principal Investigators within 10 working days after BVT first receives notice of the event (21 CFR 812.46(b), 812.150(b)(1)). If BVT determines an event or event rate presents an unreasonable risk to subjects, the study or parts of the study presenting that risk will be terminated, as soon as possible. Termination of the

study will occur no later than five (5) working days after BVT makes this determination and no later than fifteen (15) days after BVT or its designee first receives notice of the event.

10.0 STUDY MANAGEMENT

10.1 Data Collection

All study data will be collected on standardized electronic Case Report Forms (eCRFs) provided by BVT.

Electronic CRFs must be signed electronically by the Principal Investigator listed in the Clinical Trial Agreement and Delegation of Authority Log. If for any reason an eCRF is unavailable and/or inaccessible, a paper CRF will be provided by the trial Sponsor to be completed, signed by the Principal Investigator or designee and submitted to BVT. Case Report Form Completion Instructions will be provided by BVT to assist the Principal Investigator(s) and appropriate staff with eCRF completion and data entry processes.

BVT or their designee is responsible for database development, validation, control and management using systems that are compliant with 21 CFR Part 11. Databases shall include input(s) from each eCRF, issuance and resolution of queries, database maintenance, and statistical support.

10.2 Source Documentation

BVT and their representatives, review boards (IRB/IEC), and applicable regulatory authorities will be granted access to a subject's medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the study must be recorded and maintained.

10.3 Data Confidentiality

To protect subject confidentiality, a unique study identifier will be used on all data collected for study purposes. Any data, imaging media, or other form of study record collected shall be de-identified. Original copies of all data must be kept at the site.

10.4 Record Retention

Study documentation and records shall be retained in accordance BVT's internal procedures or those of authorized designee Per FDA regulation 21 CFR, 812.140, records of each subject's participation in the study must be maintained for a period of two (2) years after trial closure and submission of the final report to the IRB.

At a minimum, a copy of the study documents must be retained by the Site for at least five (5) years following the study completion.

Study documentation will not be destroyed without prior written agreement between BVT and the Principal Investigator.

The Principal Investigator is to allow representatives of BVT to inspect all study-related documentation throughout the duration of the study.

10.5 Study Monitoring

BVT or its designee will conduct periodic site monitoring to ensure that all Principal Investigators are in compliance with the protocol and the investigator's agreement. The monitor will verify source documentation against completed eCRFs and resolve any queries/discrepancies.

10.6 Study Oversight and Compliance

Each study site will be visited periodically to ensure that the study is conducted in full compliance with all applicable regulations and this protocol.

BVT or designee shall maintain regular contact with the study site throughout the investigation by telephone, mail, e-mail, and on-site visits. Periodic monitoring visit shall be conducted to ensure continued protocol compliance, adequate subject enrolment, and accurate data reporting.

Following study closure at the study site, BVT or its designee will make a final study visit, to collect any outstanding documentation, ensure that the Principal Investigator's files are accurate and complete, review record retention requirements with the Principal Investigator, make a final accounting of all study supplies shipped to the Principal Investigator, provide for appropriate disposition of any remaining study supplies, and ensure that all applicable requirements for the study are met.

10.6.1 Study Non-Compliance

If BVT or its designee becomes aware that a Principal Investigator is not complying with all study requirements, BVT will evaluate the non-compliance and if necessary, either secure compliance or take other actions until the non-compliance has been resolved.

If the non-compliance is severe or cannot be resolved, BVT retains the right to remove either the Principal Investigator or a study site from the trial.

10.7 Investigational Device Inventory

An initial shipment of investigational devices will be supplied by BVT to IRB/IEC approved study sites. Additional investigational devices will be supplied to the study site as needed throughout the conduct of the study.

10.7.1 Investigational Device Accountability

Device accountability will be documented and maintained by the Principal Investigator at the study site, to include all investigational devices received, used, and disposed at the end of the study. Investigational device accountability records shall be maintained with clinical study files and be available for review during monitoring visits.

10.7.2 Investigational Device Storage

Investigational devices for use in this study will be stored in a locked, cool, dry and clean area, with controlled accessibility. Only study staff authorized by the investigation will have access to the investigational device.

