NCT#04920929

Title of Protocol: A Prospective, Randomized, PICC Asymptomatic Thrombosis Study: A Pilot Study
Version: C
Date: 28Apr2021
Date and Version of Previous Protocol: Version A; 31Aug2020: Version B; 26Oct2020

Sponsor Name and Address:
Access Vascular, Inc
175 Middlesex Turnpike
Suite 1A
Bedford, MA 01730

Investigational and Comparator Product(s):
4 French Single Lumen:
HydroPICC
[redacted]

Protocol Author(s):
[redacted]

1. Signatures

1.1. Principal Investigator Signature Page

This page will be returned to Access Vascular Inc. and a copy retained at the investigational site.

I have read the attached protocol entitled "A Prospective, Randomized, PICC Asymptomatic Thrombosis Study: A Pilot Study" version C, dated 28 April 2021 and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in the Clinical Trial Agreement.

[redacted]

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Access Vascular Inc.

Name, Title	Signature	Date Signed (DD/MMM/YYYY)

2. Summary of Changes Table

DOCUMENT HISTORY			
Version	**Date**	**Description of Change**	**Brief Rationale**
A	*31 Aug 2020*	*Initial Version*	*Initial Version*
B	*26 Oct 2020*	*Added 14 day time point throughout the protocol* *Updated wording of primary endpoint and added additional "other end points"* **Primary endpoint:** "By using ultrasound technology, the site will measure incidence of all early asymptomatic thrombosis inclusive of superficial thrombophlebitis (SVT) and deep venous thrombosis (DVT) at the first follow up visit (7 days post insertion)." **Other endpoints:** [redacted]	[redacted]
C	*28 Apr 2021*	*Administrative Changes only:* *Updated to Version C and date in header and title page.* *Updated the wording in the protocol signature page.* [redacted]	[redacted]

		[redacted]	

3. CONTENTS

Contents

4. Protocol Synopsis

Title of Protocol:	A Prospective, Randomized PICC Asymptomatic Thrombosis Study (PROPATH)
Study Design:	This is a single-site, pilot, nonblinded randomized controlled trial to compare two brands of single lumen PICC lines.
Study Product:	HydroPICC
Comparison Group(s)*: (*if applicable)	Standard of care devices- 4 French Single Lumen PICC line [redacted]
Study Purpose:	The study purpose is [redacted] evaluating thrombosis incidence that were observed [redacted] using UltraSound technology in-vivo.
Primary Objective:	The primary purpose is to evaluate the incidence of early asymptomatic thrombosis between the HydroPICC arm and the comparison arm.
Primary Endpoint:	By using ultrasound technology, [redacted] incidence of all early asymptomatic thrombosis [redacted] (7 days post insertion).
Secondary Objective(s):	[redacted] symptomatic thrombosis rate in the two groups by using ultrasound technology.
Secondary Endpoint(s):	By using ultrasound technology, the site will measure all subjects to look for incidence of symptomatic thrombosis.
Other Objective(s):	1.) [redacted]
Other Exploratory Endpoint(s):	[redacted]
Sample Size:	10 HydroPICC 10 Standard of care-[redacted]

Number of Study Sites:	Single Center Study
Inclusion Criteria:	1) Patient is indicated for a medically necessary PICC for therapeutic delivery medication 2) Patient is eligible to receive a single lumen PICC 3) Patient is an adult who is prescribed a PICC line 4) Patient's expected duration of treatment requiring a PICC for a minimum of 16 days post device implantation 5) Patient understands and is willing to comply with all study requirements and has voluntarily signed the Informed Consent Form (ICF).
Exclusion Criteria:	1) Is pregnant, lactating, or is planning to become pregnant during the time of the study 2) Has been previously enrolled in this post market clinical evaluation, or is participating in another clinical study that is contraindicative to the treatment or outcomes of this investigation 3) Venous thrombosis in any portion of the vein to be catheterized 4) Conditions that impede venous return from the extremity such as paralysis or lymphedema after mastectomy 5) Orthopedic or neurological conditions affecting the extremity 6) Anticipation or presence of dialysis grafts or other intraluminal devices, including pacemakers, within a month of patient enrollment start 7) Patients who are on anticoagulation therapy prior to the study (10-14 days). *Note: (If patients are placed on anticoagulation (low dose) therapy while hospitalized, these patients are allowed.)* 8) Patient has relinquished control of care to a guardian and/or facility 9) Patient has any significant medical or physical condition that, in the opinion of the PI, would make the subject unsuitable for participation in the post market clinical evaluation 10) Inability to complete the protocol in the opinion of the clinical staff due to safety or other reasons
Study Duration:	[redacted] Enrollment is expected to take about 2 months. Data collection completed when Last Subject Last Visit occurs. (Calculated by date of procedure + 12 days for the last subject) [redacted]
Reported Adverse Event Data:	Product observations and adverse events will be collected and reviewed per [redacted] (product complaints). Additional safety evaluations will be performed if needed.

Schedule of Activities

Subject Timepoints	Visit 1 Screening (- 7 days)*	Visit 2 Procedure (0 day)	Visit 3 7 day evaluation (± 5 days)	Visit 4 14 day evaluation and End of Study (± 7 days)***	Unscheduled visits (as needed)
ICF	X				
Inc/Ex criteria	X				
Medical History	X				
Demographics	X				
Con Meds	X	X	X	X	X
Labs (specific per protocol and standard of care)	X	X	X	X	X
Randomization	X**	X**			
Surgical Summary		X			
Ultrasound (as needed per DVT, AND at these specific timepoints)		X	X	X	X
AE/SAEs		X	X	X	X
Follow up form/ unscheduled visit form			X	X	X
End of study forms				X	

*Screening can happen on the same day of the procedure. Screening can also happen 7 days prior to the procedure.
**Randomization can occur at screening or prior to procedure.
***Visit 4 to be scheduled at least **four days** post visit 3 to avoid overlap. The windows are needed to accommodate scheduling.