10.7.3 Investigational Device Return

BVT will provide directions for investigational device return at either study termination or closure. All unused devices and/or those in opened packages must be returned to BVT. The Principal Investigator must document any unused devices that are returned.

10.8 Protocol Deviations

A protocol deviation occurs when the Principal Investigator or study staff do not conduct the study in accordance with the protocol or other agreed upon study terms without prior approval from BVT. Any deviation will be documented and reported to BVT regardless of severity or rationale for deviation.

10.9 Investigator/Site Training

Investigators and site staff will be trained on the study in total, use of the investigational device, and any specialized procedures required for the study. BVT will provide clinical support to site for any questions or concerns related to the investigational device; however, BVT will not have influence on subject care.

10.10 Study Changes

10.10.1 Change to the Protocol

BVT will initiate and document any changes to the protocol in writing. BVT shall submit such changes to the Principal Investigators and applicable regulatory authorities. Approval of the changes must be received by BVT in writing before the may be implemented at the study sites.

10.10.2 IRB/IEC Approval Withdrawal

Withdrawal of IRB/IEC approval must be submitted to BVT within five (5) business days of the change.

10.11 Study Completion

Each Principal Investigator shall be notified in writing upon termination or conclusion of the study. BVT retains the right to suspend or terminate this study at any time.

10.12 Study Reports

Study progress reports shall be prepared and submitted to regulatory authorities per the applicable regulations, or upon request.

A final clinical study report (CSR) will be compiled and submitted once all data collection and analyses have been completed. CSRs shall include all information required and outlined in this protocol that is available at the time of the report. A copy of the final CSR will be provided to applicable regulatory agencies and participating Principal Investigators. The final CSR will be filed and maintained with study documentation.

11.0 STUDY ADMINISTRATION

11.1 Statement of Compliance

This study will be conducted in compliance with GCP guidelines, all applicable US Federal regulations pertaining to investigational devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, Good Clinical Practice (GCP) standards, and Health and Insurance Portability and Accountability Act (HIPAA), and all other applicable standards, regulations, guidelines, and institutional policies.

11.2 CLINICALTRIALS.GOV REGISTRATION

A description of this study will be available on http://www.ClinicalTrials.gov as required by U.S. law. This

website will not include information that identifies study subjects. At most, the website will include a summary of the results of the study and will be available for public review at any time.

11.3 Investigator Responsibilities

Investigator(s) and study staff will adhere to the Statement of Compliance governing this study (Section 11.1). The investigator is responsible for obtaining proper regulatory approvals, and reporting study information to regulatory authorities per all applicable regulations. A summary of specific Investigator responsibilities per 21 CFR, 812.100 given below:

- Investigator must wait for regulatory approval to conduct the study.
- Investigator shall conduct the study in accordance with a signed agreement with BVT
- Investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.
- Investigator shall disclose to BVT sufficient financial information to allow for financial disclosure as described in CFR Part 54.

Upon completion or termination of a clinical study or Investigator's part in the study, or at BVT's request, an investigator shall return to BVT any remaining supply of the device or otherwise dispose of the device as BVT directs.

12.0 BVT GENERAL RESPONSIBILITIES

BVT is responsible for selecting qualified investigators and providing them with the information they need to conduct this study properly, ensuring proper monitoring of the study, ensuring that IRB review and approval are obtained, and ensuring that the FDA and participating investigators are promptly informed of significant new information about the study.

13.0 PUBLICATION POLICY

All clinical information obtained in this study will be considered confidential. The identity of individual subjects will be kept confidential in so far as the law and safe medical practice allow. It is planned that the results of this study will be submitted for publication in scientific journals; patient identities will not be disclosed.

BVT will be furnished with a copy of any proposed publication for review and comment prior to

submission for publication. Manuscripts will be forwarded to BVT at least 30 days prior to submission and abstracts at least 7 days prior to submission. At the expiration of the 30 or 7-day period, the investigator may proceed with submission for publication.

In addition, each investigator must agree that no publications will be submitted without permission of BVT or that will jeopardize a multi-center publication, and all clinical data gathered during the study will be pooled in a common database that is the property of BVT.