5. Introduction

5.1. Background

Access Vascular has developed a novel, bulk-hydrophilic catheter material represents a fundamental shift in material technology. Catheters used for vascular access are commonly prepared from polyurethanes or silicones that provide flexibility, durability, and strength (Renner, 1998), (JM, 1995); however, these polymeric materials are hydrophobic and therefore susceptible to non-specific protein adsorption (Jordon SW, 2007), (Tal MG, 2008). Access Vascular has developed a [redacted] hydrogel material PICC line used to access the central venous system via a peripheral vein. Hydrogels have found use in many different medical applications due to their high tolerability. As a result of several factors, including a high-water content and neutral surface charge, Access Vascular's material may mask the catheter from the body significantly more effectively than traditional catheters, resulting in a significantly lower rate of thrombosis. [redacted]

The study purpose is to perform a preliminary evaluation of the Hydrogel technology to confirm the performance of the catheter, including evaluating thrombosis incidence [redacted] by using UltraSound technology in-vivo. The secondary objective of this study is to evaluate the symptomatic thrombosis incidence rate in the two groups by using ultrasound technology. [redacted]

5.2. Disease and Medical Condition State

Venous catheters are used to enable intravenous access for delivery of therapeutics such as antibiotics, chemotherapy, or parenteral nutrition, and for other applications such as blood draws. In the US, approximately 500 million procedures involving venous catheters are performed each year (McGee, 2003), (O'Grady, et al., 2011), (Kornbau, Lee, Hughes, & Firstenberg, 2015).

Thrombosis is the formation and accumulation of blood platelets inside a blood vessel. There were many doctors who had theories about thrombosis, but it was through the works of Rudolf Virchow who described 3 factors that contribute to the development of venous thrombosis: hypercoagulability, statis of blood flow, and endothelial injury (Bagot & Arya, 2008). When the body detects a potential threat to a blood vessel, such as blood vessel injury or a foreign object, one of the body's responses is to trigger the clumping of platelets against the perceived threat, creating blood clots. In most situations, this reaction is vital to the organism's survival, as the clumping prevents further blood loss or neutralizes a threatening foreign object. However, this response can be harmful in the case of venous access, since the body interprets the catheter as a foreign object and triggers clotting against the catheter.

Several factors can contribute to the formation of thrombus, including, but not limited to, patient disease states inducing elevated systemic prothrombotic states (Van Rooden, 2005), peripheral versus central insertion (Fallouh, 2015), catheter tip malposition (Luciani, 2001), ratio of catheter size to vein diameter (O'Brien, 2013), catheter and/or infusate composition (Caroline Berube, 2017). Although symptomatic line-related thrombosis incidence rates for PICCs range between 3-20% (Zochios, 2014), (Abdullah, 2005), the total rate of upper extremity thrombosis related to the insertion of PICC devices is much higher, with one study measuring 38.5% of patients experiencing a UEVT, and some patient populations at higher risk (i.e. cancer) reaching rates as high as 60% (Luciani, 2001). Although asymptomatic, UEVT has been associated with elevated rates of more serious adverse events such as pulmonary embolism and catheter-related sepsis.

There is a lack of research in regards to adult asymptomatic thrombosis (Pinelli & Balsorano, 2019). The current asymptomatic research study is from the pediatric population where they found a high rate of asymptomatic catheter-related thrombosis (22%) in pediatric patients needing central venous catheters (Pinelli & Balsorano, 2019).

The terminology also needs to be defined clearly because there is some confusion. In a study conducted by Baskin et al., they referred to asymptomatic thrombosis as "fibrin sheath". Other terminology used is also "pericatheter thrombosis" and "pericatheter thrombotic apposition" (Pinelli & Balsorano, 2019). We must be clear about the definition for this study. In this protocol, we are looking for asymptomatic thrombosis using ultrasound technology. This specifically means we are looking for PICCs with echogenic mass in or on the lumen, but no limb swelling, tenderness, or any symptomatic issues.

More recently, in 2020, there was a study published on Chinese cancer patients using ultrasound and looking at asymptomatic venous thrombosis. In this study by Wang et. al, they were able to find that the incidences of PICC related upper limb asymptomatic thrombosis was 48.82%, and the median to observe these thrombi was 3 days. Within 24 hour of PICC insertion, there were 37.1% of patients with asymptomatic thrombosis, and within 1 week, that rate jumped to 85.49% (Wang, et al., 2020). They showed that asymptomatic thrombosis can occur at an early stage. Asymptomatic thrombosis is the way for some bodies to adapt to the trauma of PICC insertion. If this can be detected earlier, then patients will be treated appropriately, and veins for future vascular access needs can be saved.

As a result of thrombus related complications, catheter manufacturers have commercialized products focused on addressing these complications. Nearly all venous catheters are made from polyurethane, and several manufacturers, including the market leader, continue to sell standard, undifferentiated polyurethane catheters. Some companies have added anti-microbial coatings to their devices to provide anti-infective ability. Others have incorporated additives which attempt to mask the device from the body. While somewhat effective, these catheters are nonetheless primarily made of polyurethane and silicone. Although little difference exists in complications rates between the two materials (Seckold, 2015), both materials remain susceptible to the thrombus related complications described above.

5.3. Overview of Non-Clinical Studies

[redacted]

[redacted]

5.4. Overview of Clinical Studies

No clinical studies have been conducted with the current HydroPICC.

6. Study Rationale

6.1. Risk/Benefit Assessment

The current products in this study are FDA 510k cleared. The HydroPICC will be referred to as the investigational product for the purposes of this protocol. There are no study risks associated with the use of the HydroPICC or the competitor PICC. The benefit would be to analyze if a new material in this space would have better outcomes for patients who are in need of this type of medical device.

Though rates of symptomatic thrombosis vary from 3-23% (Chin, Zimmerman, & Grant, 2005), rates of asymptomatic venous thrombosis have been reported as much higher at 48% (Wang, et al., 2020). This study will assess the rate and severity of asymptomatic upper extremity venous thrombosis associated with the use of Access Vascular's FDA-cleared HydroPICC as compared to a competitor device.

7. Study Objective (s) and Endpoints

The study purpose is to take a preliminary look at the Hydrogel technology to examine the asymptomatic thrombosis incidents [redacted] by using Ultrasound technology in-vivo.

7.1. Primary Objective and Endpoints

The primary purpose is to examine the incidents of early asymptomatic thrombosis between the HydroPICC arm and the comparison arm.

By using ultrasound technology, the site will measure early incidents of all asymptomatic thrombosis inclusive of superficial thrombophlebitis (SVT) and deep venous thrombosis (DVT). Subjects will be requested to have the PICC line scanned at 7 days (± 5 days), and at any unscheduled visit where a symptomatic SVT or DVT is suspected.

The ultrasound evaluation will be classified as (1) without thrombosis or (2) with limited (~2-4mm), (3) large (~4 mm), or (4) occlusive thrombosis, as compared to baseline. Please see the ultrasound section below for more details.

7.2. Secondary Objective and Endpoints

The secondary objective of this study is to evaluate the symptomatic thrombosis rate in the two groups by using ultrasound technology.

By using ultrasound technology, the site will measure all subjects to look for incidents of symptomatic thrombosis. Subjects will be requested to have the PICC line scanned at 7 days (±5 days), 14 days (±7 days and at any unscheduled visit where a DVT is suspected.

The ultrasound evaluation will be classified as (1) without thrombosis or (2) with limited (~2-4mm), (3) large (~4 mm), or (4) occlusive thrombosis, as compared to baseline. Please see the ultrasound section below for more details.

7.3. Other Objectives and Endpoints

[redacted]

8. Study Design

This is a single-site, pilot, nonblinded randomized controlled performance evaluation to compare two brands of commercially-available single lumen PICC lines. This is a postmarket clinical evaluation and not a statistically powered study.

8.1. Study Overview

This post market clinical evaluation is a prospective, randomized post-market assessment. Each eligible subject will receive a single lumen PICC device and will be placed per the manufacturer's IFU and in accordance with institutional policy.

[redacted]

Per institution policy, due to the fact that the HydroPICC is not a standard of care device, the patient will be consented prior to insertion. This consent will follow the institution's standard of care policies.

[redacted] any patient receiving a single lumen PICC will be approached to join this study. After the patient consents, and the site reviews the inclusion criteria, the subject can be randomized.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. There is an exclusion criteria which requires an ultrasound, and a subject can still be screen failed at the time of insertion.

The following treatments will be used:

AVI device: Access Vascular HydroPICC Single Lumen PICC
Comparator device: [redacted] Single Lumen PICC
Vein: Preference is Basilic Vein followed by Brachial Vein, then Cephalic Vein

Once a subject is inserted with a PICC line, they are considered enrolled.

Total duration of subject participation will be the duration for which the catheter is indwelling in the patient up to 16 days. The total study duration is expected to not exceed 23 days, including procedural pre-screen. Insertion of the PICCs will be prioritized with the following: Basilic vein then Brachial vein followed by Cephalic vein. Diagnosis of both asymptomatic and symptomatic vein thrombosis will be established by Doppler ultrasound examination. Examinations will be performed prior to device insertion to establish patient baselines.