14.0 REFERENCES

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15.0 APPENDIX A

DEFINITIONS OF POTENTIAL RISKS

- **Pain -** Acute discomfort conveyed to the brain by sensory neurons associated with a symptom or disease.
- **Infection–** An infection is invasion and multiplication of microorganisms in body tissues accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic).
- **Bleeding** – overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of two or three units of whole blood/RBC and does not meet criteria of life threatening or disabling bleeding.
- **Adverse Tissue Reaction; Allergic Reaction** - Localized or systemic hypersensitivity to contrast media, anesthesia or other medications used characterized by rash, nausea, vomiting, itching, shortness of breath, vasovagal reaction or anaphylaxis. The specific allergen should be reported if known.
- **Cardiovascular Sequela, including perforation, tamponade, spasm or effusion; Perforation-** Perforation detected by the clinical site requiring additional treatment including efforts to seal the perforation. **Tamponade -** The term cardiac tamponade will be used to describe a pericardial effusion sufficiently to cause circulatory compromise and require drainage. Any cardiac tamponade is considered serious and procedure related. **Spasm -** A transient constriction of the lumen of one or more vessels due to contraction of vascular smooth muscle effusion **– Pericardial effusion** is defined as a new fluid collection within the pericardial space, with or without cardiac tamponade, as identified by echocardiography or CT imaging.
- **Lymphatic System Sequelae -** Lymphatic system sequelae is recognized by the new occurrence of lymph drainage at the procedure site, or a new accumulation of lymphatic fluid (lymphocele) near the procedure site.

- **Pulmonary Sequelae including: pneumothorax and pulmonary embolism – Pneumothorax** - abnormal collection of air in the pleural space that causes an uncoupling of the lung from the chest wall. **Pulmonary embolism** is defined as obstruction of one or more pulmonary arteries by dislodged venous thrombi or foreign materials.
- **Vascular sequelae including vasospasm, vessel perforation, dissection, or aneurysm; Vasospasm -** A transient constriction of the lumen of one or more vessels due to contraction of vascular smooth muscle. **Vessel Perforation -** Complete penetration of the vessel wall, with or without self-limited extravasation of blood into surrounding tissues. **Vessel Dissection**- This term applies to unintended injury of femoral or pelvic vessels or the inferior vena cava. Dissection is defined as disruption of the intimal layer that can be detected by contrast angiography, ultrasound, or other imaging modalities. **Aneurysm-** an abnormal blood-filled bulge of a blood vessel and especially an artery resulting from weakening (as from disease) of the vessel.
- **Unintended Embolization or Thrombosis - Embolism** is defined as the unintended entry of air, thrombus, or foreign bodies into the circulation. **Thrombosis** - local coagulation or clotting of the blood in a part of the circulatory system.
- **Arrhythmias**- Development of a new atrial and/or ventricular arrhythmia, exacerbation of a prior arrhythmia or a significant increase in the severity of the current arrhythmia. Event that requires cardioversion or introduction of a pacemaker will be considered a Serious Adverse Event.
- **Neurologic Sequelae including stroke; transient ischemic attack; nerve injury: Stroke -** Acute cerebral infarction or hemorrhage confirmed by brain imaging (CT or MRI), or with new neurological abnormalities persisting more than 72 hours. A stroke that occurs within 24 hours of the procedure will be considered procedure related. All stroke events are considered serious. **Transient Ischemic Attack (TIA) -** New focal neurological deficit with rapid symptom resolution (usually 1-2h), always within 24 h. **Nerve Injury-** includes total or partial transection of a nerve from stretching, cutting (laceration), compression, shearing, or crushing injuries

- **Arteriovenous fistula -** A dilation of an artery with actual disruption of one or more layers of its walls, rather than with expansion of all wall layers. An arteriovenous fistula is an abnormal channel or passage between an artery and a vein.
- **Death -** Cessation of brain and heart activity documented by physician, laboratory or diagnostic test. Device related death is defined as death related to the investigational device. This may be a device malfunction, misuse, or any death in which the relation of the device cannot be ruled out.
- **Surfacer System component failure or malfunction -** Any failure or malfunction of the device or a component when used as intended per the Clinical Investigational Plan or Instructions for Use. System or component failures are by definitions device related.