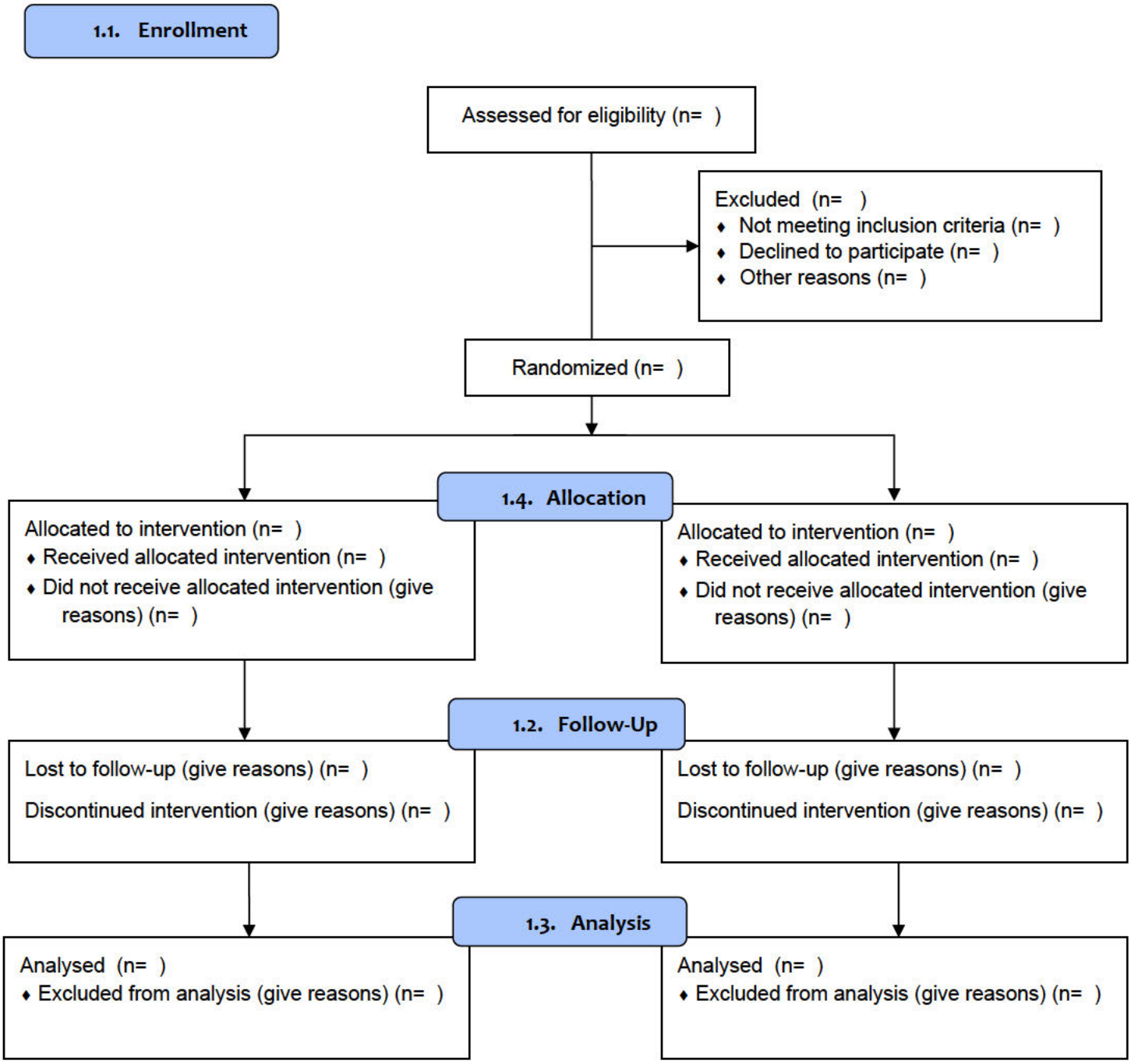
Ultrasound will be performed pre-insertion of the device, at 7 days post-insertion (±5 days) and 14 days (±7 days). Data will be collected using a scale defined previously.

9. Study Methods and Measurements

9.1. Methods Used to Minimize Bias and Maximize Validity

This study will be randomized using CONSORT guidelines stated below (www.consort-statement.org). The randomization will be conducted via sealed envelope. The specific randomization will be discussed in further detail below.

CONSORT 2010 Flow Diagram



10. Subject Selection

10.1. Screening

All subjects who are indicated for a medically necessary Single Lumen PICC line will be screened for eligibility for the study.

10.2. Consent

If the patient is interested in moving forward with this study, then they will sign the study informed consent. Those who do not consent will be logged as "declined to participate" in the screening log. Those who consent will be screened by the site staff using the inclusion and exclusion criteria.

10.3. Inclusion Criteria

1) Patient is indicated for a medically necessary PICC for therapeutic delivery medication
2) Patient is eligible to receive a single lumen PICC
3) Patient is an adult prescribed a PICC line
4) Patient's expected duration of treatment requiring a PICC for a minimum of 16 days post device implantation
5) Patient understands and is willing to comply with all study requirements and has voluntarily signed the Informed Consent Form (ICF).

10.4. Exclusion Criteria

1) Is pregnant, lactating, or is planning to become pregnant during the time of the study
2) Has been previously enrolled in this post market clinical evaluation, or is participating in another clinical study that is contraindicative to the treatment or outcomes of this investigation
3) Venous thrombosis in any portion of the vein to be catheterized
4) Conditions that impede venous return from the extremity such as paralysis or lymphedema after mastectomy
5) Orthopedic or neurological conditions affecting the extremity
6) Anticipation or presence of dialysis grafts or other intraluminal devices, including pacemakers, within a month of patient enrollment start
7) Patients who are on anticoagulation therapy prior to the study (10-14 days). *Note: (If patients are placed on anticoagulation (low dose) therapy while hospitalized, these patients are allowed.)*
8) Patient has relinquished control of care to a guardian and/or facility
9) Patient has any significant medical or physical condition that, in the opinion of the PI, would make the subject unsuitable for participation in the post market clinical evaluation
10) Inability to complete the protocol in the opinion of the clinical staff due to safety or other reasons

10.5. Randomization

After consent and review of the inclusion/exclusion criteria, the Investigator can assign a randomization prior to baseline ultrasound. If during the ultrasound procedure, the subject meets an exclusion criterion, then this subject will be considered a screen fail.

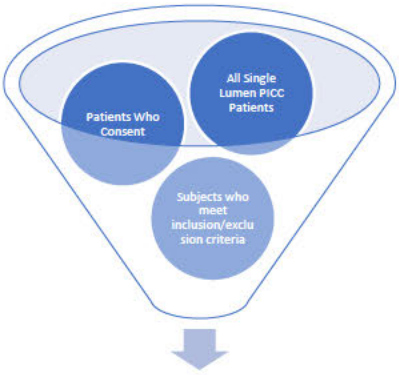
10.6. Screen Failures

Any subject who signs an informed consent but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects will have their demographic information captured in the appropriate CRF with the reason for screen failure specified. No other information will be collected or analyzed. Since this is a pilot study, the analysis will be conducted on 10 subjects on each arm. If a

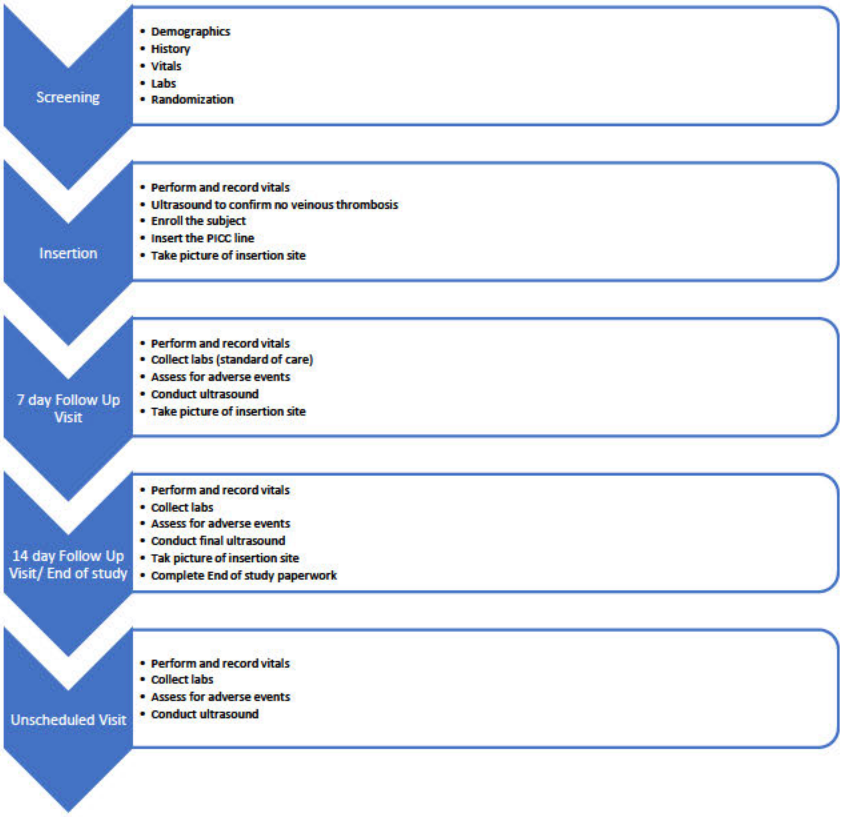
screen failure occurs, the investigator will need to continue to consent, randomize, and enroll until the 10 subjects for each arm is completed. A second set of randomization envelopes will be used for the recruitment of these screen failed subjects.

10.7. Enrollment

A subject is considered enrolled when the assigned PICC is inserted. Due to the current situation with COVID, the sponsor is concerned about lost to follow up rates. To prepare for this, the site will enroll 4 extra subjects bringing the total to 24. The plan is to analyze 10 enrolled subjects on each arm, but the site will recruit for 12 in case of COVID related follow up issues.



Screening process



11. Discontinued Subjects

If a subject is unable to complete the study for any reason, then the investigator will use the screen failed randomization envelope to recruit for this discontinued subject. Data from the discontinued subject will not be used for the per protocol analysis. However, demographics will be used for the recruitment analysis. Any subjects in section 12 described below will be replaced using the method mentioned in this paragraph.

11.1. Early Discontinuation of Study Subject

A subject may be discontinued at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Protocol violation requiring discontinuation
- Sponsor request for early termination of study
- Positive pregnancy test (females)

All subjects who discontinue should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

11.2. Lost to Follow-Up

The site should document at least 3 attempts to contact the subject before a subject is considered lost to follow-up. This will be documented in the end of study CRF.

11.3. Investigator Withdrawal

Investigators have the authority to withdraw a subject at any time, for any reason, specified or unspecified, and without prejudice. The investigator is requested to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and recorded on the end of study CRF.

11.4. Subject's Withdrawal of Consent

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and recorded on the end of study CRF.

11.5. Use of Data Following Withdrawal

Data collected while the subject provided will be used for the overall analysis. No data will be collected or analyzed from the date that the subject withdrew from the study.

12. Study Treatment

12.1. Method of Assigning Subjects to Treatment Groups

The subjects will be randomized to the two different treatment groups. A match and replace method will be used to ensure that screen failed randomized subjects will be replaced appropriately. The randomization assignment methodology will be documented in the Statistical Analysis Plan.

12.2. Blinding

There is no blinding in this protocol.

12.3. Description of HydroPICC

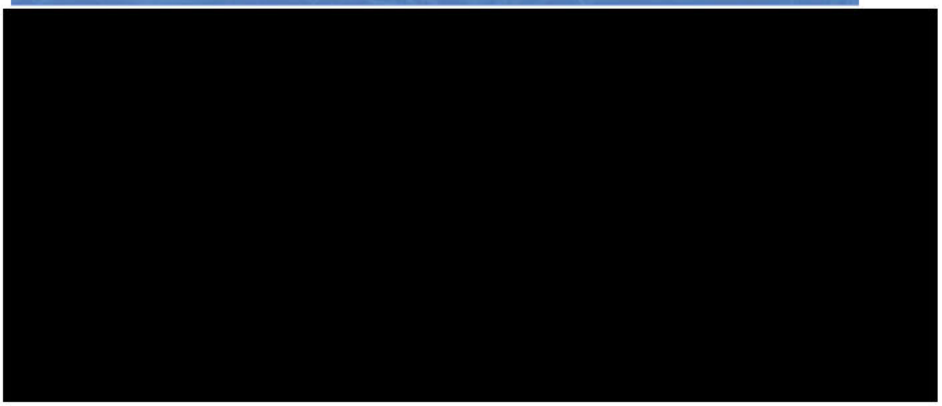
The HydroPICC peripherally inserted central catheter (PICC) is commercially available a single lumen catheter comprised of a radiopaque, hydrophilic base with a suture wing, Luer lock hub, and extension tube. The catheter has a maximum power injection rate of 3.5 mL/sec. The maximum usable length of the catheter is 55cm.

HydroPICC has been shown to be effective in reducing thrombus accumulation when evaluated using *in vitro* and *in vivo* models. Pre-clinical *in vitro* and *in vivo* evaluations to not necessarily predict clinical performance with respect to thrombus formation.

HydroPICC is manufactured and commercialized by Access Vascular, Inc.

HydroPICC Kit Components

HydroPICC Kit Components (continued)



12.4. Description of Comparator Product

The [redacted] is manufactured by [redacted]. According to their IFU, [redacted]

13. Study Procedures

13.1. Demographics

Demographic information will be recorded at Screening after a subject has signed the consent. This will include, but not limited to:

- Date of birth
- Race
- Ethnicity
- Gender

13.2. Medical History

Relevant medical history, including history of current disease, other pertinent venous history, and information regarding underlying diseases will be recorded at Screening.

13.3. Physical Examination

A complete physical examination will be performed by either the investigator or a sub-investigator who is a physician at Visit 1. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

13.4. Vital Signs

Body temperature, blood pressure, Oxygen levels, heart rate and respirations will be performed. Blood pressure is only to be performed in the supine position on the non-treatment appendage in the study.

13.5. Concomitant Medications

All concurrent therapies will be documented at Screening, at follow up visits, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

13.6. Clinical Laboratory Measurements

13.6.1. Laboratory Safety Measurements

Safety laboratory tests for this study [e.g. chemistry, hematology, coagulation (for applicable subjects), and urinalysis] are to be performed by the local institution per their standard of care.

13.6.2. Pregnancy Test

A urine or serum pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study. If a positive test returns, they are to be excluded.

All subjects will be urged to use birth control during the length of the study, however, if a subject does become pregnant during the length of the study, this will be noted, and data can continue to be collected if the Investigator deems it safe. All pregnancy related adverse events will be collected, but will be classified as pregnancy related.

13.7. Ultrasound Measurements

Ultrasound methodology: The patient will be placed supine. Their palm will face upward with their arm abducted at 90˚to conduct an ultrasound scan of the PICC line.

Ultrasonography will be performed on the vein that the PICC line is inserted. The vein will be scanned axially and transversely in two distinct sections. The first section is from insertion to the axillary junction. The second section is from the axillary junction to the superior vena cava

(SVC). The technician will pay particular attention to 2 cm above the insertion site, and at 10 cm above the insertion site as these will be specific data points to be recorded. The form used will have a picture of the vein and the technician can note where thrombosis was found. They will then measure the size of the thrombosis and note the approximate location in the form.

The diagnostic criteria will be based on any of the three US signs: (a) lack of normal vein compressibility, (b) lack of color signal from the vessel on the color Doppler scan, and (c) lack of signal from the vessel on the spectral Doppler scan. If technical problems or anatomical barriers hamper visualization, findings from the ultrasonographic screening will be considered indeterminate and appropriately recorded.

Based on ultrasound evaluation, veins will be classified as (1) without thrombosis or (2) with limited (2 to 4 mm), (3) large (~4 mm), or (4) occlusive thrombosis, as compared to baseline.

The person reading the ultrasound will use a data collection form to review the classification of the veins. The length and/or the depth of the thrombosis will be used to assess the classification. For example, if a thrombosis is 5mm long, but does not fully occlude the vessel, then it would be classified as a (3) large. However, if a thrombosis is 5mm long AND occludes the vessel, then it would be classified as a (4) occlusive thrombosis. The primary investigator will be responsible for confirming the classifications.

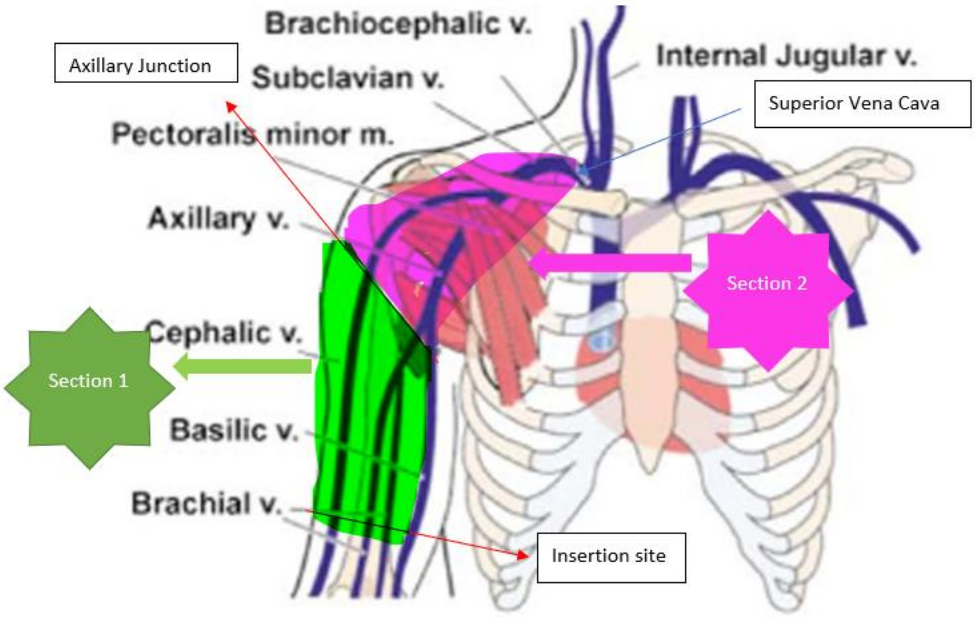


Image of veins from: (Chin, Zimmerman, & Grant, 2005)

14. Evaluations by Visit

14.1. Screening Visit (Visit 1)

1. Assign the subject a unique screening number.
2. Perform informed consent process; subjects to sign and date the Informed Consent Form.
3. Record demographics data.

4. Record medical history, including a history of condition(s) requiring chemotherapy or antibiotics, diagnosis date, and prior treatments related to the relevant condition(s).
5. Record baseline labs, if available.
6. Perform a complete physical examination.
7. Perform and record vital signs.
8. Schedule subject for Procedure visit in no more than 5 days
9. Randomize the subject

14.2. Surgical Visit- (Visit 2)

1. Perform and record vital signs.
2. Record labs, if available.
3. Conduct Ultrasound prior to insertion of the assigned PICC. Screen fail if necessary.
4. Insert device per assigned randomization, IFU, and institutional procedures.
5. Confirm patient entry into study.
6. Take picture of insertion site.
7. Record adverse events (if any).

14.3. Follow Up Visit- (Visit 3) (7 days post placement ± 5 days)

1. Perform and record vital signs.
2. Record Adverse Events (if any).
3. Record changes to concomitant medications (if any).
4. Record labs, if available.
5. Conduct ultrasound assessment of treatment extremity.
6. Take picture of insertion site.

14.4. Follow Up Visit- (Visit 4) (14 days post placement ± 7 days)/ MUST be at least 4 days after the Visit 3

7. Perform and record vital signs.
8. Record Adverse Events (if any).
9. Record changes to concomitant medications (if any).
10. Record labs, if available.
11. Conduct ultrasound assessment of treatment extremity.
12. Take picture of insertion site.
13. Complete the end of study CRF. Indicate reason for end of study (completion of study, therapy, or otherwise).

14.5. Unscheduled Visit(s)

1. Perform and record vital signs.
2. Record Adverse Events (if any).
3. Record changes to concomitant medications.
4. Record labs, if available.
5. Conduct ultrasound assessment of treatment extremity.
6. Take picture of insertion site.
7. Remove or treat the PICC line per IFU and institutional protocols if necessary.
8. If a subject is discontinued from the study due to a Serious Adverse Device Effect, the institution should notify their IRB per the IRB reporting requirements.

15. Adverse Event Reporting

These definitions are for the purposes of this post market clinical evaluation only. Medical Device Reporting (MDR) will be conducted using the normal AVI definitions for reporting to the FDA. We will follow [redacted].

Adverse Event (AE) (ISO 14155:2020): untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.
Note 1: This definition includes events related to the investigational medical device or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE) (ISO 14155:2020): is an adverse event that is related to the use of an investigational medical device.
Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.
Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Note 3: This includes "comparator" if the comparator is a medical device.
Comparator: *medical device, therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation.*

Serious Adverse Event (ISO 14155:2020):
A Serious Adverse Event (SAE) is an adverse event that:

a) Led to death,

b) Led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:1) A life-threatening illness or injury, or
2) A permanent impairment of a body structure or a body function including chronic diseases, or
3) In-patient or prolonged hospitalization, or
4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

AE Severity
The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant (US Department of Health and Human Services, 2017). The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guideline below is used. The term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate (2)	minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*.
Severe (3)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
Life-threatening (4)	Life-threatening consequences; urgent intervention indicated.
Death (5)	Death related to AE

Activities of Daily Living (ADL)
**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*
***Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

AE Relationship to Device
The relationship of an AE to the study device should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Device

Relationship to Device	Comment
Definitely	Previously known hazard related to this class and type of device; or an event that follows a reasonable temporal sequence from implantation of the device; that follows a known or expected response pattern to the suspected device; that is confirmed by stopping and removal of the device; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from implantation of the device; that follows a known or expected response pattern to the device; that is confirmed by stopping or removal of the device; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from implantation of the device; that follows a known or expected response pattern to that device; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study device.

AE Relationship to Study Procedure
The relationship of an AE to the study procedure should be assessed using the following the guidelines in Table 3.

Table 3. AE Relationship to Study Procedure

Relationship to Device	Comment
Definitely	Previously known hazard related to this procedure; or an event that follows a reasonable temporal sequence from the procedure; that follows a known or expected response pattern to the suspected procedure; that is confirmed by stopping the procedure; and that is not explained by any other reasonable hypothesis.

Probably	An event that follows a reasonable temporal sequence from the procedure; that follows a known or expected response pattern to the procedure; that is confirmed by stopping the procedure; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from the procedure; that follows a known or expected response pattern to the procedure; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the procedure.

15.1. Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note 1: Device deficiencies includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device (3.29) or the comparator

15.2. Reporting Procedures

AE of any kind and DD will be recorded in the applicable CRF and source notes. The collection of AE's is started at the time of the procedure.

The Investigator will evaluate all AE for seriousness, severity and relationship to the device and procedure. The following reporting timelines should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee:

- ADE and DD – will be reported in a timely manner (within 3 working days of the investigator being informed about the event)
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)

To report: Enter data into the EDC system. This will generate an automated email to the clinical team. If you do not have access to the EDC system, call Access Vascular at [redacted] and/or email the clinical team at [redacted]

For ADE, SADE and DD, details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to the sponsor via the return kits. Depending on the nature of the adverse event, the sponsor may request copies of the subject's medical records, Imaging, Operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by the sponsor and should be forwarded as soon as it becomes available. A narrative of these ADE, SADE, or DD may be required to provide a summary of the event.

The Investigator and investigative site will also be responsible for required reporting to the site's Institutional Review Board / Independent Ethics Committee (IRB/IEC) for all AEs, SAEs, and UADEs.

Ongoing Adverse Events at Study Discontinuation

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

16. Statistical Design

16.1. General Considerations

Study data will be made available in listings or electronic files as needed. The study results will be reported in tabular form using descriptive statistics, confidence intervals, or statistical tests as indicated.

All summaries will be done by randomized treatment group. Numeric descriptive statistics include the n, mean, standard deviation (SD), median, minimum value, and maximum value. These will be calculated for all numeric baseline data. Categorical summaries will show the number and percent of subjects in the levels associated with the variable summarized and the analysis performed. Percentages will be calculated based on the total number of subjects with non-missing data for the assessment. The denominator should be included for each summary to indicate the set of subjects being summarized.

For any inferential analyses, a two-sided p-value of less than or equal to 0.05 will be considered statistically significant. Any confidence intervals provided will be two-sided 95% intervals. The primary effectiveness assessment is considered the primary analysis. This study is not intended to support claims and the other statistical tests included are intended to assist with reporting, hence, no other adjustment for multiplicity will be used.

[redacted]

16.2. Sample Size Justification

This is a pilot study to see if the ultrasound endpoint is feasible for a larger study. No power analysis was conducted for this study.

16.3. Analysis Populations

The primary analysis will be based on a Full Analysis Set (FAS) analysis population defined as those who were randomized and met all inclusion and exclusion criteria. A Per-Protocol (PP) population will be completed that excludes subjects who have one or more major protocol deviations. Major protocol deviations will be identified prior to locking the database for the final analysis and will include, but are not limited to, not receiving the randomized treatment, not completing the study, and not have met all inclusion and exclusion criteria. Information for subjects not in the FAS population will be listed if available.

16.4. Accountability and Baseline Data

Study completion information including reasons for discontinuation and visits completion information will be summarized. Baseline demographics, medical history, and BMI (kg/m2) will be summarized descriptively.

16.5. Analyses

16.5.1. Analysis of Primary Endpoint

The primary endpoint will be summarized categorically based on the scale previously described regarding an ultrasound result of asymptomatic subject thrombosis severity. These results will be summarized by treatment group at each visit (pre-insertion, post-insertion, and at 7-day follow-up visit). A Cochran-Armitage trend test will be used to assess the null hypothesis that there is not trend associated with the treatment and the highest level of thrombosis.

Additionally, the presence of any asymptomatic thrombosis will be evaluated as a binary outcome and Fisher's Exact test will be used to evaluate the null hypothesis that the rate of any thrombosis is homogeneous in the treatment arms.

If COVID-19 subjects are identified in the study, the primary endpoint and any thrombosis outcomes will be summarized separately in those subjects.

16.5.2. Analysis of Secondary Endpoint(s)

The secondary endpoint of symptomatic thrombosis severity will be analyzed in the same manner as the primary endpoint.

16.5.3. Analysis of Other Endpoint(s)

Failure and safety endpoints will also be compared between the HydroPICC group and control group using Fisher's exact tests.

16.6. Adverse Event Analyses

A listing of all individual AEs will be provided. Summary tables will be presented by system organ class based on the Medical Dictionary for Regulatory Activities (MedDRA Version 18.0 or higher) terminology list (preferred terms). The number and percentage of subjects with one or more event will be summarized by treatment group along with the total number of events. This summary will be provided for all AEs, SAEs, device-related AEs, and device-related SAEs.

All SAEs will also have a detailed narrative provided.

17. Data Management

The data collected in the CRFs will be entered into a database. The data will be subject to verification, validation and archiving according to the standard operating procedures of the Sponsor. The data will be analysed with reference to the analysis plan. Any deviations from the planned analysis will be documented in the final study report.

17.1. Confidentiality

Data will be de-identified on forms and in the clinical database, and subjects will be identified only by a code or subject number. All information and data sent to sponsor or designee concerning patients or their participation in this study will be considered confidential, and confidentiality shall be observed by all parties involved at all times during the study. All data used in analysis and reports will be used without identifiable reference to the subject. All data will be secured against unauthorized access. The Investigator and investigative site will be responsible for compliance with all local privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

18. Sponsor and Monitor Responsibilities

Monitoring visits will be conducted by representatives of the Sponsor according to the study Clinical Monitoring Plan in compliance with U.S. CFR Title 21 Parts 50, 56, and 812 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The post market clinical evaluation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if

applicable, with GCP regulations, and with applicable regulatory requirements. Due to COVID, these monitoring visits may be conducted virtually/remotely. The sponsor and institution will evaluate the best solution for monitoring, and the monitoring plan will provide details for multiple scenarios.

The Sponsor or designee will record, report and analyse all protocol deviations. The Sponsor will also ensure corrective and preventive actions are taken, including assessment of principal investigator disqualification criteria.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

19. Administrative, Ethical, Regulatory Considerations

19.1. Statement of Compliance

This evaluation will not commence until the required approval/favorable opinion from the IRB or regulatory authority has been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed.

In compliance with the Food and Drug Administration Amendments Act of 2007 (FDAAA), this study will be listed in www.clinicaltrials.gov.

This post market clinical evaluation will be performed in compliance with the ethical principles of the Declaration of Helsinki: Clinical investigation of medical devices – Good Clinical Practice.

19.2. Informed Consent Forms (ICF)

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. As this is evaluation is assessing a commercially-available device per the cleared indication, informed consent will primarily confirm the subject's willingness to provide their data and be randomized.

The Investigator will prepare the informed consent form and provide it to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the applicable ICH and federal guidelines and will also comply with local regulations for a post market evaluation of a commercially-available device. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the ICF, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

19.3. Publication Policy of Study Data

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all

applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

19.4. End of Study

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor.

19.5. Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the post market clinical evaluation (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 812.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 812 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 812.

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